CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 022309/S-001

Trade Name: **ANDROGEL 1.62%**

Generic Name: **Testosterone Gel**

Sponsor: **Abbott Products, Inc.**

Approval Date: 09/07/2012

Indications: AndroGel 1.62% is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022309/S-001

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022309/S-001

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309/S-001

SUPPLEMENT APPROVAL

AbbVie Inc.
Attention: Janel Boyce-Rustay, Ph.D.
Manager, Regulatory Affairs
1 N. Waukegan Road
North Chicago, IL 60064

Dear Dr. Boyce-Rustay:

Please refer to your Supplemental New Drug Application (sNDA) submitted and received on August, 16, 2011, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AndroGel® (testosterone gel) 1.62%.

We acknowledge receipt of your amendments dated March 7, November 18 and 29, 2011, and September 6, 2012, and your risk evaluation and mitigation strategy (REMS) assessment dated November 29, 2011.

The March 7, 2012, submission constituted a complete response to our February 21, 2012, action letter.

This Prior Approval supplemental new drug application proposes:

- The addition of a new container closure system for use in packaging and delivery of the product.

- Modifications to your REMS, which consists of a Medication Guide.

We have completed our review of this supplemental application, as amended. It 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, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, and Medication

Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the 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 July 26, 2012, enclosed carton and immediate container labels 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 (June 2008)." 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 "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 022309/S-001**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for AndroGel® (testosterone gel) 1.62% was originally approved on September 18, 2009. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of a revised Medication Guide to include information for a new container closure system and for language that is more consistent with Androgel 1%.

The proposed modified REMS submitted on November 29, 2011, and appended to this letter is approved.

The timetable for submission of assessments of the REMS will remain the same as that approved on September 18, 2009.

There are no changes to the REMS assessment plan described in our September 18, 2009 letter.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

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.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 022309 REMS CORRESPONDENCE**
> **(insert concise description of content in bold capital letters, e.g.,**
> **UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)**

If you currently distribute or plan to distribute an authorized generic product under this NDA, you must submit a complete proposed REMS that relates only to the authorized generic product. Submit a proposed REMS, REMS supporting document, and any required appended documents as a prior approval supplement. Approval of the proposed REMS is required before you may market your authorized generic product.

Prominently identify the submission containing the 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 as appropriate:

NDA 022309 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022309
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022309
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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}

Hylton V. Joffe, M.D., M.M.Sc.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
REMS

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

/s/

HYLTON V JOFFE
09/07/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022309/S-001

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309/S-001

COMPLETE RESPONSE

Abbott Laboratories
Attention: Troy ZumBrunnen
Director, Regulatory Affairs Liaison
200 Abbott Park Road
Dept PA76/AP34-3200
Abbott Park, IL 60064-6188

Dear Mr. ZumBrunnen:

Please refer to your Supplemental New Drug Application (sNDA) submitted and received on August 16, 2011, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AndroGel® (testosterone gel) 1.62%.

We acknowledge receipt of your amendments dated November 18 and 29, 2011.

This Prior Approval labeling supplemental new drug application (REMS modification) provides for additional packaging configuration, 1.25g and 2.5g stickpack (unit-dose) presentations, new container/carton and changes to the Full Prescribing Information and Medication Guide.

We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. The three commercial scale batches were manufactured with an amount of the absorption [redacted (b) (4)], which is not the amount of [redacted (b) (4)] in the AndroGel 1.62% formulation. Any change to the formulation with regard to the amount of ethyl alcohol must be supported by bioequivalence/clinical data. Therefore, the batches presented are not acceptable to support the proposed changes. Explain why the amount of ethyl alcohol used in the registration batches, [redacted (b) (4)] differs from the amount approved for AndroGel 1.62%, [redacted (b) (4)]

2. The submission is not consistent with regard to how alcohol is reported in the Composition Table and in the Specification Tables. For example, in section 3.2.P.2.1.1., Composition, the weight of ethyl alcohol is in terms of the weight as absolute alcohol. In Section 3.2.P.2.1.1.2, the weight of ethyl alcohol is shown in terms of the amount in [redacted (b) (4)]. In the batch formula, the

alcohol used is shown in terms of weight in [redacted]. In the stability data tables, the acceptance range for alcohol is in terms of weight in absolute alcohol. Explain why the weight of ethyl alcohol is not shown in the identical way in all tables. Update all composition and batch formula tables to include the amount of each component in grams per 100 grams gel.

2. Provide the calculation that demonstrates the weight of ethyl alcohol in a [redacted] is equivalent to a particular weight in a [redacted] and a particular weight in absolute alcohol. For example, that [redacted] is equivalent to [redacted] and equivalent to [redacted]

3. The submission proposes use of a [redacted] of the [redacted], isopropyl myristate (IPM), in the manufacture of AndroGel 1.62% to provide a 1% amount of IPM at release. Any change in the IPM content must be justified from a bioequivalence/clinical perspective. Justify the proposed [redacted] of IPM. Amend the proposed IPM acceptance criteria in the drug product release specification to [redacted]

4. Stability data include a stability time point PS0 that occurs prior to the T0 test point. Explain what the stability time point PS0 represents. Clarify if PS0 is a newly instituted time point; clarify if PS0 differs from a time point used in the analysis of the 22-309 original product.

5. Stability data for IPM obtained at the PS0 time point range in value from [redacted]. Additionally, these amounts are greater than amounts present in the clinical batches. Values obtained that are greater than amounts studied clinically must be supported with bioequivalence/clinical data.

6. Justify why the drug product specification does not include a test for minimum fill.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The risk evaluation and mitigation strategy (REMS) for AndroGel® 1.62% was originally approved on April 29, 2011. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS. We acknowledge receipt of your voluntary submission of a proposed REMS modification dated August 16, 2011. Your proposed modifications to the REMS consists of a revised Medication Guide to include information for the 1.25g and 2.5g stickpack (unit-dose). This amendment was not reviewed for this action. We will continue discussion of your proposed REMS modification after your complete response to this action letter has been submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

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

Sincerely,

{See appended electronic signature page}

Audrey Gassman, M.D.
Acting Deputy Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

AUDREY L GASSMAN
02/21/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022309/S-001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ANDROGEL 1.62% safely and effectively. See full prescribing information for ANDROGEL 1.62%.

AndroGel® (testosterone gel) 1.62% for topical use CIII
Initial U.S. Approval: 1953

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **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 (2.2, 5.2).**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use (2.2, 5.2, 17).**

-------RECENT MAJOR CHANGES-------

Indications and Usage. (1) 09/2012

-------INDICATIONS AND USAGE -------

AndroGel 1.62% is an androgen indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired) (1)
- Hypogonadotropic hypogonadism (congenital or acquired) (1)

Important limitations of use:

- Safety and efficacy of AndroGel 1.62% in males less than 18 years old have not been established. (1, 8.4)
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure. (1, 12.3)

-------DOSAGE AND ADMINISTRATION-------

- **Dosage and Administration for AndroGel 1.62% differs from AndroGel 1%. For dosage and administration of AndroGel 1% refer to its full prescribing information. (2)**
- Starting dose of AndroGel 1.62% is 40.5 mg of testosterone (2 pump actuations or a single 40.5 mg packet), applied topically once daily in the morning. (2.1)
- Apply to clean, dry, intact skin of the shoulders and upper arms. Do not apply AndroGel 1.62% to any other parts of the body including the abdomen or genitals. (2.2, 12.3)
- Dose adjustment: AndroGel 1.62% can be dose adjusted between a minimum of 20.25 mg of testosterone (1 pump actuation or a single 20.25 mg packet) and a maximum of 81 mg of testosterone (4 pump actuations or two 40.5 mg packets). The dose should be titrated based on the pre-dose morning serum testosterone concentration at approximately 14 days and 28 days after starting treatment or following dose adjustment. Additionally, serum testosterone concentration should be assessed periodically thereafter. (2.1)
- Patients should wash hands immediately with soap and water after applying AndroGel 1.62% and cover the application site(s) 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. (2.2)

-------DOSAGE FORMS AND STRENGTHS -------

AndroGel (testosterone gel) 1.62% for topical use is available as follows:

- a metered-dose pump that delivers 20.25 mg testosterone per actuation. (3)
- packets containing 20.25 mg testosterone. (3)
- packets containing 40.5 mg testosterone. (3)

-------CONTRAINDICATIONS -------

- Men with carcinoma of the breast or known or suspected prostate cancer (4, 5.1)
- Pregnant or breast-feeding women. Testosterone may cause fetal harm (4, 8.1, 8.3)

-------WARNINGS AND PRECAUTIONS -------

- Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH (5.1)
- Avoid unintentional exposure of women or children to AndroGel 1.62%. Secondary exposure to testosterone can produce signs of virilization. AndroGel 1.62% should be discontinued until the cause of virilization is identified (5.2)
- Exogenous administration of androgens may lead to azoospermia (5.5)
- Edema with or without congestive heart failure (CHF) may be a complication in patients with preexisting cardiac, renal, or hepatic disease (5.7)
- Sleep apnea may occur in those with risk factors (5.9)
- Monitor serum testosterone, prostate specific antigen (PSA), hemoglobin, hematocrit, liver function tests and lipid concentrations periodically (5.1, 5.3, 5.6, 5.10)
- AndroGel 1.62% is flammable until dry (5.13)

-------ADVERSE REACTIONS-------

The most common adverse reaction (incidence ≥ 5%) is an increase in prostate specific antigen (PSA). (6.1)

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

-------DRUG INTERACTIONS -------

- Androgens may decrease blood glucose and therefore may decrease insulin requirements in diabetic patients (7.1)
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended (7.2)
- Use of testosterone with adrenocorticotrophic hormone (ACTH) or corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3)

-------USE IN SPECIFIC POPULATIONS -------

There are insufficient long-term safety data in geriatric patients using AndroGel 1.62% to assess the potential risks of cardiovascular disease and prostate cancer. (8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: SECONDARY EXPOSURE TO TESTOSTERONE

- **Virilization has been reported in children who were secondarily exposed to testosterone gel *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]*.**
- **Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.**
- **Healthcare providers should advise patients to strictly adhere to recommended instructions for use *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Patient Counseling Information (17)]*.**

1 INDICATIONS AND USAGE

AndroGel 1.62% is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

Important limitations of use:

- Safety and efficacy of AndroGel 1.62% in males less than 18 years old have not been established *[see Use in Specific Populations (8.4)]*.
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure *[see Indications and Usage (1), and Clinical Pharmacology (12.3)]*.

2 DOSAGE AND ADMINISTRATION

Dosage and Administration for AndroGel 1.62% differs from AndroGel 1%. For dosage and administration of AndroGel 1% refer to its full prescribing information. (2)

2.1 Dosing and Dose Adjustment

The recommended starting dose of AndroGel 1.62% is 40.5 mg of testosterone (2 pump actuations or a single 40.5 mg packet) applied topically once daily in the morning to the shoulders and upper arms.

The dose can be adjusted between a minimum of 20.25 mg of testosterone (1 pump actuation or a single 20.25 mg packet) and a maximum of 81 mg of testosterone (4 pump actuations or two 40.5 mg packets). To ensure proper dosing, the dose should be titrated based on the pre-dose morning serum testosterone concentration from a single blood draw at approximately 14 days and 28 days after starting treatment or following dose adjustment. In addition, serum testosterone concentration should be assessed periodically thereafter. Table 1 describes the dose adjustments required at each titration step.

Table 1: Dose Adjustment Criteria

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or the equivalent of one 20.25 mg packet)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue on current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or the equivalent of one 20.25 mg packet)

The application site and dose of AndroGel 1.62% are not interchangeable with other topical testosterone products.

2.2 Administration Instructions

AndroGel 1.62% should be applied to clean, dry, intact skin of the upper arms and shoulders. Do not apply AndroGel 1.62% to any other parts of the body, including the abdomen or genitals *[see Clinical Pharmacology (12.3)]*. Area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt. Patients should be instructed to use the palm of the hand to apply AndroGel 1.62% and spread across the maximum surface area as directed in Table 2 (for pump) and Table 3 (for packets) and in Figure 1.

Table 2: Application Sites for AndroGel 1.62%, Pump

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations Per Upper Arm and Shoulder	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0
40.5 mg	2	1	1
60.75 mg	3	2	1
81 mg	4	2	2

Table 3: Application Sites for AndroGel 1.62%, Packets

Total Dose of Testosterone	Total packets	Gel Applications Per Upper Arm and Shoulder

		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	One 20.25 mg packet	One 20.25 mg packet	0
40.5 mg	One 40.5 mg packet	Half of contents of One 40.5 mg packet	Half of contents of One 40.5 mg packet
60.75 mg	One 20.25 mg packet AND One 40.5 mg packet	One 40.5 mg packet	One 20.25 mg packet
81 mg	Two 40.5 mg packets	One 40.5 mg packet	One 40.5 mg packet

The prescribed daily dose of AndroGel 1.62% should be applied to the right and left upper arms and shoulders as shown in the shaded areas in Figure 1.

Figure 1. Application Sites for AndroGel 1.62%

Once the application site is dry, the site should be covered with clothing *[see Clinical Pharmacology (12.3)]*. Wash hands thoroughly with soap and water. Avoid fire, flames or smoking until the gel has dried since alcohol based products, including AndroGel 1.62%, are flammable.

The patient should avoid swimming or showering or washing the administration site for a minimum of 2 hours after application *[see Clinical Pharmacology (12.3)]*.

To obtain a full first dose, it is necessary to prime the canister pump. To do so, with the canister in the upright position, slowly and fully depress the actuator three times. Safely discard the gel from the first three actuations. It is only necessary to prime the pump before the first dose.

After the priming procedure, fully depress the actuator once for every 20.25 mg of AndroGel 1.62%. AndroGel 1.62% should be delivered directly into the palm of the hand and then applied to the application sites.

When using packets, the entire contents should be squeezed into the palm of the hand and immediately applied to the application sites. When 40.5 mg packets need to be split between the left and right shoulder, patients may squeeze a portion of the gel from the packet into the palm of the hand and apply to application sites. Repeat until entire contents have been applied. Alternatively, AndroGel 1.62% can be applied directly to the application sites from the pump or packets.

Strict adherence to the following precautions is advised in order to minimize the potential for secondary exposure to testosterone from AndroGel 1.62%-treated skin:

- Children and women should avoid contact with unwashed or unclothed application site(s) of men using AndroGel 1.62%.
- AndroGel 1.62% should only be applied to the upper arms and shoulders. The area of application should be limited to the area that will be covered by a short sleeve t-shirt.
- Patients should wash their hands with soap and water immediately after applying AndroGel 1.62%.
- Patients should cover the application site(s) with clothing (e.g., a t-shirt) after the gel has dried.
- Prior to situations in which direct 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 1.62% 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.

3 DOSAGE FORMS AND STRENGTHS

AndroGel (testosterone gel) 1.62% for topical use only, is available as follows:

- A metered-dose pump. Each pump actuation delivers 20.25 mg of testosterone in 1.25 g of gel.
- A unit dose packet containing 20.25 mg of testosterone in 1.25 g of gel.
- A unit dose packet containing 40.5 mg of testosterone in 2.5 g of gel.

4 CONTRAINDICATIONS

- AndroGel 1.62% is contraindicated in men with carcinoma of the breast or known or suspected carcinoma of the prostate *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.
- AndroGel 1.62% is contraindicated in women who are or may become pregnant, or who are breastfeeding. AndroGel 1.62% may cause fetal harm when administered to a pregnant woman. AndroGel 1.62% may cause serious adverse reactions in nursing infants. Exposure of a fetus or nursing infant to androgens may result in varying degrees of virilization. Pregnant women or those who may become pregnant need to be aware of the potential for transfer of testosterone from men treated with AndroGel 1.62%. If a pregnant woman is exposed to AndroGel 1.62%, she should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening of Benign Prostatic Hyperplasia (BPH) and Potential Risk of Prostate Cancer

- Patients with BPH treated with androgens are at an increased risk for worsening of signs and symptoms of BPH. Monitor patients with BPH for worsening signs and symptoms.
- Patients treated with androgens may be at increased risk for prostate cancer. Evaluation of patients for prostate cancer prior to initiating and during treatment with androgens is appropriate *[see Contraindications (4)]*.

5.2 Potential for Secondary Exposure to Testosterone

Cases of secondary exposure resulting in virilization of children have been reported in postmarketing surveillance of testosterone 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 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 the topical testosterone product. Children and women should avoid contact with unwashed or unclothed application sites in men using AndroGel 1.62% *[see Dosage and Administration (2.2), Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

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.

5.3 Polycythemia

Increases in hematocrit, reflective of increases in red blood cell mass, may require lowering or discontinuation of testosterone. Check hematocrit prior to initiating treatment. It would also be appropriate to re-evaluate the hematocrit 3 to 6 months after starting treatment, and then annually. If hematocrit becomes elevated, stop therapy until hematocrit decreases to an acceptable concentration. An increase in red blood cell mass may increase the risk of thromboembolic events.

5.4 Use in Women

Due to the lack of controlled evaluations in women and potential virilizing effects, AndroGel 1.62% is not indicated for use in women *[see Contraindications (4) and Use in Specific Populations (8.1, 8.3)]*.

5.5 Potential for Adverse Effects on Spermatogenesis

With large doses of exogenous androgens, including AndroGel 1.62%, spermatogenesis may be suppressed through feedback inhibition of pituitary FSH possibly leading to adverse effects on semen parameters including sperm count.

