CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22309Orig1s000

OTHER REVIEW(S)

Attachment B: PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Hand washing trial following application of (b) (4)

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	July 2011
	Study/Clinical trial Completion Date:	October 2011
	Final Report Submission Date:	July 2012
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- ☐ Unmet need
- ☐ Life-threatening condition
- ☐ Long-term data needed
- ☐ Only feasible to conduct post-approval
- ☒ Prior clinical experience indicates safety
- ☐ Small subpopulation affected
- ☐ Theoretical concern
- ☐ Other

The male to female testosterone transfer studies demonstrated that the testosterone can be transferred by contact. In addition, there have been postmarketing reports of secondary exposure of testosterone to non-users including children. Testosterone transfer potential after the washing of primary user's hands to assess the risk of secondary testosterone exposure was not studied for AndroGel 1.62%. Therefore, hand washing trial following application of AndroGel 1.62% should be conducted as a PMR.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of this clinical trial is to evaluate potential secondary testosterone exposure following washing primary user's hands. Secondary exposure to testosterone can lead to hypertrophy of clitoris, coarsening of the voice, and excessive hair growth in females as well as advanced bone age, clitoromegaly, and penile enlargement in pediatrics.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☒ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☒ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☒ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A clinical trial that will measure the amount of residual testosterone before and after washing primary user's hands.

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☒ Other (provide explanation)

A clinical trial entitled "An Evaluation of the Effect of Hand Washing on the Amount of Residual Testosterone on the Hands after Application of Testosterone Gel 1.62%" to assess the amount of residual testosterone before and after washing primary user's hands.

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

☐ Other

5. Is the PMR/PMC clear, feasible, and appropriate?

☒ Does the study/clinical trial meet criteria for PMRs or PMCs?
☒ Are the objectives clear from the description of the PMR/PMC?
☒ Has the applicant adequately justified the choice of schedule milestone dates?
☒ Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:
☒*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

JEANNIE M ROULE
04/29/2011

AUDREY L GASSMAN
04/29/2011

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 22-309
APPLICANT	Abbott Products, Inc.
PRODUCT NAME	ANDROGEL (testosterone gel) 1.62%
SUBMISSION DATE	October 29, 2010 (clinical efficacy)
PDUFA DATE	April 29, 2011
SEALD SIGN-OFF DATE	April 28, 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Ann Marie Trentacosti for Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed April 26, 2011, have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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/s/

ANN M TRENTACOSTI
04/28/2011
Ann Marie Trentacosti for Laurie Burke

Department of Health and Human Services **Public Health Service** **Food and Drug Administration** **Center for Drug Evaluation and Research** **Office of Surveillance and Epidemiology**	
Date:	April 27, 2011
Application Type/Number:	NDA 022309
To:	Scott Monroe, MD, Director Division of Reproductive and Urologic Products
Through:	Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis (DMEPA)
From:	Irene Z. Chan, PharmD, BCPS, Team Leader Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Memo
Drug Name(s):	AndroGel (Testosterone Gel) 1.62% 20.25 mg of Testosterone per pump actuation
Applicant/sponsor:	Abbott
OSE RCM #:	2010-2433

MEMO TO FILE

Abbott submitted revised container labels and carton labeling on April 22, 2011, that incorporated all of DMEPA's previous recommendations. We find the revised labels and labeling acceptable, and we do not have any additional comments at this time.

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/s/

IRENE Z CHAN
04/27/2011

CAROL A HOLQUIST
04/27/2011

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 22-309
APPLICANT	Abbott Products, Inc.
PRODUCT NAME	ANDROGEL (testosterone gel) 1.62%
SUBMISSION DATE	October 29, 2010
PDUFA DATE	April 29, 2011 (clinical efficacy)
SEALD REVIEW DATE	April 26, 2011
SEALD LABELING REVIEWER	Jeanne Marie Delasko, RN, MS Label Initiatives Specialist

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission. **[JMDComment: A waiver has been granted.]**
- ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☒ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. (b) (4) [redacted]
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are

known, it must state “None”)
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**

  ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

- **Product Title**

  ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**

  ☒ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action. **[JMDComment: Initial U.S. approval does not appear to be immediately beneath the product title. There appears to be a space between the two lines.]**

- **Boxed Warning**

  ☐ All text in the boxed warning is **bolded**.

  ☐ Summary of the warning must not exceed a length of 20 lines.

  ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").

  ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary. **[JMDComment: Boxed Warning (BW) in HL is identical to BW in FPI.]**

- **Recent Major Changes (RMC)**

  ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

  ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."

  ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.

  ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.

☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

  ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☐ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

  ☐ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

  ☒ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide")**.

  (b) (4)

- **Revision Date**

☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.

☒ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI. (b) (4) [redacted]

☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.

☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

8.1 Pregnancy

8.3 Nursing Mothers (not 8.2)

8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

☒ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed." (b) (4) [redacted]

Full Prescribing Information (FPI)

- **General Format**

☐ A horizontal line must separate the TOC and FPI.

☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.

☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).
  - ☒ **[JMDComment: The boxed warning is in the center of the page and should be left justified.]**

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "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 clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these 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."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of

patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)"
- “See FDA-approved patient labeling (Instructions for Use)"
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

☒ (b) (4) [redacted]

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/s/

JEANNE M DELASKO
04/26/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: April 13, 2011

To: Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A., Regulatory Review Officer
Beth Carr, Pharm.D., Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Re: **NDA 022309**
DDMAC labeling comments for AndroGel (testosterone gel) 1.62% for topical use CIII

Background

This consult is in response to DRUP's November 16, 2010 request for DDMAC's review on labeling materials for AndroGel (testosterone gel) 1.62% for topical use CIII (AndroGel 1.62%). DDMAC has reviewed the following labeling materials for AndroGel 1.62%:

Healthcare Provider Directed:

- Prescribing Information (PI)
- 1.62% Front Label
- 1.62% Back Label
- 1.62% Carton Label
- 1.62% Placebo Front Label
- 1.62% Placebo Back Label
- 1.62% Placebo Carton Label
- 1.62% Professional Sample Front Label
- 1.62% Professional Sample Back Label
- 1.62% Professional Sample Carton Label

Consumer Directed:

- Medication Guide (MG)

Please note that our comments are based on the substantially complete version of the draft label sent to DDMAC on March 29, 2011. In addition, we have considered the AndroGel 1% PI and MG (approved March 2011), Axiron PI and MG (approved March 2011) and Fortesta PI and MG (approved December 2010) in our review of the draft AndroGel 1.62% labeling.

We offer the following comments:

(b) (4)

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
  (301) 796-3821, or janice.maniwang@fda.hhs.gov

- Beth Carr (Consumer directed materials)
  (301) 796-3674, or beth.carr@fda.hhs.gov

19 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (CCI/ TS) IMMEDIATELY FOLLOWING THIS PAGE

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/s/

JANICE L MANIWANG
04/13/2011

BETH M CARR
04/14/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date:	**April 11, 2011**
To:	Scott Monroe, MD., Director **Division of Reproductive and Urologic Products (DRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management (DRISK)** Melissa Hulett, MSBA, BSN, RN Patient Labeling Reviewer, Acting Team Leader **Division of Risk Management (DRISK)**
From:	Shawna Hutchins, MPH, BSN, RN Patient Labeling Reviewer **Division of Risk Management (DRISK)**
Subject:	DRISK Review of Patient Labeling (Medication Guide)
Drug Name (established name):	ANDROGEL 1.62% (testosterone gel)
Dosage Form and Route:	for Topical Use
Application Type/Number:	NDA 22-309
Applicant:	Abbott Products Inc.
OSE RCM #:	2010-2434

1 INTRODUCTION

This review is written in response to a request by the Division of Reproductive and Urologic Products (DRUP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG), for ANDROGEL 1.62% (testosterone gel) for topical use.

On October 25, 2010 the applicant's submitted NDA 22-309 for ANDROGEL 1.62% (testosterone gel) for topical use in the treatment of males with a deficiency or absence of endogenous testosterone.

DRISK's review of the applicant's proposed Risk Evaluation and Mitigation Strategy (REMS) will be provided under separate cover.

2 MATERIAL REVIEWED

- Draft ANDROGEL 1.62% (testosterone gel) Medication Guide (MG) received on October 29, 2010, and sent to DRISK on March 29, 2011.
- Draft ANDROGEL 1.62% (testosterone gel) Prescribing Information (PI) received on October 29, 2010, revised by the Review Division throughout the current review cycle, and received by DRISK on March 29, 2011.
- Approved comparator labeling for AXIRON (testosterone), dated November 23, 2010.

3 REVIEW METHODS

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 DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK 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
04/11/2011

LASHAWN M GRIFFITHS
04/11/2011

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 4, 2011

To: Scott Monroe, M.D., Director
Division of Reproductive and Urologic Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: James M. Tolliver, Ph.D., Pharmacologist, CSS

Subject: Consult on NDA 22-309 - AndroGel (testosterone gel)1.62% - Indicated for testosterone replacement therapy in hypogonadal males.
Sponsor: Unimed Pharmaceuticals

Materials reviewed: All materials submitted and comprising NDA 22-309.

Addendum

This memorandum is an addendum to a CSS consult review dated August 19, 2009, concerning NDA 22-309 for AndroGel (Testosterone gel) 1.62% indicated for testosterone replacement therapy in hypogonadal males. NDA 22-309 was originally submitted in February, 2009 and received a Complete Response letter in March, 2010. The application was resubmitted in October 2010. Based on reviews of material submitted in the