5.6 Hepatic Adverse Effects

Prolonged use of high doses of orally active 17-alpha-alkyl androgens (e.g., methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice). Peliosis hepatis can be a life-threatening or fatal complication. Long-term therapy with intramuscular testosterone enanthate has produced multiple hepatic adenomas. AndroGel 1.62% is not known to cause these adverse effects.

5.7 Edema

Androgens, including AndroGel 1.62%, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease *[see Adverse Reactions (6.2)]*.

5.8 Gynecomastia

Gynecomastia may develop and persist in patients being treated with androgens, including AndroGel 1.62%, for hypogonadism.

5.9 Sleep Apnea

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.

5.10 Lipids

Changes in serum lipid profile may require dose adjustment or discontinuation of testosterone therapy.

5.11 Hypercalcemia

Androgens, including AndroGel 1.62 %, should be used with caution in cancer patients at risk of hypercalcemia (and associated hypercalciuria). Regular monitoring of serum calcium concentrations is recommended in these patients.

5.12 Decreased Thyroxine-binding Globulin

Androgens, including AndroGel 1.62%, may decrease concentrations of thyroxin-binding globulins, resulting in decreased total T4 serum concentrations and increased resin uptake of T3 and T4. Free thyroid hormone concentrations remain unchanged, however, and there is no clinical evidence of thyroid dysfunction.

5.13 Flammability

Alcohol based products, including AndroGel 1.62%, are flammable; therefore, patients should be advised to avoid fire, flame or smoking until the AndroGel 1.62% has dried.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

AndroGel 1.62% was evaluated in a two-phase, 364-day, controlled clinical study. The first phase was a multi-center, randomized, double-blind, parallel-group, placebo-controlled period of 182 days, in which 234

hypogonadal men were treated with AndroGel 1.62% and 40 received placebo. Patients could continue in an open-label, non-comparative, maintenance period for an additional 182 days *[see Clinical Studies (14.1)]*.

The most common adverse reaction reported in the double-blind period was increased prostate specific antigen (PSA) reported in 26 AndroGel 1.62%-treated patients (11.1%). In 17 patients, increased PSA was considered an adverse event by meeting one of the two pre-specified criteria for abnormal PSA values, defined as (1) average serum PSA >4 ng/mL based on two separate determinations, or (2) an average change from baseline in serum PSA of greater than 0.75 ng/mL on two determinations.

During the 182-day, double-blind period of the clinical trial, the mean change in serum PSA value was 0.14 ng/mL for patients receiving AndroGel 1.62% and -0.12 ng/mL for the patients in the placebo group. During the double-blind period, seven patients had a PSA value >4.0 ng/mL, four of these seven patients had PSA less than or equal to 4.0 ng/mL upon repeat testing. The other three patients did not undergo repeat PSA testing.

During the 182-day, open-label period of the study, the mean change in serum PSA values was 0.10 ng/mL for both patients continuing on active therapy and patients transitioning onto active from placebo. During the open-label period, three patients had a serum PSA value > 4.0 ng/mL, two of whom had a serum PSA less than or equal to 4.0 ng/mL upon repeated testing. The other patient did not undergo repeat PSA testing. Among previous placebo patients, 3 of 28 (10.7%), had increased PSA as an adverse event in the open-label period.

Table 4 shows adverse reactions reported by >2% of patients in the 182-day, double-blind period of the AndroGel 1.62% clinical trial and more frequent in the AndroGel 1.62% treated group versus placebo.

Table 4: Adverse Reactions Reported in >2% of Patients in the 182-Day, Double-Blind Period of AndroGel 1.62% Clinical Trial

	Number (%) of Patients	
Adverse Reaction	**AndroGel 1.62% N=234**	**Placebo N= 40**
PSA increased*	26 (11.1%)	0%
Emotional lability**	6 (2.6%)	0%
Hypertension	5 (2.1%)	0%
Hematocrit or hemoglobin increased	5 (2.1%)	0%
Contact dermatitis***	5 (2.1%)	0%

**PSA increased* includes: PSA values that met pre-specified criteria for abnormal PSA values (an average change from baseline > 0.75 ng/mL and/or an average PSA value >4.0 ng/mL based on two measurements) as well as those reported as adverse events.

***Emotional lability* includes: mood swings, affective disorder, impatience, anger, and aggression.

****Contact dermatitis* includes: 4 patients with dermatitis at non-application sites.

Other adverse reactions occurring in less than or equal to 2% of AndroGel 1.62%-treated patients and more frequently than placebo included: frequent urination, and hyperlipidemia.

In the open-label period of the study (N=191), the most commonly reported adverse reaction (experienced by greater than 2% of patients) was increased PSA (n=13; 6.2%) and sinusitis. Other adverse reactions reported by less than or equal to 2% of patients included increased hemoglobin or hematocrit, hypertension, acne, libido decreased, insomnia, and benign prostatic hypertrophy.

During the 182-day, double-blind period of the clinical trial, 25 AndroGel 1.62%-treated patients (10.7%) discontinued treatment because of adverse reactions. These adverse reactions included 17 patients with PSA increased and 1 report each of: hematocrit increased, blood pressure increased, frequent urination, diarrhea, fatigue, pituitary tumor, dizziness, skin erythema and skin nodule (same patient – neither at application site), vasovagal syncope, and diabetes mellitus. During the 182-day, open-label period, 9 patients discontinued treatment because of adverse reactions. These adverse reactions included 6 reports of PSA increased, 2 of hematocrit increased, and 1 each of triglycerides increased and prostate cancer.

Application Site Reactions

In the 182-day double-blind period of the study, application site reactions were reported in two (2/234; 0.9%) patients receiving AndroGel 1.62%, both of which resolved. Neither of these patients discontinued the study due to application site adverse reactions. In the open-label period of the study, application site reactions were reported in three (3/219; 1.4%) additional patients that were treated with AndroGel 1.62%. None of these subjects were discontinued from the study due to application site reactions.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of AndroGel 1%. 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 (Table 5).

Table 5: Adverse Reactions from Post Approval Experience of AndroGel 1% by System Organ Class

System Organ Class	Adverse Reaction
Blood and lymphatic system disorders:	Elevated hemoglobin or hematocrit, polycythemia, anemia
Endocrine disorders:	Hirsutism
Gastrointestinal disorders:	Nausea
General disorders:	Asthenia, edema, malaise
Genitourinary disorders:	Impaired urination*
Hepatobiliary disorders:	Abnormal liver function tests
Investigations:	Lab test abnormal**, elevated PSA, electrolyte changes (nitrogen, calcium, potassium [includes hypokalemia], phosphorus, sodium), impaired glucose tolerance, hyperlipidemia, HDL, fluctuating testosterone levels, weight increase
Neoplasms:	Prostate cancer
Nervous system disorders:	Dizziness, headache, insomnia, sleep apnea
Psychiatric disorders:	Amnesia, anxiety, depression, hostility, emotional lability,

	decreased libido, nervousness
Reproductive system and breast disorders:	Gynecomastia, mastodynia, oligospermia, priapism (frequent or prolonged erections), prostate enlargement, BPH, testis disorder***
Respiratory disorders:	Dyspnea
Skin and subcutaneous tissue disorders:	Acne, alopecia, application site reaction (discolored hair, dry skin, erythema, paresthesia, pruritus, rash), skin dry, pruritus, sweating
Vascular disorders:	Hypertension, vasodilation (hot flushes)

*** *Impaired urination* includes** nocturia, urinary hesitancy, urinary incontinence, urinary retention, urinary urgency and weak urinary stream

****Lab test abnormal* includes** elevated AST, elevated ALT, elevated testosterone, elevated hemoglobin or hematocrit, elevated cholesterol, elevated cholesterol/LDL ratio, elevated triglycerides, or elevated serum creatinine

*****Testis disorder* includes** atrophy or non-palpable testis, varicocele, testis sensitivity or tenderness

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 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)]*.

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may decrease insulin requirements.

7.2 Oral Anticoagulants

Changes in anticoagulant activity may be seen with androgens, therefore more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking anticoagulants, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with adrenocorticotropic hormone (ACTH) or corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4)]*: AndroGel 1.62% is contraindicated during pregnancy or in women who may become pregnant. Testosterone is teratogenic and may cause fetal harm. Exposure of a fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be made aware of the potential hazard to the fetus.

8.3 Nursing Mothers

Although it is not known how much testosterone transfers into human milk, AndroGel 1.62% is contraindicated in nursing women because of the potential for serious adverse reactions in nursing infants. Testosterone and other androgens may adversely affect lactation *[see Contraindications (4)]*.

8.4 Pediatric Use

The safety and effectiveness of AndroGel 1.62% in pediatric patients less than 18 years old has not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

8.5 Geriatric Use

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing AndroGel 1.62% to determine whether efficacy in those over 65 years of age differs from younger subjects. Of the 234 patients enrolled in the clinical trial utilizing AndroGel 1.62%, 21 were over 65 years of age. Additionally, there is insufficient long-term safety data in geriatric patients to assess the potentially increased risks of cardiovascular disease and prostate cancer.

Geriatric patients treated with androgens may also be at risk for worsening of signs and symptoms of BPH.

8.6 Renal Impairment

No studies were conducted involving patients with renal impairment.

8.7 Hepatic Impairment

No studies were conducted in patients with hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

AndroGel 1.62% contains testosterone, a Schedule III controlled substance in the Controlled Substances Act.

9.2 Abuse

Anabolic steroids, such as testosterone, are abused. Abuse is often associated with adverse physical and psychological effects.

9.3 Dependence

Although drug dependence is not documented in individuals using therapeutic doses of anabolic steroids for approved indications, dependence is observed in some individuals abusing high doses of anabolic steroids. In general, anabolic steroid dependence is characterized by any three of the following:

- Taking more drug than intended
- Continued drug use despite medical and social problems
- Significant time spent in obtaining adequate amounts of drug
- Desire for anabolic steroids when supplies of the drugs are interrupted
- Difficulty in discontinuing use of the drug despite desires and attempts to do so
- Experience of a withdrawal syndrome upon discontinuation of anabolic steroid use

10 OVERDOSAGE

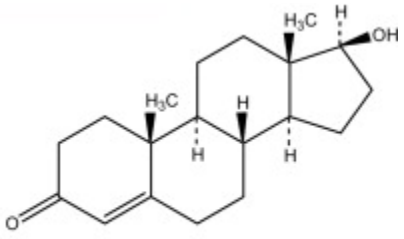
There is a single report of acute overdosage after parenteral administration of an approved testosterone product in the literature. This subject had serum testosterone concentrations of up to 11,400 ng/dL, which were implicated in a cerebrovascular accident. There were no reports of overdosage in the AndroGel 1.62% clinical trial.

Treatment of overdosage would consist of discontinuation of AndroGel 1.62%, washing the application site with soap and water, and appropriate symptomatic and supportive care.

11 DESCRIPTION

AndroGel 1.62% for topical use is a clear, colorless gel containing testosterone. Testosterone is an androgen. AndroGel 1.62% is available in a metered-dose pump or unit dose packets.

The active pharmacologic ingredient in AndroGel 1.62% is testosterone. Testosterone USP is a white to almost white powder chemically described as 17-beta hydroxyandrost-4-en-3-one. The structural formula is:



Testosterone

$C_{19}H_{28}O_2$ MW 288.42

The inactive ingredients in AndroGel 1.62% are: carbopol 980, ethyl alcohol, isopropyl myristate, purified water, and sodium hydroxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement; vocal chord thickening; and alterations in body musculature and fat distribution. Testosterone and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism can present as primary hypogonadism caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia while secondary hypogonadism is the failure of the hypothalamus or pituitary to produce sufficient gonadotropins (FSH, LH).

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using AndroGel 1.62%.

12.3 Pharmacokinetics

Absorption

AndroGel 1.62% delivers physiologic amounts of testosterone, producing circulating testosterone concentrations that approximate normal levels (300 – 1000 ng/dL) seen in healthy men. AndroGel 1.62% provides continuous transdermal delivery of testosterone for 24 hours following once daily application to clean, dry, intact skin of the shoulders and upper arms. Average serum testosterone concentrations over 24 hours (C_{avg}) observed when AndroGel 1.62% was applied to the upper arms/shoulders were comparable to average serum testosterone concentrations (C_{avg}) when AndroGel 1.62% was applied using a rotation method utilizing the abdomen and upper arms/shoulders. The rotation of abdomen and upper arms/shoulders was a method used in the pivotal clinical trial *[see Clinical Studies (14.1)]*.

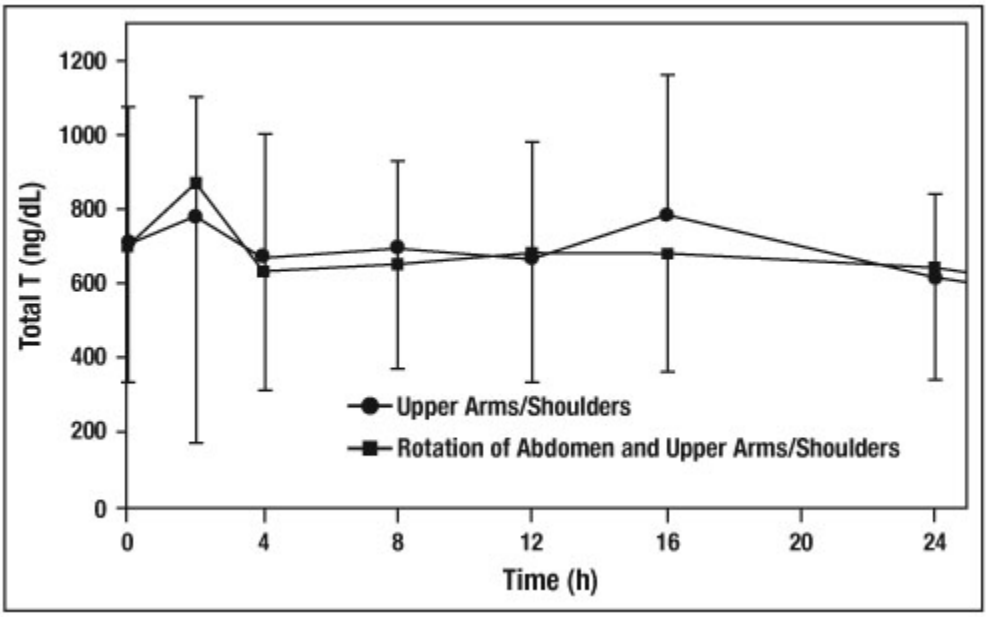


Figure 2: Mean (±SD) Serum Total Testosterone Concentrations on Day 7 in Patients Following AndroGel 1.62% Once-Daily Application of 81 mg of Testosterone (N=33) for 7 Days

Distribution

Circulating testosterone is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is loosely bound to albumin and other proteins.

Metabolism

Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are estradiol and DHT.

Excretion

There is considerable variation in the half-life of testosterone concentration as reported in the literature, ranging from 10 to 100 minutes. About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic acid and sulfuric acid conjugates of testosterone and its metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

When AndroGel 1.62% treatment is discontinued, serum testosterone concentrations return to approximately baseline concentrations within 48-72 hours after administration of the last dose.

Potential for testosterone transfer

The potential for testosterone transfer following administration of AndroGel 1.62% when it was applied only to upper arms/shoulders was evaluated in two clinical studies of males dosed with AndroGel 1.62% and their

untreated female partners. In one study, 8 male subjects applied a single dose of AndroGel 1.62% 81 mg to their shoulders and upper arms. Two (2) hours after application, female subjects rubbed their hands, wrists, arms, and shoulders to the application site of the male subjects for 15 minutes. Serum concentrations of testosterone were monitored in female subjects for 24 hours after contact occurred. After direct skin-to-skin contact with the site of application, mean testosterone C_{avg} and C_{max} in female subjects increased by 280% and 267%, respectively, compared to mean baseline testosterone concentrations. In a second study evaluating transfer of testosterone, 12 male subjects applied a single dose of AndroGel 1.62% 81 mg to their shoulders and upper arms. Two (2) hours after application, female subjects rubbed their hands, wrists, arms, and shoulders to the application site of the male subjects for 15 minutes while the site of application was covered by a t-shirt. When a t-shirt was used to cover the site of application, mean testosterone C_{avg} and C_{max} in female subjects increased by 6% and 11%, respectively, compared to mean baseline testosterone concentrations.

A separate study was conducted to evaluate the potential for testosterone transfer from 16 males dosed with AndroGel 1.62% 81 mg when it was applied to abdomen only for 7 days, a site of application not approved for AndroGel 1.62%. Two (2) hours after application to the males on each day, the female subjects rubbed their abdomens for 15 minutes to the abdomen of the males. The males had covered the application area with a T-shirt. The mean testosterone C_{avg} and C_{max} in female subjects on day 1 increased by 43% and 47%, respectively, compared to mean baseline testosterone concentrations. The mean testosterone C_{avg} and C_{max} in female subjects on day 7 increased by 60% and 58%, respectively, compared to mean baseline testosterone concentrations.

Effect of showering

In a randomized, 3-way (3 treatment periods without washout period) crossover study in 24 hypogonadal men, the effect of showering on testosterone exposure was assessed after once daily application of AndroGel 1.62% 81 mg to upper arms/shoulders for 7 days in each treatment period. On the 7th day of each treatment period, hypogonadal men took a shower with soap and water at either 2, 6, or 10 hours after drug application. The effect of showering at 2 or 6 hours post-dose on Day 7 resulted in 13% and 12% decreases in mean C_{avg}, respectively, compared to Day 6 when no shower was taken after drug application. Showering at 10 hours after drug application had no effect on bioavailability. The amount of testosterone remaining in the outer layers of the skin at the application site on the 7th day was assessed using a tape stripping procedure and was reduced by at least 80% after showering 2-10 hours post-dose compared to on the 6th day when no shower was taken after drug application.

Effect of sunscreen or moisturizing lotion on absorption of testosterone

In a randomized, 3-way (3 treatment periods without washout period) crossover study in 18 hypogonadal males, the effect of applying a moisturizing lotion or a sunscreen on the absorption of testosterone was evaluated with the upper arms/shoulders as application sites. For 7 days, moisturizing lotion or sunscreen (SPF 50) was applied daily to the AndroGel 1.62% application site 1 hour after the application of AndroGel 1.62% 40.5 mg. Application of moisturizing lotion increased mean testosterone C_{avg} and C_{max} by 14% and 17%, respectively, compared to AndroGel 1.62% administered alone. Application of sunscreen increased mean testosterone C_{avg} and C_{max} by 8% and 13%, respectively, compared to AndroGel 1.62% applied alone.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rats. Testosterone was negative in the *in vitro* Ames and in the *in vivo* mouse micronucleus assays. The administration of exogenous testosterone has been reported to suppress spermatogenesis in the rat, dog and non-human primates, which was reversible on cessation of the treatment.

14 CLINICAL STUDIES

14.1 Clinical Trials in Hypogonadal Males

AndroGel 1.62% was evaluated in a multi-center, randomized, double-blind, parallel-group, placebo-controlled study (182-day double-blind period) in 274 hypogonadal men with body mass index (BMI) 18-40 kg/m^2 and 18-80 years of age (mean age 53.8 years). The patients had an average serum testosterone concentration of <300 ng/dL, as determined by two morning samples collected on the same visit. Patients were Caucasian 83%, Black 13%, Asian or Native American 4%. 7.5% of patients were Hispanic.

Patients were randomized to receive active treatment or placebo using a rotation method utilizing the abdomen and upper arms/shoulders for 182 days. All patients were started at a daily dose of 40.5 mg (two pump actuations) AndroGel 1.62% or matching placebo on Day 1 of the study. Patients returned to the clinic on Day 14, Day 28, and Day 42 for predose serum total testosterone assessments. The patient's daily dose was titrated up or down in 20.25 mg increments if the predose serum testosterone value was outside the range of 350-750 ng/dL. The study included four active AndroGel 1.62% doses: 20.25 mg, 40.5 mg, 60.75 mg, and 81 mg daily.

The primary endpoint was the percentage of patients with C_{avg} within the normal range of 300-1000 ng/dL on Day 112. In patients treated with AndroGel 1.62%, 81.6% (146/179) had C_{avg} within the normal range at Day 112. The secondary endpoint was the percentage of patients, with C_{max} above three pre-determined limits. The percentages of patients with C_{max} greater than 1500 ng/dL, and between 1800 and 2499 ng/dL on Day 112 were 11.2% and 5.5%, respectively. Two patients had a C_{max} >2500 ng/dL on Day 112 (2510 ng/dL and 2550 ng/dL, respectively); neither of these 2 patients demonstrated an abnormal C_{max} on prior or subsequent assessments at the same dose.

Patients could agree to continue in an open-label, active treatment maintenance period of the study for an additional 182 days.

Dose titrations on Days 14, 28, and 42 resulted in final doses of 20.25 mg – 81 mg on Day 112 as shown in Table 6.

Table 6: Mean (SD) Testosterone Concentrations (C_{avg} and C_{max}) by final dose on Days 112 and 364

Parameter	Final Dose on Day 112					
	Placebo (n=27)	**20.25 mg (n=12)**	**40.5 mg (n=34)**	**60.75 mg (n=54)**	**81 mg (n=79)**	**All Active (n=179)**
C_{avg} (ng/dL)	303 (135)	457 (275)	524 (228)	643 (285)	537 (240)	561 (259)
C_{max} (ng/dL)	450 (349)	663 (473)	798 (439)	958 (497)	813 (479)	845 (480)
	Final Dose on Day 364					
		20.25 mg (n=7)	**40.5 mg (n=26)**	**60.75 mg (n=29)**	**81 mg (n=74)**	**Continuing Active (n=136)**
C_{avg} (ng/dL)		386 (130)	474 (176)	513 (222)	432 (186)	455 (192)
C_{max} (ng/dL)		562 (187)	715 (306)	839 (568)	649 (329)	697 (389)

Figure 3 summarizes the pharmacokinetic profile of total testosterone in patients completing 112 days of AndroGel 1.62% treatment administered as a starting dose of 40.5 mg of testosterone (2 pump actuations) for the initial 14 days followed by possible titration according to the follow-up testosterone measurements.

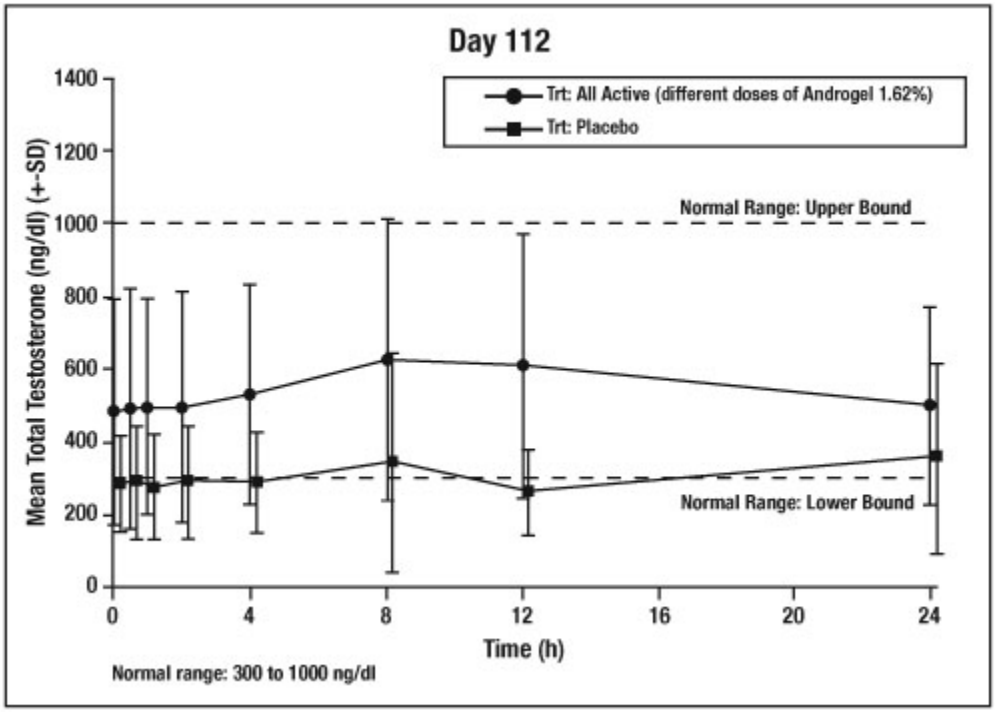


Figure 3: Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 112

Efficacy was maintained in the group of men that received AndroGel 1.62% for one full year. In that group, 78% (106/136) had average serum testosterone concentrations in the normal range at Day 364. Figure 4 summarizes the mean total testosterone profile for these patients on Day 364.

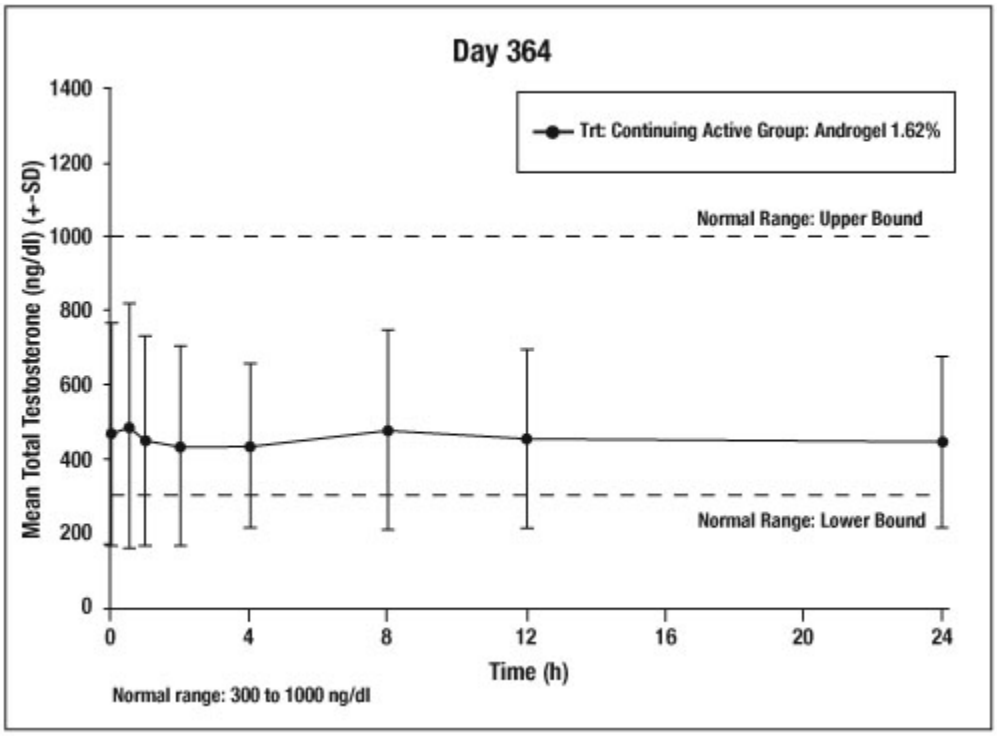


Figure 4: Mean (±SD) Steady-State Serum Total Testosterone Concentrations on Day 364

The mean estradiol and DHT concentration profiles paralleled the changes observed in testosterone. The levels of LH and FSH decreased with testosterone treatment. The decreases in levels of LH and FSH are consistent with reports published in the literature of long-term treatment with testosterone.

16 HOW SUPPLIED/STORAGE AND HANDLING

AndroGel 1.62% is supplied in non-aerosol, metered-dose pumps that deliver 20.25 mg of testosterone per complete pump actuation. The pumps are composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. Each 88 g metered-dose pump is capable of dispensing 75 g of gel or 60-metered pump actuations; each pump actuation dispenses 1.25 g of gel.

AndroGel 1.62% is also supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 1.25 g or 2.5 g gel contains 20.25 mg or 40.5 mg testosterone, respectively.

NDC Number	**Package Size**
0051-8462-33	88 g pump (each pump dispenses 60 metered pump actuations with each pump actuation containing 20.25 mg of testosterone in 1.25 g of gel)
0051-8462-12	Each unit dose packet contains 20.25 mg of testosterone provided in 1.25 g of gel
0051-8462-31	30 packets (each unit dose packet contains 20.25 mg of testosterone provided in 1.25 g of gel)
0051-8462-01	Each unit dose packet contains 40.5 mg of testosterone provided in 2.5 g of gel
0051-8462-30	30 packets (each unit dose packet contains 40.5 mg of testosterone provided

	in 2.5 g of gel)

Store at controlled room temperature 20°-25°C (68°-77°F); excursions permitted to 15°- 30°C (59°- 86°F) [see USP Controlled Room Temperature].

Used AndroGel 1.62% pumps or used AndroGel 1.62% packets should be discarded in household trash in a manner that prevents accidental application or ingestion by children or pets.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide

Patients should be informed of the following:

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 1.62% *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

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.

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.
- AndroGel 1.62% 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 AndroGel 1.62% in men *[see Medication Guide]*:

- **Children and women should avoid contact with unwashed or unclothed application site(s)** of men using AndroGel 1.62%.
- Patients using AndroGel 1.62% should apply the product as directed and strictly adhere to the following:
    - **Wash hands** with soap and water immediately 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 AndroGel 1.62% 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 *[see Dosage and Administration (2.2), Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

17.3 Potential Adverse Reactions with Androgens

Patients should be informed that treatment with androgens may lead to adverse reactions which include:

- Changes in urinary habits such as increased urination at night, trouble starting the urine stream, passing urine many times during the day, having an urge to go to the bathroom right away, having a urine accident, being unable to pass urine and weak urine flow.
- Breathing disturbances, including those associated with sleep, or excessive daytime sleepiness.
- Too frequent or persistent erections of the penis.
- Nausea, vomiting, changes in skin color, or ankle swelling.

17.4 Patients Should Be Advised of the Following Instructions for Use

- **Read the Medication Guide before starting AndroGel 1.62% therapy and to reread it each time the prescription is renewed.**
- **AndroGel 1.62% should be applied and used appropriately to maximize the benefits and to minimize the risk of secondary exposure in children and women.**
- Keep AndroGel 1.62% out of the reach of children.
- **AndroGel 1.62% is an alcohol based product and is flammable; therefore avoid fire, flame or smoking until the gel has dried.**
- It is important to adhere to all recommended monitoring.
- Report any changes in their state of health, such as changes in urinary habits, breathing, sleep, and mood.
- AndroGel 1.62% is prescribed to meet the patient's specific needs; therefore, the patient should never share AndroGel 1.62% with anyone.
- Wait 2 hours before swimming or washing following application of AndroGel 1.62%. This will ensure that the greatest amount of AndroGel 1.62% is absorbed into their system.

Marketed by:
Abbott Laboratories
North Chicago, IL, 60064, U.S.A.

Revised: September 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022309/S-001

CHEMISTRY REVIEW(S)

CHEMIST REVIEW #4
OF SUPPLEMENT
SLR changed from PA

1. **ORGANIZATION**: ONDQA-Division II
2. **NDA/SUPP NUMBER: 22-309 S001**

3. **SUPPLEMENT DATES:**
Letter/Stamp Date: 15-Aug-2011/16-Aug-2011
Resubmission Ltr/Rec Dates: 7-Mar-2012/8-Mar-2012
Action Date: 8-Sept-2012
4. **AMENDMENT:** 6-Sept-2012
RECEIVED BY CHEMIST: Sept 2011

6. **APPLICANT NAME AND ADDRESS**
Abbott Products
Marietta, GA

7. **LABELING SUPPLEMENT PROVIDES FOR**: additional packaging configurations, 1.25 g and 2.5g stickpack (unit-dose) presentations, and an increase in the amount of isopropyl myristate used in the manufacture of AndroGel in stickpacks

8.	**DRUG PRODUCT:**	AndroGel
9.	**NONPROPRIETARY NAME:**	Testosterone Gel
10.	**DRUG SUBSTANCE:**	Testosterone
11.	**DOSAGE FORM/STRENGTH**:	Topical Gel; 1.62%
12.	**ROUTE OF ADMINSTRATION:**	Transdermal
13.	**INDICATION:**	Hormone replacement
14.	**HOW DISPENSED:**	Rx
15.	**RELATED IND/NDA/DMF:**	21-015, AndroGel 1.00 %

16. **COMMENTS:**
The approved container/closure for NDA 22-309 is a multi-dose pump. (b) (4) **This supplement proposes a 1.25 g and a 2.5 g unit dose container, called a stickpack.** See chemistry reviews 1 and 2, which found the supplement to be acceptable, and chemistry review #3 which found the cartons and containers to be acceptable.

Chemistry review #4 provides an acceptable recommendation for the Package Insert.

17. **CONCLUSIONS AND RECOMMENDATIONS**
The information/data provided is acceptable. This supplement, therefore, is recommended for Approval.

Action: OND will issue the action Letter.

18. REVIEWER NAME	**DATE COMPLETED**
J. Salemme, Ph.D., chemistry reviewer	7-Sept-2012

K.A. Jennings, PM, and Dr. T. Oliver, Branch Chief, ONDQA

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/s/

JEAN SALEMME
09/06/2012

THOMAS F OLIVER
09/07/2012

CHEMIST REVIEW #3
OF SUPPLEMENT
SLR changed from PA

1. ORGANIZATION: ONDQA-Division II
2. NDA/SUPP NUMBER: 22-309 S001

3. SUPPLEMENT DATES:
Letter/Stamp Date: 15-Aug-2011/16-Aug-2011
Resubmission Ltr/Rec Dates: 7-Mar-2012/8-Mar-2012
Action Date: 8-Sept-2012
4. AMENDMENT: None
RECEIVED BY CHEMIST: Sept 2011

6. APPLICANT NAME AND ADDRESS
Abbott Products
Marietta, GA

7. LABELING SUPPLEMENT PROVIDES FOR: additional packaging configurations, 1.25 g and 2.5g stickpack (unit-dose) presentations, and an increase in the amount of isopropyl myristate used in the manufacture of AndroGel in stickpacks

8.	**DRUG PRODUCT:**	AndroGel
9.	**NONPROPRIETARY NAME:**	Testosterone Gel
10.	**DRUG SUBSTANCE:**	Testosterone
11.	**DOSAGE FORM/STRENGTH**:	Topical Gel; 1.62%
12.	**ROUTE OF ADMINSTRATION:**	Transdermal
13.	**INDICATION:**	Hormone replacement
14.	**HOW DISPENSED:**	Rx
15.	**RELATED IND/NDA/DMF:**	21-015, AndroGel 1.00 %

16. COMMENTS:
The approved container/closure for NDA 22-309 is a multi-dose pump, (b) (4) **This supplement proposes a 1.25 g and a 2.5 g unit dose container, called a stickpack,** (b) (4)

Responses received in the Complete Response resubmission are acceptable. The data/information support that an (b) (4) isopropyl myristate is required during manufacturing due to absorption of isopropyl myristate to the product-contact polymer of the stickpack. Additionally, clarifications regarding the amount of ethyl alcohol used in the AndroGel formulation in the stickpacks are acceptable and show no change is made in the ethyl alcohol content. The stated amount of ethyl alcohol was incorrectly stated in the original submission.

Chemistry review #3 provides the final carton/container label.

17. CONCLUSIONS AND RECOMMENDATIONS

The information/data provided is acceptable. This supplement, therefore, is recommended for Approval.

Action: OND will issue the action Letter.

18. REVIEWER NAME	**DATE COMPLETED**
J. Salemme, Ph.D., chemistry reviewer	27-Jul-2012

PM: B. McKnight

Dr. T. Oliver, Branch Chief, ONDQA

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/s/

JEAN SALEMME
08/10/2012

THOMAS F OLIVER
08/10/2012

CHEMIST REVIEW #2
OF **SUPPLEMENT**
SLR changed from PA

1. **ORGANIZATION**: ONDQA-Division II
2. **NDA/SUPP NUMBER: 22-309 S001**

3. **SUPPLEMENT DATES:**
Letter/Stamp Date: 15-Aug-2011/16-Aug-2011
Resubmission Ltr/Rec Dates: 7-Mar-2012/8-Mar-2012
Action Date: 8-Sept-2012
4. **AMENDMENT:** None
RECEIVED BY CHEMIST: Sept 2011

6. **APPLICANT NAME AND ADDRESS**
Abbott Products
Marietta, GA

7. **SUPPLEMENT PROVIDES FOR**: additional packaging configurations, 1.25 g and 2.5g stickpack (unit-dose) presentations, and an increase in the amount of isopropyl myristate used in the manufacture of AndroGel in stickpacks

8.	**DRUG PRODUCT:**	AndroGel
9.	**NONPROPRIETARY NAME:**	Testosterone Gel
10.	**DRUG SUBSTANCE:**	Testosterone
11.	**DOSAGE FORM/STRENGTH**:	Topical Gel; 1.62%
12.	**ROUTE OF ADMINSTRATION:**	Transdermal
13.	**INDICATION:**	Hormone replacement
14.	**HOW DISPENSED:**	Rx
15.	**RELATED IND/NDA/DMF:**	21-015, AndroGel 1.00 %

16. **COMMENTS:**
The approved container/closure for NDA 22-309 is a multi-dose pump, (b) (4) **This supplement proposes a 1.25 g and a 2.5 g unit dose container, called a stickpack,** (b) (4)

Responses received in the Complete Response resubmission are acceptable. The data/information support that an (b) (4) isopropyl myristate is required during manufacturing due to absorption of isopropyl myristate to the product-contact polymer of the stickpack. Additionally, clarifications regarding the amount of ethyl alcohol used in the AndroGel formulation in the stickpacks are acceptable and show no change is made in the ethyl alcohol content. The stated amount of ethyl alcohol was incorrectly stated in the original submission.

17. CONCLUSIONS AND RECOMMENDATIONS

The information/data provided is acceptable. This supplement, therefore, is recommended for Approval.

Action: OND will issue the action Letter.

18. REVIEWER NAME	**DATE COMPLETED**
J. Salemme, Ph.D., chemistry reviewer	22-Mar-2012

PM: B. McKnight

Dr. T. Oliver, Branch Chief, ONDQA

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/s/

JEAN SALEMME
05/25/2012

THOMAS F OLIVER
05/25/2012

CHEMIST REVIEW
OF **SUPPLEMENT**
SLR changed from PA

1. ORGANIZATION: ONDQA-Division II
2. NDA/SUPP NUMBER: 22-309 S001

3. SUPPLEMENT DATES:
Letter/Stamp Date: 15-Aug-2011/16-Aug-2011
Action Date: 16-Feb-2012
4. AMENDMENT: None
RECEIVED BY CHEMIST: Sept 2011

6. APPLICANT NAME AND ADDRESS
Abbott Products
Marietta, GA

7. SUPPLEMENT PROVIDES FOR: additional packaging configurations, 1.25 g and 2.5g stickpack (unit-dose) presentations, and an increase in the amount of isopropyl myristate used in the manufacture of AndroGel

8.	**DRUG PRODUCT:**	AndroGel
9.	**NONPROPRIETARY NAME:**	Testosterone Gel
10.	**DRUG SUBSTANCE:**	Testosterone
11.	**DOSAGE FORM/STRENGTH**:	Topical Gel; 1.62%
12.	**ROUTE OF ADMINSTRATION:**	Transdermal
13.	**INDICATION:**	Hormone replacement
14.	**HOW DISPENSED:**	Rx
15.	**RELATED IND/NDA/DMF:**	21-015, AndroGel 1.00 %

16. COMMENTS:
The approved container/closure for NDA 22-309 is a multi-dose pump, [redacted (b) (4)] **This supplement proposes a 1.25 g and a 2.5 g unit dose container, called a stickpack,** [redacted (b) (4)] The 1.25 g stickpack provides 20.25 mg testosterone per 1.25 g of gel and the 2.5 g stickpack provides 40.50 mg testosterone per 2.5 g of gel.

Three batches manufactured to support this supplement have been manufactured with amounts of the [redacted (b) (4)], ethyl alcohol and isopropyl myristate, that differ from the approved amounts. These additional amounts have not been justified. The batches manufactured, therefore, are not acceptable.

17. CONCLUSIONS AND RECOMMENDATIONS
The information/data provided are not acceptable. This supplement, therefore, is recommended for a Complete Response.

Action: OND will issue the action Letter. Issue a Complete Response Action letter with requests provided on the following page.

18. REVIEWER NAME	**DATE COMPLETED**
J. Salemme, Ph.D., chemistry reviewer	9-Feb-2012

PM: B. McKnight

Dr. T. Oliver, Branch Chief, ONDQA

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/s/

JEAN SALEMME
02/14/2012

THOMAS F OLIVER
02/15/2012

Initial Quality Assessment and Triage

ONDQA Branch VI

OND Division: HFD-580 (DRUP)
NDA: 22-309
Supplement: S-001
DARRTS Document Number: SDN125
Applicant: Abbott Laboratories
Letter Date: 15-AUGUST-2011
Stamp Date: 16-AUGUST-2011
ONDQA Receipt Date: delivered to CMC lead on 19-SEPTEMBER-2011 (5 weeks late)
ONDQA CMC Lead triage date: 19-SEPTEMBER-2011
Application Type: electronic
Proprietary Name: AndroGel®
Established Name: testosterone gel 1.62%
Dosage Form: gel
Route of Administration: topical
Submission Type: prior-approval supplement (PAS)
Recommended submission type: PAS

This electronic PAS was submitted by the applicant on 16-AUGUST-2011, but was not delivered to the post-approval CMC lead until 19-SEPTEMBER-2011.

The drug product for NDA 22-309 is testosterone gel, formulated at 1.62% strength. NDA 22-309 was approved on April 29th, 2011. Abbott owns another NDA for Androgel®, NDA 21-015, for a lower strength (1%); NDA 21-015 was approved on 28-FEBRUARY-2000.

The 1% formulation of AndroGel® is approved for packaging in two different presentations, a metered-dose pump, and a foil sachet, intended for unit-dose application (designated as a "stick-pack"). The "stick-pack was approved in July of 2006 (for NDA 21-015/S-014).

The higher-strength (1.62%) product, approved under NDA 22-309 is currently approved for manufacture and distribution in the metered-dose pump. Supplement S-001 proposes manufacture and distribution of the 1.62% product in unit-dose "stick-packs". (b) (4)

The PAS submission is appropriate for this type of change.

The applicant supports the packaging of the 1.62% product in unit-dose "stick-packs" with 12 months of stability data (25/60, results from 0, 3, 6, 9, and 12 months) for three batches (split into 1.25 and 2.5-gram sachets). In addition, the applicant provides 6 months accelerated stability for the same exhibit batches.

It is noted that the "stick-pack" (b) (4) See sections 3.2.P.4 and 3.2.P.5 for specifications (excipient and product).

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/s/

DAVID B LEWIS
10/05/2011
IQA; PAS is appropriate, as submitted

THOMAS F OLIVER
10/05/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022309/S-001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA 022309	Submission Dates: 03/08/2012 and 9/6/2012
Brand Name	Androgel
Generic Name	Testosterone (T) gel
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products (DRUP)
Sponsor	Abbott Products, Inc.
Relevant IND, NDA	IND 050377, NDA 021015
Submission Type	Labeling supplement
Formulation and Strength	Androgel 1.62% in a multi-dose pump (20.25 mg of T per actuation) and in packets (20.25 mg or 40.5 mg of T per packet), 20.25 mg – 81 mg T
Indication	T replacement therapy in male hypogonadism o Primary hypogonadism (congenital or acquired) o Hypogonadotrophic hypogonadism (congenital or acquired)

Table of Contents

1 Executive Summary

Androgel 1.62% (a multi-dose pump, 20.25 mg of testosterone (T) per actuation) was approved for the indication of testosterone (T) replacement therapy in male hypogonadism on 4/29/2011. After the approval, the sponsor developed a new dosage form of Androgel 1.62%, packets containing either 20.25 mg or 40.5 mg of T. In the current submission, the sponsor submitted a supplemental labeling revision (SLR) to include the information for this new dosage form. The final agreement was reached on 9/6/2012 and there are no pending issues from the Office of Clinical Pharmacology. The highlights of the prescribing information and Clinical Pharmacology relevant sections of the final agreed upon package insert labeling are included in Section 2 of this review.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the SLR61 of NDA 022309 submitted on 09/06/2012 acceptable.

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/s/

HYUNJIN KIM
09/06/2012

MYONG JIN KIM
09/06/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022309/S-001

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Date:	August 2, 2012
To:	Julie Beitz, MD, (Acting) Director Division of Reproductive and Urologic Products (DRUP)
Through:	Claudia B. Manzo, PharmD, Director Division of Risk Management (DRISK)
From:	Mary Dempsey, BS, Risk Management Programs Coordinator, DRISK Cynthia LaCivita, PharmD, Risk Management Analyst TL, DRISK
Subject:	Prior Approval Supplement (PAS); REMS Modification; REMS Assessment
Drug Name:	Angrogel (testosterone) 1.62% gel
Application Type/ Number:	NDA 022309
Applicant/Sponsor:	Abbott Laboratories
OSE RCM #:	2012-1746

1 Background

The Division of Reproductive and Urologic Products (DRUP) requested the Division of Risk Management (DRISK) review the Androgel 1.62% proposed Risk Evaluation Mitigation Strategy (REMS) Modification for the New Drug Application (NDA) 022309 submitted by Abbott Laboratories August 16, 2011 and amended November 18, 2011 November 29, 2011, and March 7, 2012. The sponsor was required to submit a proposed REMS modification that resulted from revisions to the Prescribing Information (PI) and Medication Guide (MG) to include a new container closure system. The container closure system review by the Division of Medication Error Prevention and Analysis (DMEPA) was provided under separate cover June 7, 2012. The Medication Guide review by Division of Medical Policy Programs (DMPP) was provided under separate cover July 30, 2012. The subject of this review is the REMS document.

The Androgel 1.62% REMS was initially approved was April 29, 2011 with the following elements:

- Medication Guide
- Timetable for Submission of Assessments

2 Material Reviewed

- April 29, 2011 initial REMS approval
- August 16, 2011 REMS modification
- August 22, 2011 General Correspondence regarding Corporate Entity Change
- November 18, 2011 amendment to REMS modification
- November 29, 2011 amendment to REMS modification
- February 21, 2012 FDA issued Complete Response Letter
- March 7, 2012 Abbott Laboratories Complete Response Letter

3 Proposed REMS Modifications

The November 29, 2011 cover letter states the following:

> "Reference is made to NDA 22309, and to our Prior Approval Supplement with REMS modification (#001) submitted to the Agency on August 16, 2011….
> Of note, the attached REMS contain changes to the Sponsor and Contact Information for the Sponsor. With this correspondence we advise that the Medication Guide would be adequate with the proposed REMS modification to achieve its purpose."

The March 7, 2012 cover letter states the following:

> "Responses to the deficiencies in the FDA letter did not require any changes to the previously submitted REMS (Medication Guide) and labeling. "

4 Discussion and Conclusion

DRISK compared the proposed REMS Modification to the approved REMS and found then to be identical with the exception of the change in Corporate Entity name and contact information.

DRISK also revised the Timetable for Submission of Assessments to include the date of the initial REMS approval. (See appended REMS)

5. Recommendation to DRUP

The REMS appended to this review is acceptable.

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/s/

MARY J DEMPSEY
08/02/2012

CLAUDIA B MANZO
08/02/2012
concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022309/S-001

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	**July 30, 2012**
To:	Hylton Joffee, MD, Director **Division of Reproductive and Urologic Products (DRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Supervisor, Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Review of Patient Labeling (Medication Guide)
Drug Name (established name):	AndroGel 1.62% (testosterone gel)
Dosage Form and Route:	Gel for Topical Use
Application Type/Number:	NDA 22-309
Supplement Number:	S-001
Tracked Safety Issue (TSI) Number:	585
Applicant:	**Abbott Pharmaceuticals**

1 INTRODUCTION

On August 16, 2011, Abbott Pharmaceuticals submitted a Prior Approval Supplement (PAS) to the New Drug Application (NDA 22-309) for AndroGel 1.62% (testosterone gel), indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The purpose of the PAS was to provide for the additional packaging configurations of 20.25 mg and 40.5 mg packets.

On February 21, 2012 the Agency issued a Complete Response (CR) Letter sighting Chemistry, Manufacturing, and Control deficiencies. On March 07, 2012, the Applicant submitted a response to the CR letter. This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for AndroGel 1.62% (testosterone gel).

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DRUP under separate cover.

2 MATERIAL REVIEWED

- Draft ANDROGEL 1.62% (testosterone gel) Medication Guide (MG) received on November 29, 2011 and received by DMPP on July 26, 2012.
- Draft ANDROGEL 1.62% (testosterone gel) Prescribing Information (PI) received August 16, 2011, revised by the Review Division throughout the current review cycle, and received by DMPP on July 26, 2012.
- Approved ANDROGEL 1% (testosterone gel) comparator labeling dated November 30, 2011.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
07/30/2012

MELISSA I HULETT
07/30/2012

LASHAWN M GRIFFITHS
07/30/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Label and Labeling Review

Date:	June 6, 2012
Reviewer(s):	Terri Wood-Cummings, MD, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Zachary Oleszczuk, PharmD, Team Leader Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh, Division Director Division of Medication Error Prevention and Analysis
Drug Name(s):	AndroGel (Testosterone) Gel 1.62%, 20.25 mg per actuation Metered-Dose Pump, 20.25 mg Unit-Dose Packet, and 40.5 mg Unit-Dose Packet
Application Type/Number:	NDA 022309/S-001
Applicant/sponsor:	Abbott Laboratories
OSE RCM #:	#2011-4304 and #2012-776

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the container labels, carton labeling, prescribing information labeling, and medication guide labeling for AndroGel (Testosterone) 1.62 % which provide for the introduction of a proposed new container closure system (unit-dose foil packets) containing either 20.25 mg or 40.5 mg of testosterone for AndroGel (Testosterone) 1.62%, NDA 022309.

[redacted] (b) (4)

1.1 REGULATORY HISTORY

AndroGel (Testosterone) 1.62% was approved on April 29, 2011. DMEPA completed a previous review of the labels, labeling, and communication plan for AndroGel 1.62% on March 12, 2010 (RCM #2009-334). DMEPA completed a second review on March 2, 2011 (RCM #2010-2433) of the labels, labeling, and communication plan for AndroGel 1.62% submitted by the Applicant on October 28, 2010 to address Clinical and Clinical Pharmacology deficiencies noted in a Complete Response letter dated March 12, 2010. On August 16, 2011, the Applicant submitted an amendment with carton labels, container labeling, insert labeling, and medication guide to introduce the proposed new container closure systems. However, when the proposed sizes of the cartons and containers were modified due to technical constraints, the Applicant submitted a subsequent amendment on November 18, 2011 modifying the text size and placement for the labels and labeling of the modified cartons and containers.

1.2 PRODUCT INFORMATION

AndroGel is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. AndroGel is currently marketed in two strengths, 1% Gel and 1.62% Gel. Both strengths are available in a metered dose pump presentation in cartons of two, and AndroGel 1% is also available in 2.5 g (25 mg of testosterone) or 5 g (50 mg of testosterone) unit-dose foil packets in cartons of 30.

The recommended starting dose of AndroGel 1.62% is 40.5 mg of testosterone applied to the clean, dry, intact skin of the upper arms and shoulders once daily in the morning. The dose should be adjusted to achieve and maintain serum testosterone levels in the normal range. AndroGel 1.62% is currently supplied in an 88 g metered dose pump which delivers 60 metered pump actuations. Each pump actuation delivers 20.25 mg of testosterone in 1.25 g of gel. It should be stored between 20 ºC to 25ºC (68 to 77ºF) with excursions permitted to 15ºC to 30ºC (59ºF to 86ºF), and freezing should be avoided.

2 METHODS AND MATERIALS

Using Failure Mode and Effects Analysis[1], the principals of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated for areas of vulnerability that can lead to medication errors.

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES

DMEPA conducted two previous AERS searches on May 27, 2009 (RCM #2009-334 dated March 12, 2010) and on January 14, 2011 (RCM #2010-2433 dated March 2, 2011) for medication errors involving AndroGel products which covered a time period through January 14, 2011. Therefore, we conducted an updated search on January 11, 2012 and limited the dates from January 15, 2011 to January 11, 2012. The search terms used included: active ingredient "testosterone," trade name "AndroGel," and verbatim term "Andro%." The MedRA reaction terms used were High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues." The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error associated with the labels and labeling for AndroGel 1.62% and other similar topical testosterone products were deemed not applicable to this review were excluded from further analysis.

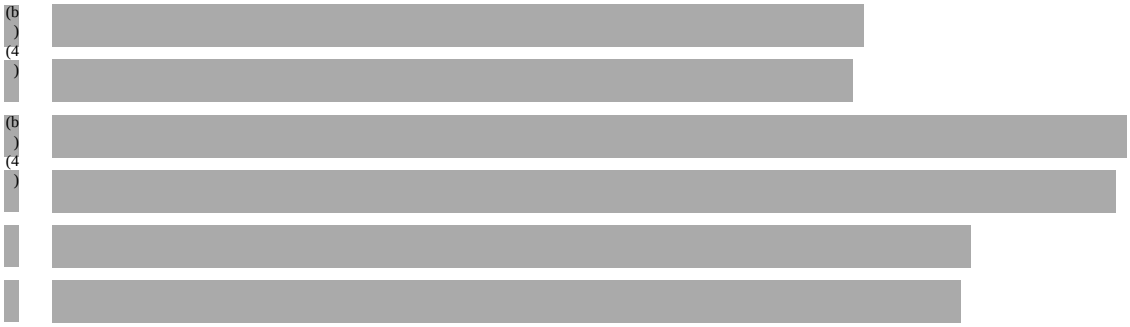
2.2 LABELS AND LABELING

The Division of Medication Error Prevention and Analysis (DMEPA) utilized Failure Mode and Effects Analysis[2] (FMEA) and the principals of human factors and medication error post marketing experience to evaluate the container labels, carton labeling, the prescribing information labeling, and medication guide labeling to identify areas of vulnerability that can lead to medication errors.

For this review, DMEPA evaluated the following labels and labeling (See Appendices B, C, and D for images):

- 20.25 mg unit-dose foil packet container label submitted on November 18, 2011
- 40.5 mg unit-dose foil packet container label submitted on November 18, 2011
- 20.25 mg unit-dose foil packet carton labeling submitted on November 18, 2011
- 40.5 mg unit-dose foil packet carton labeling submitted on November 18, 2011

(b)(4)



- Prescribing Information (no image) submitted on August 16, 2011
- Medication Guide (no image) submitted on August 16, 2011

[2] Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

3 RESULTS AND DISCUSSION

The following section describes the findings and analysis of the AERS cases and the labels and labeling.

3.1 ADVERSE EVENT REPORTING SYSTEM SEARCH RESULTS

The previous AERS searches conducted on May 27, 2009 and January 14, 2011, yielded 11 cases which were categorized as accidental transfers (n=6), wrong route of administration (n=2), wrong technique (n=1), and complaints due to product labels and labeling (n=2).

The updated AERS search conducted on January 11, 2012 yielded 53 additional cases. Of these, 19 were excluded from further evaluation for the reasons outlined above in Section 2.1 (See Appendix D). The remaining 34 cases are considered relevant to this review (see Appendix E for ISR numbers and case narratives). Six cases described 13 medication errors (two or more errors per case). Thus, the number of medication errors reported (n=41) is more than the number of cases. The 41 medication errors were categorized as wrong route of administration (n= 13), accidental transfers (n= 13), wrong dose (n= 9), dose omission (n=4), and dispensing errors (n-2). The medication error cases are described in the following subsections.

3.1.1 Wrong Route of Administration (n=13)

Thirteen cases involved patients applying AndroGel or other topical testosterone products to the wrong application sites including the chest, abdomen, underarms, forearms, legs, and face. In three cases, the causality was attributed to the physician instructing the patient to apply the gel to the chest and/or upper arms. In the case of underarm application, the patient stated that he interpreted shoulders, upper arms, and underarms from the diagram in the labeling. In a fifth case, the patient applied the product to his face in an attempt to self-treat facial poison ivy. No specific causality was given for the other eight cases.

3.1.2 Accidental Transfer (n=13)

Twelve of the thirteen cases described accidental transfer of the product to another person. These cases, which led to adverse outcomes such as development of aggression, facial acne, facial hair, pubic hair, clitoral or phallic enlargement, accelerated growth, and precocious puberty, occurred from January 2011 to November 2011 and involved children and adults.

In the thirteenth case, a pregnant woman speculated that exposure to her husband's topical testosterone product caused her to miscarry. However, we have no information on the status of the woman’s pregnancy prior to the exposure, and we have no follow-up information from the manufacturer or medical providers involved which definitively links the exposure to the product to the miscarriage.

In accordance with the REMS established September 18, 2009 for AndroGel products and for Testim 1%, a medication guide which accompanies the insert labeling for AndroGel 1.62% addresses this issue and is to be dispensed to each patient along with the medication.

3.1.3 Wrong Dose (n=9)

Nine cases reported the use of an incorrect dose. Seven of the nine cases involved overdoses. In two cases, the patient was prescribed more than the recommended maximum daily dose. In five

cases, patients used more than their prescribed dose due to their perception of no improvement in their baseline symptoms.

Two cases involved underdosing. In the eighth case, the patient was initially prescribed less than the recommended starting dose which was later increased to within recommended ranges. In the ninth case, the patient stopped his AndroGel for one month after developing side effects then restarted his medication at a lower dose than prescribed.

3.1.4 Dose Omission (n=4)

Four cases described dose omission. In one case, the patient missed doses for one month due to re-ordering complications then restarted the product after it had been delivered and left exposed to the sun for several hours. In two cases, the patients stopped using the product when either irritation occurred at the application site, or the patient did not perceive any improvement in his original symptoms. No reason or root cause analysis was offered in the forth case and could not be determined from the narrative.

3.1.5 Dispensing Errors (n=2)

Two cases described dispensing errors. In one case, the wrong medication was dispensed when the patient was given AndroGel 1.62% instead of the prescribed AndroGel 1%. In the second case, the identity of the topical testosterone product could not be determined from the Medwatch report. The narrative states that the patient was given the wrong strength of drug, 100 mg/mL liquid instead of the prescribed 200 mg/mL liquid.

3.2 Labels and Labeling

The proposed strengths for the new container closure system, 20.25 mg testosterone in 1.25 grams of gel and 40.5 mg testosterone in 2.5 grams of gel, are appropriate given the current dosing and administration instructions for AndroGel 1.62%. Our review of the container labels and carton labeling identified the following deficiencies:

3.2.1 All Container Labels and Carton Labeling

- The container labels and carton labeling for the [redacted (b) (4)] proposed unit-dose packets do not clearly state that the exposure level for testosterone may differ for AndroGel 1.62% compared to other topical testosterone products.

3.2.2 Container Labels and Carton Labeling for the Unit-Dose Foil Packet

- The [redacted (b) (4)] color text over the gray shaded background for the strength statement on the unit-dose packet labels and unit-dose packet carton labeling does not provide sufficient contrast and makes the statement less prominent and more difficult to read.
- [redacted (b) (4)]
- The container labels and carton labeling for both strengths lack the statement, "*For Topical Use Only*" on the principal display panel.

3.2.3 Container Labels for the Unit-Dose Foil Packets

- The blue boxed warning statement for non-child-resistant enclosure and product flammability on the label of the 40.5 mg strength (b) (4) makes them more difficult to read.
- The container labels for both strengths lack a lot number, expiration date, and bar code.

3.2.4 (b) (4)

-

3.2.5

-

3.2.6 Prescribing Information Labeling

- In the Indications and Usage section of the Highlights of Prescribing Information, and in Section 1 Indications and Usage and Section 8.4 Pediatric Use in the Full Prescribing Information, the statement (b) (4)
- The insert labeling does not clearly state that the exposure level for testosterone may differ for AndroGel 1.62% compared to other topical testosterone products.
- Table 3 in the Section 2.2 Administration Instructions (b) (4)

3.2.7 Medication Guide Labeling

The dosing table in the section "How should I use ANDROGEL 1.62%- If you are using AndroGel packets" (b) (4)

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation noted areas where information in the insert labeling, the container labels, and the carton labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1, Comments to the Division. Section 4.2 (Comments to the Applicant) contains our recommendations to the Applicant for changes to the container labels and carton labeling. We request these recommendations be communicated to the Applicant prior to approval of this supplement.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

4.1 COMMENTS TO THE DIVISION

4.1.1 Insert Labeling for AndroGel 1.62 %

A. General Comments

1. Revise the Indications and Usage section of the Highlights of Prescribing Information, and Section 1 Indications and Usage and Section 8.4 Pediatric Use in the Full Prescribing Information, to revise (b) (4) [redacted]

2. Revise the Indications and Usage section of the Highlights of Prescribing Information and Section 1 Indications and Usage in the Full Prescribing Information to include a Limitations of Use section that includes a statement warning healthcare providers that testosterone products may not be interchangeable. We recommend the following statement:

   "Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure."

B. Section 2 Dosage and Administration Section, Full Prescribing Information

In Table 3 in Section 2.2 Administration Instructions, (b) (4) [redacted] For example:

Table 3: Application Sites for AndroGel 1.62%, Packets

Total Dose of Testosterone	Total packets	Gel Applications Per Upper Arm and Shoulder	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	one 20.25 mg packet	one 20.25 mg packet	0
40.5 mg	one 40.5 mg packet	Half of contents of one 40.5 mg packet	Half of contents of one 40.5 mg packet
60.75 mg	one 20.25 mg packet AND one 40.5 mg packet	one 40.5 mg packet	one 20.25 mg packet
81 mg	two 40.5 mg packets	one 40.5 mg packet	one 40.5 mg packet

C. Section 16 How Supplied/Storage and Handling, Full Prescribing Information

1. DMEPA recommends revising the statements in Section 16 describing containers and cartons as follows:

   AndroGel 1.62% is supplied in non-aerosol, metered-dose pumps. Each 88 g metered-dose pump is capable of dispensing 75 g of gel or 60-metered

1.25 g doses of gel; each pump actuation dispenses 20.25 mg of testosterone in 1.25 g of gel.

AndroGel 1.62% is also supplied in unit-dose aluminum foil packets in cartons of 30:

20.25 mg unit-dose packet- each packet contains 20.25 mg of testosterone in 1.25 g of gel

40.5 mg unit-dose packet- each packet contains 40.5 mg of testosterone in 2.5 g of gel

4.1.2 Medication Guide

1. Revise the dosing table in the section **"How should I use ANDROGEL 1.62%?-** (b) (4) to spell out numbers instead of using numerals when referring to the number of packets that should be applied. The use of numerals to designate the number of unit-dose packets directly adjacent to the numerals to designate the specific strength of unit-dose packet is confusing and may be misinterpreted. For example, the statement "1 20.25 mg packet" could be misinterpreted as "120.25 mg packet" instead of the intended "one 20.25 mg packet." DMEPA recommends modifying the table as follows:

   "one 20.25 mg packet," "one 40.5 mg packet," "one 40.5 mg packet AND one 20.25 mg packet," and "two 40.5 mg packets"

2. Revise the dosing table in the section **"Applying ANDROGEL 1.62%:"**

   The language used within the dosing table (Figure 1) which refers to *"PUMP DEPRESSIONS'* under "Find Your Dose as Prescribed by Your Physician" is not consistent with the language within the equivalent table in Section 2.2 Administration Instructions of the Full Prescribing Information which refers to *"Pump Actuations"* and *"Total Pump Actuations."* It is also not consistent with the language used throughout the Dosage and Administration section of the Highlights of Prescribing Information and Section 2 Dosage and Administration of the Full Prescribing Information which refer to pump actuations to describe metered pump dosing.

   Revise the statements in the dosing table in Figure 1 of the Medication Guide to read "*Pump Actuations"* to maintain consistency.

4.2 COMMENTS TO THE APPLICANT

(b) (4)

B. Container Labels and Carton Labeling for the Unit-Dose Foil Packets

1. The (b) (4) color text over the gray shaded background for the strength statement does not provide sufficient contrast and makes the statement less prominent and more difficult to read. Increase the contrast of the strength (i.e. "Contains 20.25 mg of testosterone" and "Contains 40.5 mg of testosterone") and quantity ("1.25 Grams of gel" and "2.5 Grams of gel") statements by changing the font color and increasing the font size.

2. Revise the container labels and carton labeling to provide more differentiation between the two packet sizes. (b) (4) increase the differentiation between the two products by using different colors on the labels and labeling of one of the packet sizes.

C. Container Labels for the Unit-Dose Foil Packets

1. Decrease the prominence of the boxed warning statement on non-child-resistant enclosure and product flammability on the 40.5 mg label by decreasing the size of the boxed warning. Although these warnings are important, it is also important for healthcare practitioners and patients to be able to easily identify the different product strengths.

2. Revise the container labels to include a lot number, expiration date, and bar code per 21 CFR 201.10(i)(1) and 21 CFR 201.17.

3. If space permits, add the statement, "*For Topical Use Only,"* to the principal display panel.

D. Carton Labeling for the Unit-Dose Foil Packets

1. Relocate the statement, "*For Topical Use Only*," from the side panel to the principal display panel.

2. Relocate the statement, *"Rx Only,"* from the side panel to the principal display panel.

(b) (4)

REFERENCES

1. OSE Review #2009-334, Label and Labeling Review for AndroGel (Testosterone) 1.62%, March 12, 2010, Canton, L.

2. OSE Review #2010-2433, Label and Labeling Review for AndroGel (Testosterone) 1.62%, March 2, 2011, Toombs, L.

8 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix E: Excluded AERS Search Results

The AERS search conducted on January 18, 2012 yielded 53 cases. Of these cases, 19 were excluded from further evaluation for the reasons listed below.

- Adverse events or product quality issues not related to medication errors. (n= 16)
- Medication errors not associated with topical testosterone products (n= 1)
- Duplicated case (n=1)
- Accidental exposure; patient accidentally splashed AndroGel into eye during application process (n=1)

Non-Relevant AERS search results

	ISR #		ISR #		ISR #		ISR #		ISR #
1	7599973	5	7942282	9	7927850	13	8011241	17	7408011
2	7749125	6	7945118	10	7883869	14	7457216	18	7478995
3	7989240	7	7456113	11	7327766	15	7718516	19	7903573
4	7698566	8	7718405	12	7648201	16	7483439		

Appendix E: Relevant AERS Search Results

ISR #	Recv Date	Narratives
7364658	15-Mar-11	Patient had been using Androderm for 30 days without problem. Then when he refilled his prescription he has been experiencing a rash/hypersensitivity reaction at each application site. The reaction is so bothersome the patient has discontinued use of product after between 5-10 days of therapy with this new box of patches. Pertinent product information: - manufactuer: Watson Pharma - NDC: 52544-0470-30 - LOT: 345934 - expiration: 10/20/2012
7516719	23-May-11	On 29-Mar-2011, an initial spontaneous consumer report was received from the patient's mother concerning a 8-year old female (date of birth unknown) with no reported medical history who's father was placed on therapy with Testim (testosterone) 50mg daily on 25-Mar-2011 for an unknown indication. No concomitant medications were reported. On 25-Mar-2011 the patient's father began Testim, one tube per day and applied the product to his shoulders and upper back daily and covered the areas with clothing after each application. The reporter stated that she noticed a "nice floral smell" from the product. She also noticed the same smell on her 8-year-old daughter's arm (left or right arm unknown) (exact date unknown). She washed her daughter's arm with soap and water at that time. She also reported this event to the prescribing physician at the time of the report but had not heard back from the physician at the time of this report. The reporter did not notice any adverse reactions at the time of this report. Auxilium Drug Safety placed call with the reporter to obtain further information from the reporter but was unable to reach the reporter. Voicemail was left for the reporter to contact Auxilium Drug Safety Dept. This case is also linked to fathers AER number#201103072 At the time of reporting, therapy with Testim was unknown, and the current condition remains unknown. No further information was available,
7473331	3-May-11	On 19-Apr-2011, an initial spontaneous report was received concerning a 28-year-old female patient who was exposed to Testim 1% (testosterone) therapy through causal touch/exposure in 2011 (exact date unknown). No medical history was reported. Concomitant medications included multivitamins and vitamin C. According to the reporter, who was prescribed Testim for low testosterone, he applied Testim to his shoulders and sometimes would put on a t-shirt or shirt to

ISR #	Recv Date	Narratives
		cover the shoulders but sometimes, more often than not, he did not cover the area with clothing. The reported stated that on approximately 10-Apr-2011, his girlfriend was more aggressive, complaining about a headache, feeling nauseous, developed facial acne, and mentioned that she had missed her period. His girlfriend is not on oral contraceptives. Neither the male patient nor female patient consulted a physician about the symptoms. At the time of reporting, the outcome of the events was not resolved. No other information was available.
7455966	26-Apr-11	On 15-Apr-2011, an initial spontaneous consumer report was received from a 58-year-old male with a medical history of knee replacement, gastric bypass surgery in [redacted] (b) (6) obesity, depression, anxiety, edema of feet, high blood pressure and wheelchair dependent who was placed on therapy with Testim (testosterone) 50 mg transdermal gel daily in Apr-2009 (exact date unknown) for the indication of testosterone replacement therapy. Concomitant medications included morphine, furosemide, fluxoetine (Prozac), duloxetine HCL (Cymbalta) and atenolol. The patient reported that since using Testim, his energy had improved, but his testosterone level remained low. He was increased to Testim 100mg daily over the years (exact date unknown) but his testosterone level in Feb-2011 was reported to be 80 mg/dl. His physician instructed him to start using Testim 150 mg daily (date unknown) which he applied to his shoulders most of the time, but sometimes he applied Testim to his stomach. The patient reported that in the beginning of Testim therapy (date unknown) he developed breakouts". He also noticed more hair growth especially in the underarm areas during the course of Testim therapy. Approximately 1 1/2 years after using Testim (date unknown), he developed "enlarged breasts due to the therapy and had undergone a surgery for removal". At the time of this report the outcome of the events was unknown. No further information was available at this time. The patient refused permission to contact his physician regarding the events.
7508177	19-May-11	On 05-May-2011 an initial spontaneous consumer report was received from a spouse of an 82-year-old male, with a history of pain and gout who was started on Testim 1% (testosterone) 50mg gel once daily on approximately Jan-2011 (exact date unknown) for the indication of low testosterone with the symptom of low energy. Concomitant medications included allopurinol, (diltiazem hydrochloride) Cardizem LA, (ergocalciferol) vitamin D, and (fentanyl citrate) Fentanyl. Per the physician's instructions, the patient had been applying the Testim on his shoulders, upper arms and upper chest area. The reporter stated that she sometimes helped the patient by applying the Testim to the patient's shoulders, upper arms and upper chest area. In Apr-2011 (unknown exact date), the reporter noticed that the patient's upper chest area was "blue and purple like a sunburn". On 05-May-2011, the reporter noticed that the vessel were "blue and purple" in the upper chest area". Sometime in Apr-2011 (unknown exact date), she noticed that the patient's nipples were "bigger and yellow in color", which remained at the time of this report. On 5-May-2011, Auxilium Drug Safety called the reporter to clarify events and method reporter was using to assist with Testim application. The reporter stated that she has only assisted with her husband's Testim application on 4-May-2011. She used her index and middle finger then thoroughly washed with soap and water immediately after the application. She read the package insert and is now aware not to apply Testim to her husband's chest area. She clarified that the chest is not "blue and purple but a deep sunburn", "but they live in Florida and go into the sun". She stated she was upset yesterday when calling the call center and was getting mixed up. She added that she noticed that "his nipples seemed a little larger and pale yellow in color" (unknown exact date). At the time of reporting, therapy with Testim was continued and the outcome of the events was unchanged. No further information was available.
7716530	29-Aug-11	Spontaneous report from the USA of non-serious NAUSEA, HEADACHES and MEDICATION ERROR APPLIED TO CHEST with ANDROGEL 1.62% (TESTOSTERONE). On 20 Jun 2011, the patient experienced NAUSEA, HEADACHES and MEDICATION ERROR APPLIED TO CHEST.
7942254	28-Nov-11	Spontaneous report from the USA of non-serious HOT FLASHES, SWEATING, DECREASED DOSE and STOPPED TAKING MEDICATION with ANDROGEL 1.62% (TESTOSTERONE). In October 2011, the patient experienced HOT FLASHES and SWEATING. In Oct 2011, after

ISR #	Recv Date	Narratives
		the medication was applied, the patient developed hot flashes and sweating every thirty minutes. The patient stated that he noticed the sweating more apparent to the top of his head, but he had it all over his body. On 29 Oct 2011, the patient experienced STOPPED TAKING MEDICATION. On 29 Oct 2011, the patient stopped taking the medication for three days, and the hot flashes and sweating resolved. On 29 Oct 2011, the HOT FLASHES and SWEATING resolved. On 01 Nov 2011, the patient experienced DECREASED DOSE. On 01 Nov 2011, the patient restarted ANDROGEL 1.62% therapy, but decreased his dose from two pumps daily to one pump daily. The patient had not informed his prescribing physician of the events, and what he had done with the medication. The patient was instructed to follow up with his prescribing physician. The patient declined physician information, declined physician contact, and declined to provide any further information.
7516718	23-May-11	On 16-Feb-2011, an initial spontaneous consumer report was received from the father of a 5-year old female, whose father was prescribed Testim (testosterone) gel 100 mg daily approximately three years ago (unknown dates of administration) for the treatment of low testosterone). History for the daughter included ADHD, Concomitant medications for the daughter included (dexamfetamine sulfate) Adderall XR. The father reported he has two daughters. Approximately one year ago, he and his wife began to noting that his five year old daughter began showing signs of exposure to testosterone. he stated she was showing signs of premature puberty. She developed enlarged clitoris, body hair, underarm odor, and acne. She also showed signs of increased libido, evidenced by self stimulation. This past. week he and his wife noticed hair growth in her genitalia. Approximately six months ago, she began to see a pediatric endocrinologist and her free testosterone was 46 ng/dl. Per reporter, her level at this age should be less than 10 ng/dl. Her bone scan was normal and her growth chart is on target. She currently is undergoing further tests to rule out other hormonal or physiologic causes of her symptoms. He reported that he does not know if Testim is related to his daughter's symptoms. He stated that he is very careful about avoiding transference. He applies Testim using gloves, He does not share towels with his daughter, and his laundry is washed separately. He stated that the only possible route of exposure is through the bath tub. He showers in the same tub but not at the same time that his daughter bathes in. His other daughter also bathes in the same tub, however, his other daughter does not show signs of testosterone exposure. The reporter mentioned the his daughter is adopted from Russian descent. He reported he continues to use Testim but will discuss further with his physician and his daughter's endocrinologist. On 22-Feb-2011, the reporter called the Auxilium Drug Information Center and stated that he had discontinued Testim and switched back to the patch. He stated that he had used a testosterone patch in the past and it "burned the heck out of him". He added that he also tried Androgel. and that it "brought him up and down then dropped him". At the time of reporting, therapy with Testim was stopped, and the outcome of the events were unchanged. No further information was available. Manufacturer letter's were sent to Abbott Laboratories for reported adverse events associated with the medication Androgel and Watson Pharma Inc. for the medication of testosterone patch.
7516707	23-May-11	On 07-Feb-2011, an initial spontaneous consumer report was received from the father of a 14-year-old female, whose father was prescribed Testim (testosterone) gel 50 mg daily approximately two years ago (since an unspecified date in 2009) for the treatment of low testosterone. No concomitant medications were reported for the teenage female. The father of the female reported that he recently noticed within the past two weeks (an unspecified date in Jan-2011) that his 14-year-old daughter appeared to be growing sideburns further described as hair by the ears and cheeks. The father indicated that he is very careful applying Testim to avoid any direct skin-to-skin contact with either is 13-year-old son, 14-year-old daughter or his wife. He denied that his daughter ever touched his Testim application sites and that she does not do his laundry or use his same towels. He did report that the daughter will sleep in his bed on occasion and on the same sheets as he does, and this could be a possible route of transference. On 15-Mar-2011, medically confirmed additional information was received from the daughter's physician who provided date of birth as 26-Aug-1996, weight as 122.5 and not pregnant. She added that the

ISR #	Recv Date	Narratives
		father (reporter) claims sideburn hair on daughter started after on Testim. She added that she saw her only once on 21-Feb-2011 when the father (reporter) had the complaint. The physician does not know how long hair was present. At the time of reporting, the father continued to use Testim and the daughter's event of growth of sideburn hair continued unchanged. The father was advised to discourage his daughter from coming in contact with his bed sheets. Reference non-serious case 2011020/4 for the events reported for the father.
7403662	31-Mar-11	On 18-Mar-2011, an initial spontaneous consumer report was received from the patient's wife regarding a 50-year-old male, with a history of low testosterone and diabetes, who was placed on therapy with Testim (testosterone) gel 50 mg daily in Jan-2011 (exact date unknown) for the indication of low testosterone. Concomitant medications included metformin and glipizide. On l0-Mar-2011, the wife reported she had a miscarriage. She stated she was in her second trimester, one day shy of 15 weeks. Things were going good with the pregnancy, then she had the miscarriage. She added the doctors have not commented on the cause of the miscarriage. Currently she has seven other children and has not had a miscarriage. She is very upset and wants to have more children. She is a female Caucasian (b) (6) with no medical diagnosis, has not been taking any medications except for one prenatal vitamin daily. On 23-Mar-2011 addtional information was received from the patient's wife via a phone call from Auxilium Drug Safety to clarify possible transference. Drug Safety Associate asked the reporter three times how she was in contact with the Testim product and she did not understand the question when re-phrased numerous times. She continued to stated she is in "daily contact with Testim because her husband is using the product". I asked where he applies the Testim product and she stated that he is very careful regarding application to his upper arms and shoulders only. She added that she felt she had been in contact with Testim during sexual intercourse. When attempting to clarify this statement, I asked if he applied Testim to his penis, testicles, thighs, hips, or any part of his lower body. She denied. I further asked if she applied Testim to herself or had contact with Testim. She denied. I then questioned if she had been in contact with his laundry, sheets, bedding, clothes and she denied. No further information was provided. At the time of reporting, therapy with Testim continued and the outcome of the event was unchanged. No further information was available.
7830644	21-Oct-11	Case received from Laboratoires BESINS ?HINTERNATIONAL; reference number: 21114766. This case was reported in the literature and describes the occurrence of precocious puberty in a 10-month-old male secondary to transfer of topical TESTOSTERONE from his father, who was treated for primary hypogonadism. In early June 2006, a father who was taking topical TESTOSTERONE treatment since approximately 4 months reported to his physician that his 10-month-old son had undergone a pediatric endocrinology evaluation secondary to the development of precocious puberty. Further inquiry revealed that the infant had developed progressive penile enlargement over the previous 4-month period. It was not until the infant developed pubic hair that the parents brought this to the attention of their pediatrician. Upon our learning of the child's condition, the father's TESTOSTERONE therapy was immediately changed from topical to buccal delivery. Once the father's therapy was changed from a topical to a buccal dosage form, die symptoms in his son receded. The infant's birth history and development were documented as normal until the development of precocious pubertal signs. Pediatric endocrinology records provided to us revealed that the father had been practicing diligent hand washing, as counseled when he started topical TESTOSTERONE therapy. However, rather than applying the TESTOSTERONE to his shoulders at bedtime, he was applying it to his forearms in the morning. Additionally, the parents worked split shifts with the father serving as his son's primary caretaker during the day, and the mother serving as the primary caretaker in the evening. On May 18, 2006, the infant's physical exam revealed a weight of 11.3 kg and length of 76.2 cm, both values just above the 97th percentile. The infant was alert and active, and healthy in appearance with no facial hair. His head, eye, ear, nose, and throat examinations were normal, with no thyromegaly. His cardiovascular and respiratory examinations were also normal. His abdomen was soft and nontender, with no hepatosplenomegaly. His genitourinary exam revealed an enlarged penis

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		(approximately 5 cm long) and Tanner stage II pubic hair. His testes were 2 mL, descended bilaterally with no palpable nodules, and his scrotum was hyperpigmented with pubertal appearance. There was no skin hyperpigmentation elsewhere. His neurologic exam was intact. A congenital adrenal hyperplasia laboratory evaluation revealed markedly elevated testosterone and androstenedione, with adrenal hormones within normal limits. His bone age was reported as within the normal range. On June 5, 2006, follow-up laboratory tests revealed no change in total testosterone concentration. Approximately 4 weeks after the father discontinued topical TESTOSTERONE therapy, the son's testosterone levels declined to age appropriate ranges and his penis size receded. The son's history was then uneventful until, as a toddler, the child was diagnosed with developmental delay and subsequently with Asperger's disorder. The case was assessed as serious by Besins. Laboratory Data: Selected laboratory results for son (approximately 10 months old) Laboratory results (2006) Hormone*Units I>Normal range May 18 June 5 Jul 5 Total testosterone ng/dl. <3-10 874 938 24 Free testosterone pg/ml 0.15-0.6 159 1.2 Sex hormone binding globulin nmol/L60-252 78 48 Luteinizing hormone mIU/mL 0.02-7.0 0.03 0.08 Follicle stimulating hormone mIU/mL0.16-4.1 0. 62 0.69 17-Hydroxyprogesterone ng/dL 3-90 <10 Progesterone ng/dL <10-15 <10 17-OH Pregnenolone ng/dL 42-540 <10 Dehydroepiandrosterone ng/dL 20-100 84 Specific S ng/dL 10-156 18 Androstenedione ng/dL 6-68 91 Deoxycorlioosterone ng/dL 7-49 7.9 Cortisol microg/dL 2.8-23 3.7 Beta human chorionic gonadotropin, NS <1.0 quantitative (tumor marker) *Blood for all laboratory tests was collected in the morning. Approximately 4 weeks after father changed from topical to buccal TESTOSTERONE - = not tested; NS - not specified by the laboratory. Pharmacovigilance Comments In the CCSI, special warnings & precautions for use" of TESTOSTERONE gel 1% it is notified: Transfer of TESTOSTERONE to others (including women and children) can occur when vigorous skin-to-skin contact is made with the application site. The potential of testosterone transfer in gel user should be recognized as a possible side effect of this form of testosterone replacement therapy. Follow-up information received 13 Oct 2011 from the literature article: Reporter opinion of causality, suspect product information, adverse event information, and narrative descriptions were added or revised. Also received updates to literature citation information and reporter information.
7942270	28-Nov-11	Spontaneous report from the USA of non-serious FEELS JUMPY, PRESCRIBED TO TAKE MORE THAN RECOMMENDED MAXIMUM and FINDS BODY MUCH MORE HAIRY with ANDROGEL 1.62% (TESTOSTERONE). In 2011, the patient experienced PRESCRIBED TO TAKE MORE THAN RECOMMENDED MAXIMUM. The patient was prescribed to take about five to six pumps of ANDROGEL 1.62% daily, therefore taking more than the recommended maximum for ANDROGEL 1.62% therapy. In July 2011, the patient experienced FEELS JUMPY and FINDS BODY MUCH MORE HAIRY. Since Jul 2011, after three months of ANDROGEL 1.62% therapy, the patient experienced feeling jumpy, and would find much more body hair or was more hairy. The patient declined to provide any further information. The patient declined to have the physician contacted. CHANGE HISTORY On 24 Oct 2011, received updates to patient demographics, medical history, event information, reporter opinion of causality, suspect drug information, concomitant drug information, laboratory/diagnostic procedures and narrative description.
7272091	3-Feb-11	This case with clock date 17 JAN 2011 was received by Abbott Products (formerly Solvay Pharmaceuticals) Global Pharmacovigilance and Risk Management, on 01 FEB 2011 only. This case was provided by Laboratoires Besins-International. Besins received this report from a partner. A physician report via letter concerning a 55-year-old male patient from another country who had slightly aggressive and incorrect dose administered while being treated with TESTOGEL. The patient's concomitant conditions and medical history included non-smoker, asthma, back and shoulder pain, muscle tiredness, and hot flush. He was remitted to endocrinology for examination of secondary osteoporosis. Densitometry showed Z-score -4.52 in

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		loin (53% in comparison with same age population) and -2.22 in hip (71% in comparison with same age population). Shaves only once a week and had no interest in sex. The patient had obvious gynecomastia and small almost fibrotic testicles, small but elastic prostate with a volume of 22 ml. TESTOGEL (250mg/day) was started on an unknown date for an unknown indication. It was not reported if any concomitant drugs had been given. On an unspecified date, the patient was prescribed TESTOGEL 50 mg in dosage bag daily, but misinterpreted and took five dosage bags daily. After detailed description and correction of this, Testosterone was only about 8 nmol/L, the dosage was increased to two bags daily. The patient came to acute department at hospital after a fight with his brothers and then behaved slightly aggressive against health professionals. A careful endocrinologist decreased the dosage to 50 mg daily and the following examination gave reason to suspect that the patient had stopped with the treatment since Testosterone then was only 1.8 nmol/L. At the time of reporting, it was unknown if TESTOGEL and the reported adverse events were ongoing. Mail received from physician: The physician did not think that it had to do with the drug. The patient was uneducated, spoke another language and the conversations took place with an interpreter. He took his drugs ad libidium since the physician thought he did not understand his list of drugs. The physician met him last week and the patient told he took a shower after application since it was so sticky. This despite that he received a detailed verbal description. This explained the low values of Testosterone inspite two dosage pads daily. He got good effect with five dosage pads which was also a misunderstanding of the patient. The drug worked excellent but the communication with the patient was very difficult. Outcome: Unknown. The reporter did not assess the causal relationship between TESTOGEL and incorrect dose administered and assessed the causal relationship between TESTOGEL and slightly aggressive as 'unlikely'. Abbott Products (formerly Solvay Pharmaceuticals) judged the case as 'suspect'. Laboratoires Besins-International causality: Not assessable (slightly aggressive) / Not applicable (incorrect dose administered). Laboratoires Besins-International Remarks: Laboratoires Besins-International causality comment: Slightly aggressive, reported as a medically important event, was unlisted for Testosterone. The actual daily testosterone dosing may not be evaluated because of the patient's misunderstanding and poor adherence to the proposed drug regimen, and it was questionable whether the patient administered Testosterone gel prior to the onset of the event. Causal relationship with the drug was not assessable. The reporter assessed the case as 'serious' due to 'other medically important condition'. Pharmacovigilance title: Poorly documented case with no evidence of drug dosage and administration dates. According to the reporting physician, the event was unrelated to the use of TESTOGEL. Besins-Healthcare considered the relationship between the aggressivity and the use of ANDROGEL to be unassessable.
7941798	28-Nov-11	Pt has been exposed daily for 3 months to androgel by contact with husband. Now has enlarged painful breasts, heavy feeling in chest, hostility, skin irritation and acne, frequent urination, depression, and several other side effects. WALKERC: |*********| 2011-11-28-10.47.38 |*********| USFDAMWVOLUNTARY_196884_10154_20111126.xml Route To: AERS : Electronic
7942280	28-Nov-11	Spontaneous report from the USA of non-serious DECREASED ENERGY, ANDROGEL ISN'T HELPING WITH OUTSIDE ALLERGIES ANY MORE, MISSED DOSES and TOOK UNSTABLE MEDICATION with ANDROGEL 1.62% (TESTOSTERONE). While on ANDROGEL 1.62% for the past five years the patient experienced increased energy and noticed a decrease in his outside allergies. In August 2011, the patient experienced DECREASED ENERGY, ANDROGEL ISN'T HELPING WITH OUTSIDE ALLERGIES ANY MORE and MISSED DOSES. In Aug 2011, the patient went for a little over a month without his ANDROGEL 1.62% due to a re-ordering delay, and he began to experience a decrease in his energy. On 01 Oct 2011, the patient received a delivery of his ANDROGEL 1.62%, and it was left outside his home in the sun for a few hours. On 01 Oct 2011, the patient experienced TOOK UNSTABLE MEDICATION. The patient restarted his ANDROGEL 1.62% on that day. Upon assessment, the stability of the ANDROGEL 1.62% was not supported by Global Medical

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		Information. Since restarting the ANDROGEL 1.62% on 01 Oct 2011, the patient continued to experience a decrease in his energy and stated the ANDROGEL 1.62% was not helping with outside allergies any more.
7942288	28-Nov-11	Solicited report from the USA of non-serious TESTOSTERONE LEVELS DECREASED, ENERGY LEVEL INCREASED, UNEXPECTED THERAPEUTIC EFFECT and APPLYING ANDROGEL ON BACK OF UPPER ARMS, UNDER ARMS, AND IN ARMPITS with ANDROGEL 1.62% (TESTOSTERONE). In 2011, the patient experienced TESTOSTERONE LEVELS DECREASED, ENERGY LEVEL INCREASED, UNEXPECTED THERAPEUTIC EFFECT and APPLYING ANDROGEL ON BACK OF UPPER ARMS, UNDER ARMS, AND IN ARMPITS. The patient stated that his testosterone levels decreased. The patient reported that prior to starting on ANDROGEL 1.62%, his testosterone level was 300. The patient stated that two months later he had another blood test and his testosterone level was 121. The patient reported that his doctor thought that it could not be right and had him take another blood test on 18 Oct 2011 and his testosterone level was 232. The patient stated that his primary care doctor adjusted his dose to now apply three pumps per day. The patient denied any worsening of symptoms. The patient stated that he noticed that his energy level increased a bit after using ANDROGEL. The patient reported that he experienced a medication error and was applying ANDROGEL on the back part of his upper arms, underneath his arms, and in his armpits. The patient stated that this is what he interpreted from the diagram provided to him.
7942306	28-Nov-11	Solicited report from the USA of non-serious MEDICATION ERROR APPLYING MEDICATION TO THE WRONG AREA, FEELING NO EFFECT, TESTOSTERONE LEVELS WERE STILL BELOW NORMAL and NIGHT SWEATS with ANDROGEL 1.62% (TESTOSTERONE). In 2011, the patient experienced MEDICATION ERROR APPLYING MEDICATION TO THE WRONG AREA, FEELING NO EFFECT and NIGHT SWEATS. In November 2011, the patient experienced TESTOSTERONE LEVELS WERE STILL BELOW NORMAL. The patient has been on ANDROGEL 1.62% for several months. The patient has been feeling no effect. The patient's testosterone level was 246 prior to starting on ANDROGEL 1.62%. The patient saw his physician two weeks ago and his testosterone levels were still below normal. The patient's testosterone level at this visit was 239. The patient's physician told him he was applying the medication to the wrong area. The patient was applying the medication to the sides of his stomach. The physician told the patient it should be applied to muscle mass. The patient is now applying it to the upper arms and shoulders. The patient had night sweats that went away at first and then came back. The patient has a follow up appointment in three months. The patient declined to have the physician contacted.
7556947	16-Jun-11	Father is using a prescription, topical testosterone cream. This child was exposed to the cream indirectly through contact with the father. He developed pubic hair and phallic enlargement. His sister was also found to have elevated testoserone levels. The boy has now entered central precocious puberty with elevated LH level, likely due to priming from the exogenous testosterone exposure. He will likely require treatment with leuprolide to suppress puberty and may have a decrease in final height.
7716528	29-Aug-11	Spontaneous report from the USA of non-serious NO IMPROVEMENT IN SEX DRIVE, APPLIED SOME ANDROGEL UNDER BELLY BUTTON and NO IMPROVEMENT IN TESTOSTERONE LEVEL with ANDROGEL 1.62% (TESTOSTERONE). In 2011, the patient experienced NO IMPROVEMENT IN SEX DRIVE, APPLIED SOME ANDROGEL UNDER BELLY BUTTON and NO IMPROVEMENT IN TESTOSTERONE LEVEL. The patient has not experienced an improvement in his sex drive since he started ANDROGEL 1.62% 4-5 months ago. The patient was initially started on two pumps of ANDROGEL and increased to four pumps because of no improvement in sex drive. The patient stated that he takes a little of the gel from the four pumps of ANDROGEL and applied the gel below his umbilical area. The patient reported that his last testosterone level was 133 and has not improved because his testosterone level before starting ANDROGEL was close to this last result but the patient does not remember the exact number. The patient declined physician contact.

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7908428	10-Nov-11	Access Number: 63369 Description: Community pharmacy: Patient received testosterone 100mg/ml instead of 200mg/ml. The patient noticed it was wrong before he used it. We swapped it out without incidence. Medication Error
7942269	28-Nov-11	Spontaneous report from the USA of non-serious SECONDARY EXPOSURE TO ANDROGEL and EXTRA HAIR TO FACE with ANDROGEL 1% (TESTOSTERONE) and ANDROGEL 1.62% (TESTOSTERONE). The patient's spouse was on ANDROGEL for several years. The patient stated that her spouse did not routinely wash the ANDROGEL off prior to skin to skin contact. The physician said that the patient's spouse did not have to wash off the ANDROGEL if it had been on for several hours. On unknown dates, the patient experienced SECONDARY EXPOSURE TO ANDROGEL and EXTRA HAIR TO FACE. The patient developed extra hair to her face. The patient believed she was exposed to the ANDROGEL. The patient said she did not know exactly when the exposure started, but the patient's spouse was on ANDROGEL for several years. The patient's spouse received instructions with the ANDROGEL, but his physician told him it was not necessary to wash it off. The patient' spouse was aware of all the other recommendations regarding limiting transfer. The patient's spouse applied the ANDROGEL to his upper arms, covered the area with a T-shirt and was careful to wash his hands after application. The patient believed the exposure happened due to contact with un-washed sites of application over a period of years. The patient discussed the hair to face with her physician on an unknown date. The physician did an FSH blood test and the result was normal. The event was not resolved; it was ongoing. Minimal information was received about the events. The patient did not provide doctor information.
7942303	28-Nov-11	Spontaneous report from the USA of non-serious MEDICATION APPLIED TO LEGS, RED FACE and FLUSHING with ANDROGEL 1.62% (TESTOSTERONE). In November 2011, the patient experienced MEDICATION APPLIED TO LEGS, RED FACE and FLUSHING. The patient experienced a medication error and applied two pumps to his legs and two pumps to his shoulders. The patient experienced red face and flushing. The patient stated that this occurred once, a few days ago in Nov 2011. The patient self discontinued ANDROGEL to see if it would help and it did. The patient stated that it was his third day of not using ANDROGEL. The patient has not spoken to his physician yet.
7516097	1-Jun-11	A consumer report concerning a 55-year-old male who reported medication error applied on chest, pins and needles sensation, redness, feels lethargic, no energy and shoulders feel heavy while being treated with ANDROGEL. The consumer had a medical history of elevated blood pressure and low testosterone. He stated that his physician prescribed an unknown medication for blood pressure. At the same time he was prescribed ANDROGEL. ANDROGEL (5 grams/day, via pump) was started on an unknown date in 2010 for low testosterone. The consumer stated that he experienced redness and pins and needles sensation on his chest and abdomen off and on since starting on ANDROGEL in 2010. Consumer stated that it usually goes away in 30-45 minutes. He stated that his physician instructed him to apply ANDROGEL on his chest, upper arms and shoulders. The consumer stated that his blood pressure medication was discontinued on an unknown date in MAR 2011. He started a new pump of ANDROGEL ON 05 APR 2011. The consumer stated he experienced pins and needles sensation that seemed to last longer than 30-45 minutes. On 08 APR 2011, he also noticed that he felt lethargic, had no energy and his shoulders felt heavy. Testosterone level was measured on DEC 2010 and was not able to recall lab value. At the time of reporting ANDROGEL, pins and needles sensation, redness, medication error applied to chest, feel lethargic, no energy and shoulders feel heavy were ongoing. Outcome: Not yet recovered. The reporter assessed the causal relationship between ANDROGEL and adverse events as 'possible'. Abbott Products (formerly Solvay Pharmaceuticals) judged the case as 'suspect'. The patient declined permission to contact physician and patient declined to provide additional information. ***Additional information received on 17 MAY 2011: Physician contact information, consumer demographics (weight, age group), seven new adverse events, three new co-suspect drugs, one new concomitant drug, updated relevant history and laboratory test details were provided. The batch number and lot number were provided for the ANDROGEL pump that

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		was started on 05 APR 2011. Elevated BP, deep red color, nausea, headache and anxiety were added as originally reported non-serious adverse events. Fractured C-5 and partially collapsed disc were originally reported as non-serious but were assessed as serious by Abbott Products (formerly Solvay Pharmaceuticals). On (b) (6), the consumer had a ladder fall onto his head fracturing his C5 vertebra and partially collapsing the disc between vertebrae C5 and C6. The consumer reported being X-rayed, scanned and given a cervical brace and then released with new prescriptions changing his regular medications. Etodolac (800mg daily) for rheumatoid arthritis, Methocarbamol (1500mg daily) for muscle pain and spasms and Methylprednisolone (decreasing, self limiting dose) for broken neck were started on 27 APR 2011. All are considered suspect in this case, in addition to ANDROGEL. On 14 MAY 2011, the consumer experienced elevated BP, deep red color, nausea, headache and anxiety. He stated that he believed his new medications (Etodolac, Methocarbamol and Methylprednisolone) might be contributing to his adverse reactions. At the time of reporting, the reported adverse events and treatment with all the suspect drugs were ongoing. Outcome: Not yet recovered. The reporter assessed the causal relationship between ANDROGEL, Etodolac, Methocarbamol and Methylprednisolone and adverse events as 'possible'. Abbott Products (formerly Solvay Pharmaceuticals) judged the case as 'suspect'. This case is medically judged as serious by Abbott Products (formerly Solvay Pharmaceuticals) due to the adverse events "fractured C-5 and partially collapsed disc".
7600504	11-Jul-11	Spontaneous report from the USA of non-serious MORE FATIGUE, MORE DEPRESSED, MEDICATION DOES NOT WORK, ANGER PROBLEM, PERSONALITY CHANGE, NO ROMANTIC INCLINATION, ENERGY IS GONE AFTER 5PM EVERY DAY, MEDICATION ERROR APPLIED TO POISON IVY ON FACE, NO CHANGE IN TESTOSTERONE LEVELS, TESTOSTERONE LEVELS WERE NEARLY NOTHING, ERECTILE DYSFUNCTION, VARIED HIS DOSE TO 7-10 PUMPS PER DAY AT TIMES and DOCTOR TOLD HIM HE NEEDED TO LOSE WEIGHT AND GAIN STRENGTH with ANDROGEL (TESTOSTERONE). On unknown dates, the patient experienced MORE FATIGUE, MORE DEPRESSED, MEDICATION DOES NOT WORK, ANGER PROBLEM, PERSONALITY CHANGE, NO ROMANTIC INCLINATION, ENERGY IS GONE AFTER 5PM EVERY DAY, NO CHANGE IN TESTOSTERONE LEVELS, TESTOSTERONE LEVELS WERE NEARLY NOTHING, ERECTILE DYSFUNCTION, VARIED HIS DOSE TO 7-10 PUMPS PER DAY AT TIMES and DOCTOR TOLD HIM HE NEEDED TO LOSE WEIGHT AND GAIN STRENGTH. In June 2011, the patient experienced MEDICATION ERROR APPLIED TO POISON IVY ON FACE. The patient stated that he started on ANDROGEL a couple of years ago and has not used ANDROGEL consistently over time. The patient stated that he has varied his dose to use 7-10 pumps per day at times to see if he experienced any changes with symptoms of low testosterone. The patient stated that he started on 2 pumps per day and used this dose for about one year. The patient stated that he discontinued ANDROGEL for some time because he did not see any changes and felt that he was wasting his money. The patient described personality change as being a joker in a negative way. The patient stated that his family doctor who prescribed ANDROGEL informed him that he is not able to use any other testosterone products other than ANDROGEL and adjusted his dose of ANDROGEL to four pumps per day. The patient stated that his doctor told him that he needed to lose weight and gain strength. The patient stated he could not recall his testosterone levels but stated that there is no change in testosterone levels. The patient stated that his testosterone levels were nearly nothing. The patient stated that he applied ANDROGEL to poison ivy on the side of his face and stated that it helped the poison ivy heal quickly. The patient stated that he takes VIAGRA for erectile dysfunction and stated that it did not help.
7716544	29-Aug-11	Spontaneous report from the USA of non-serious OVERDOSE and TESTOSTERONE LEVEL WAS GREATER THAN 3000 with ANDROGEL 1% (TESTOSTERONE) and ANDROGEL 1.62% (TESTOSTERONE). On unknown dates, the patient experienced OVERDOSE and TESTOSTERONE LEVEL WAS GREATER THAN 3000. On an unknown date, ANDROGEL was changed to the 1.62%. The patient was taking 1.62% four pumps, instead of two pumps as

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		ordered. The patient's testosterone level was greater than 3000. The ANDROGEL was put on hold. On unknown dates, OVERDOSE and TESTOSTERONE LEVEL WAS GREATER THAN 3000 resolved. Testosterone level went back down, and ANDROGEL therapy was reinstated on an unknown date.
7942285	28-Nov-11	Co-Marketer report from the USA of non-serious DECREASED TESTOSTERONE LEVELS and APPLYING MEDICATION TO THIGH with ANDROGEL 1.62% (TESTOSTERONE). On unknown dates, the patient experienced DECREASED TESTOSTERONE LEVELS and APPLYING MEDICATION TO THIGH. In 2011, after ANDROGEL 1.62 percent therapy, the patient experienced decreased testosterone levels of 75 and 76 nanograms per deciliter. In 2011, the patient had been applying the medication to his thighs. The patient did not shower after application of the medication.
7942304	28-Nov-11	Spontaneous report from the USA of non-serious FELT DOWN, FELT TIRED, DECREASED TESTOSTERONE LEVEL and MEDICATION IS NOT GOOD with ANDROGEL 1.62% (TESTOSTERONE). In November 2011, the patient experienced FELT DOWN, FELT TIRED, DECREASED TESTOSTERONE LEVEL and MEDICATION IS NOT GOOD. Patient started ANDROGEL about four months ago. Patient's testosterone level was 19 when he started on ANDROGEL. Patient felt better after two months. Patient had levels checked after two months. Patient did not recall lab value and stated that it was on the low side of normal. In the last 3 - 4 weeks, patient felt down and felt tired. Patient saw his doctor this week and testosterone levels were checked. Patient experienced decreased testosterone level of 12. Doctor told patient that the only think he can think of is that maybe his medication is not good. Doctor told patient to call drug manufacturer. Patient's doctor wrote patient a new prescription for ANDROGEL at the same dose. Patient has not started prescription.
7267519	21-Jan-11	On]4-Mar-2010, an initial spontaneous consumer report was received from the father of a 27-year-old female, who was his pregnant daughter. No other medical history was reported. Concomitant medications were not provided. On 13-Mar-2010, the pregnant daughter accidentally touched the Testim application site of her 55-year-old father four hours post application. The daughter noted that her father's arm was sticky and immediately washed her hands with soap and water. The daughter was pregnant (gestational term not reported). At the time of this report, no adverse reactions were reported. No further information was available. On 05-May-2070, additional information was received from the pregnant female, regarding herself, a 27-year-old female with a history of an enlarged thyroid since age 12 years and no prior pregnancies. She accidentally touched the arm of her father four hours post application of Testim on 13-Mar-2010. Concomitant medications included levothyroxine. The patient reported that her last menstrual period was on 04-Feb-2010 and her estimated date of delivery is 12-Nov-2010. She is a nulliparous female (para 0 gravida 0) and she denied any complications or illnesses during her pregnancy thus far. No further information was available. The patient did not give permission to contact her health care provider to obtain additional information. On 11-Jan-2011 and 12-Jan-2011, follow-up information was received from the daughter regarding the course of her pregnancy and the outcome of her pregnancy. She was diagnosed at 19 weeks gestation with a placenta previa. On (b) (6), she was hospitalized and it was determined that she had a complete placenta prcvia. She was discharged home on (b) (6) with the instructions to remain on bed rest for the next eight weeks. On (b) (6), the mother was hospitalized again for bleeding associated with the placenta previa. She was in labor at the time. Due to the previa and bleeding, a caesarean section was performed on (b) (6) (31 weeks gestation). She was forced to deliver early via caesarean section due to the bleeding associated with the complete previa. She gave birth to a healthy premature male infant at 37 weeks gestation with mild hydronephrosis (which had been diagnosed at 18 weeks gestation). She was discharged home on (b) (6) and reported that she and her baby are doing well. She indicated that she did not believe that the brief exposure to her father's Testim had any effect on her or her infant. After the exposure incident occurred, her father switched to using testosterone shots and discontinued Testim gel. At the time of reporting, the mother recovered from all events and reported no further

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		exposure to Testim therapy. The patient did not give permission to contact her health care provider to obtain additional information. No further information was provided. Reference case #201101032 for the corresponding infant case.
7979565	14-Dec-11	Solicited report from the USA of RIGHT HIP ARTHRITIS and non-serious ACNE, THROMBOPHLEBITIS RIGHT FOOT and DISPENSED WRONG MEDICATION with ANDROGEL 1% (TESTOSTERONE). On an unknown date, the patient experienced RIGHT HIP ARTHRITIS. In 2008, the patient experienced ACNE. The patient developed facial acne while on ANDROGEL 1%, and the facial acne resolved after the patient stopped applying ANDROGEL on his shoulders. The patient applied the ANDROGEL 1% to his abdomen. The patient had a right hip replacement on (b) (6) due to arthritis and was in the hospital for three days. In (b) (6), the patient experienced THROMBOPHLEBITIS RIGHT FOOT. The patient had an uneventful recovery until he developed thrombophlebitis of his right foot two and a half weeks after surgery. The patient was evaluated in the emergency room and treated with ASPIRIN then discharged home. The patient was directed to take a 325 milligrams of ASPIRIN daily. In December 2011, the patient experienced DISPENSED WRONG MEDICATION. The patient was dispensed 1.62% ANDROGEL pump by his pharmacy, but the patient noted that he took the 1 % ANDROGEL, and that is what his physician prescribed. The patient did not start the ANDROGEL because he received the wrong strength of ANDROGEL. The patient planned on notifying pharmacy after speaking with Medical Services to get the correct strength of ANDROGEL. On unknown dates, ACNE and RIGHT HIP ARTHRITIS resolved. The patient was treated with ASPIRIN.
7302410	18-Feb-11	This is a report from a contactable consumer based on information received by Pfizer from Abbott (manufacturer control number SOLV00211000916). A 50-year-old male started to receive testosterone (ANDROGEL) on 08-Jan-2011 at half a packet of 5 grams (2.5 gram per day) cutaneously for low free testosterone and low bioavailable testosterone. Co-suspect medication included ibuprofen (ADVIL), which the patient started to receive in Jan2011 for his back pain, which was titrated up to a dosage of 1600 mg daily. This consumer was informed by his prescribing physician to apply the testosterone to his chest (08-Jan-2011). On 24Jan2011 the dose of testosterone was increased from half a packet of 5 grams to a full packet daily. Past product history included a sublingual testosterone medication about fifteen years prior to reporting, which caused anger and irritability. Relevant medical history included drug hypersensitivity, emotional lability, lack of motivation, homosexuality, erectile dysfunction, obsessive-compulsive disorder, anxiety/panic attacks, depression, anxiety and low testosterone. It was noted that the patient was a non-smoker and psychologically damaged in college. Concomitant medications included duloxetine hydrochloride (CYMBALTA), lorazepam, trazodone, and an herbal preparation. Gradually since 24Jan2011 the consumer noticed an increase of irritability, anxiety and depression. In mid to late Jan2011 the consumer developed sinus drainage and a cough. In Jan2011 the consumer said he coughed so hard that he hurt his back. On the advice of his physician, the consumer began taking Advil in Jan2011 for his back pain. The consumer titrated up to 1600 mg daily of Advil and began experiencing stomach upset on an unknown date in 2011. The physician was informed of the stomach upset and the consumer was advised to discontinue the Advil on 01Feb2011. Advil was considered suspect for stomach upset. Corrective therapy included acetaminophen (TYLENOL) for back pain (two days in Jan2011). At the time of reporting, treatment with testosterone was ongoing, and the events increased anxiety, increased depression, increased irritability, sinus drainage, cough, back pain, stomach upset, applies medication to chest were ongoing/not yet recovered. The reporter assessed the causal relationship between testosterone and the adverse events as possible. Abbott Products (formerly Solvay Pharmaceuticals) judged the case as suspect.
7637987	20-Jul-11	Franklin SL. Effects of unintentional exposure of children to compounded transdermal sex hormone therapy. Pediatr Endocrinol Rev. 2011;8(3):208-212. Gynecomastia and rapid growth progressed in twin brothers and pubic hair in one, over a period of 2 years. A combination of contra- and isosexual development was induced by transdermal exposure to compounded

ISR #	Recv Date	Narratives
		estradiol, estrone, and testosterone creams applied to their mother's body as part of a hormone replacement regimen. Follow-up information received on 11-Jul-2011 from Reactions Weekly abstract. Estradiol/estrone/testosterone: Gynaecomastia, rapid growth and sex hormone disorders in children following dermal transfer: 2 case reports [abstract of Franklin SL. Effects of unintentional exposure of children to compounded transdermal sex hormone therapy. Pediatr Endocrinol Rev. 2011;8(3):208-212]. React Wkly. 2011; 1359:17. Twin brothers, aged 5.25 years, developed gynaecomastia and rapid growth following secondary transdermal exposure to estradiol, estrone and testosterone creams. Twin A also developed precocious puberty, while twin B developed a possible gender identity disorder. The boys presented with gynaecomastia. Their mother reported the use of compounded transdermal estradiol, estrone and testosterone creams at steadily increasing concentrations for menopausal symptoms over the pas 2 years [dosages and duration of therapies to reaction onsets not stated]. Examination revealed both boys had breast development that was equivalent to a Tanner III stage female. They also presented with rapid growth, both with an advanced bone age of 7.5 years. Twin A also had precocious puberty, with Tanner III pubic hair and an erect penis during examination. Twin B presented with a possible gender identity disorder, with a preference for wearing female clothing. Analysis revealed both boys had elevated serum concentrations of estrone and estradiol, while twin A had elevated ALP levels. The compounded agents were discontinued. Within 2 months, the boys' serum concentrations of estrone and estradiol decreased to prepubertal levels. Twin A's pubic hair fell out and, after 3 months, his breast tissue had softened. Twin B's breast tissue also softened after 6 months and he began wearing characteristically male clothing. However, over the next 6 months the bone age of both boys advanced to 10 years. Associated cases: 2011AT000187 and 2011AT000190.
7637988	20-Jul-11	Franklin SL. Effects of unintentional exposure of children to compounded transdermal sex hormone therapy. Pediatr Endocrinol Rev. 2011;8(3):208-212. Gynecomastia and rapid growth progressed in twin brothers and pubic hair in one, over a period of 2 years. A combination of contra- and isosexual development was induced by transdermal exposure to compounded estradiol, estrone, and testosterone creams applied to their mother's body as part of a hormone replacement regimen. Follow-up information received on 11-Jul-2011 from Reactions Weekly abstract. Estradiol/estrone/testosterone: Gynaecomastia, rapid growth and sex hormone disorders in children following dermal transfer: 2 case reports [abstract of Franklin SL. Effects of unintentional exposure of children to compounded transdermal sex hormone therapy. Pediatr Endocrinol Rev. 2011;8(3):208-2121. React Wkly. 2011; 1359:17. Twin brothers, aged 5.25 years, developed gynaecomastia and rapid growth following secondary transdermal exposure to estradiol, estrone and testosterone creams. Twin A also developed precocious puberty, while twin B developed a possible gender identity disorder. The boys presented with gynaecomastia. Their mother reported the use of compounded transdermal estradiol, estrone and testosterone creams at steadily increasing concentrations for menopausal symptoms over the past 2 years [dosages and duration of therapies to reaction onsets not stated]. Examination revealed both boys hac breast development that was equivalent to a Tanner III stage female. They also presented with rapid growth, both with an advanced bone age of 7.5 years. Twin A also had precocious puberty, with Tanner III pubic hair and an erect penis during examination. Twin B presented with a possible gender identity disorder, with a preference for wearing female clothing. Analysis revealed both boys had elevated serum concentrations of estrone and estradiol, while twin A had elevated ALP levels. The compounded agents were discontinued. Within 2 months, the boys' serum concentrations of estrone and estradiol decreased to prepubertal levels. Twin A's pubic hair fell out and, after 3 months, his breast tissue had softened. Twin B's breast tissue also softened after 6 months and he began wearing characteristically shale clothing. However, over the next 6 months the bone age of both boys advanced to 10 years. Associated cases: 2011AT000188 and 2011AT000190.

ISR #	Recv Date	Narratives
7656816	4-Aug-11	Case received from Besins-International, reference number BI-S-20110057. Case report received from MHRA. Patient became amenorrhoiec for 5 months due to inadvertent exposure to testosterone gel prescribed to her male partner. Patient's partner is not registered at our practice so it took some time to realize the source of the patient's very high testosterone level. Patient's partner was apparently applying Testogel carefully as per instruction s and not clear how exposure took place. Following endocrine advice patient's partner is now changing to testosterone injections. This case was assessed as serious by the reporting authorities (other medically serious). Patient's testosterone level has returned to normal.
7942253	28-Nov-11	Spontaneous report from the USA of non-serious INCREASE IN HAIR GROWTH and INCREASED DOSE with ANDROGEL 1.62% (TESTOSTERONE). In October 2011, the patient experienced INCREASE IN HAIR GROWTH and INCREASED DOSE. Approximately in Oct 2011, the patient increased his dose from the prescribed two pumps daily to three pumps daily. In Oct 2011, about two or three weeks ago, the patient developed an increase in hair growth, especially noticeable due to how fast his beard was growing. The patient mentioned that he would need to shave twice as often than before he started taking ANDROGEL 1.62% therapy. The patient declined physician information, declined physician contact, and declined to provide further information.

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/s/

TERRI WOOD-CUMMINGS
06/06/2012

ZACHARY A OLESZCZUK
06/07/2012

CAROL A HOLQUIST
06/07/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 7, 2012

TO: NDA 22309, Androgel 1.62%

THROUGH: Jeannie Roule

SUBJECT: Comments for carton and Container

DMEPA and the CMC reviewer requested that the attached comments be sent to the Applicant.

Please see attached.

NDA 22309/S-001, Androgel 1.62%

In collaboration with the Division of Medication Errors Prevention and Assessment (DMEPA) in the Office of Surveillance and Epidemiology (OSE), we have the following comments related to your proposed container/carton labeling. Your prompt response to these comments is requested.

A. General Comments (All Container Labels and Carton Labeling)

1. The container labels and carton labeling for the [redacted] (b) (4) proposed unit-dose packets do not clearly state that the exposure level for testosterone may differ for AndroGel 1.62% compared to other topical testosterone products. Add the following statement to the principal display panel of all container labels and carton labeling:

"Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure."

B. Container Labels and Carton Labeling for the Unit-Dose Foil Packets

1. The [redacted] (b) (4) color text over the gray shaded background for the strength statement does not provide sufficient contrast and makes the statement less prominent and more difficult to read. Increase the contrast of the strength (i.e. "Contains 20.25 mg of testosterone" and "Contains 40.5 mg of testosterone") and quantity ("1.25 Grams of gel" and "2.5 Grams of gel") statements by changing the font color and increasing the font size.

2. Revise the container labels and carton labeling to provide more differentiation between the two packet sizes. [redacted] (b) (4) (b) (4) (b) (4) increase the differentiation between the two products by using different colors on the labels and labeling of one of the packet sizes.

C. Container Labels for the Unit-Dose Foil Packets

1. Decrease the prominence of the boxed warning statement on non-child-resistant enclosure and product flammability on the 40.5 mg label by decreasing the size of the boxed warning. Although these warnings are important, it is also important for healthcare practitioners and patients to be able to easily identify the different product strengths.

2. Revise the container labels to include a lot number, expiration date, and bar code per 21 CFR 201.10(i)(1) and 21 CFR 201.17.

3. If space permits, add the statement, "*For Topical Use Only,*" to the principal display panel.

D. Carton Labeling for the Unit-Dose Foil Packets

1. Relocate the statement, "*For Topical Use Only*," from the side panel to the principal display panel.

2. Relocate the statement, *"Rx Only,"* from the side panel to the principal display panel.

Roule, Jeannie

From: Roule, Jeannie
Sent: Thursday, June 07, 2012 12:21 PM
To: 'Janel M Boyce-Rustay'
Subject: NDA 22309 carton and container

Attachments: DMEPA carton and container comments June 2012.doc

Janel,

I have attached a word doc that contains comments concerning your carton/container for the 1.62%.

Regards,
Jeannie

DMEPA carton and container com...

Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: (301) 796-2130 (main)
Direct Line: (301) 796-3993
Fax: (301) 796-9897
Email: jeannie.roule@fda.hhs.gov

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/s/

JEANNIE M ROULE
06/07/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 022309/S-001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE-DMEPA

FROM: Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products (DRUP)
301-796-3993

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
3/29/12		sNDA 22309/S-01	Electronic	March 7, 2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AndroGel 1.62% Topical Gel	Standard (6 month clock)	Androgen	July 2012

NAME OF FIRM: Abbott Products

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the Label, REMS, Medguide and any other pertinent documents.
This is an electronic submission.
\\CDSESUB1\EVSPROD\NDA022309\022309.enx

March 7, 2012

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jeannie Roule	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

JEANNIE M ROULE
03/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO: **CDER-DMPP-PatientLabelingTeam**

FROM: Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products (DRUP) 301-796-3993

REQUEST DATE: 3/29/12

NDA/BLA NO.: sNDA 22309/S-01

TYPE OF DOCUMENTS: Electronic

NAME OF DRUG: Androgel 1.62 %

PRIORITY CONSIDERATION: Standard 6 month clock

CLASSIFICATION OF DRUG: Androgen

DESIRED COMPLETION DATE: July 2012

SPONSOR: Abbott Products, Inc

PDUFA Date: September 8, 2012

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☒ LABELING SUPPLEMENT
- ☐ MANUFACTURING (CMC) SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission:
\\CDSESUB1\EVSPROD\NDA022309\022309.enx

March 8, 2012

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Filing/Planning Meeting: [Insert Date(s)] N/A

Mid-Cycle Meeting: [Insert Date] N/A

Labeling Meetings: [Insert Dates] June 13 and 18, 2012

Wrap-Up Meeting: [Insert Date] N/A

SIGNATURE OF REQUESTER Jeannie Roule

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL (BLAs Only) ☐ DARRTS

Version: 12/9/2011

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/s/

JEANNIE M ROULE
03/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022309/S-001

COMPLETE RESPONSE –LABELING/REMS MODIFICATION

Abbott Laboratories
Attention: Janel Boyce-Rustay, Ph.D.
Regulatory Affairs
200 Abbott Park Road
Dept PA76/AP34-3200
Abbott Park, IL 60064-6188

Dear Dr. Boyce-Rustay:

We acknowledge receipt on March 8, 2012, of your March 7, 2012, resubmission to your supplemental new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for AndroGel® (testosterone gel) 1.62%.

This amendment constitutes a complete response to our February 21, 2012, action letter.

If you have any questions, call me at (301) 796-3993.

Sincerely,

{See appended electronic signature page}

Jeannie Roule
Senior Regulatory Health Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

JEANNIE M ROULE
03/29/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)

Jeannie Roule, Regulatory Project Manager
Division of Reproductive and Urologic Products
(301) 796-3993

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
11/18/11		22309/S-001	electronic

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Tstosterone gel 1.62%	Labeling supplement due February 16, 2012	Androgen	January 16, 2012

NAME OF FIRM: Abbott Pharmaceuticals

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
✓PACKAGE INSERT (PI)
☐ PATIENT PACKAGE INSERT (PPI)
✓ CARTON/CONTAINER LABELING
✓MEDICATION GUIDE
☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
✓ORIGINAL NDA/BLA
☐ IND
☐ EFFICACY SUPPLEMENT
☐ SAFETY SUPPLEMENT
☐ LABELING SUPPLEMENT
☐ PLR CONVERSION

REASON FOR LABELING CONSULT
✓INITIAL PROPOSED LABELING
☐ LABELING REVISION

EDR link to submission: Available in DARRTS. Submission date: August 16, 2011

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [Insert Date] N/A

Labeling Meetings: [Insert Dates] To be scheduled

Wrap-Up Meeting: [Insert Date] N/A

SIGNATURE OF REQUESTER
Jeannie Roule

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) ☐ eMAIL ☐ HAND

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/s/

JEANNIE M ROULE
11/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Patient labeling Team

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products (DRUP)
301-796-3993

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/18/11		22309/S-001	NDA	8/16/11

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AndroGel 1.62% Topical Gel	S	androgen	01/15/12

NAME OF FIRM: Abbott Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review the Medguide, PI and/or carton/container for Supp #1 in DARRTS dated August 16, 2011

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Jeannie Roule	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

JEANNIE M ROULE
11/18/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: OSE-DRISK and DMEPA

FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products (DRUP)
301-796-3993

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
11/17/11		22309/S-001	NDA	8/16/11

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
AndroGel 1.62% Topical Gel	S	androgen	01/15/12

NAME OF FIRM: Abbott Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please review the Medguide, PI and/or carton/container for Supp #1 in DARRTS dated August 16, 2011

SIGNATURE OF REQUESTOR
Jeannie Roule

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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JEANNIE M ROULE
11/18/2011

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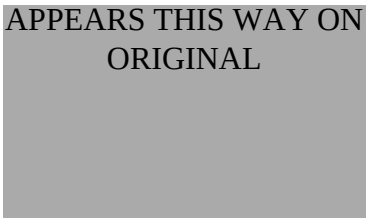

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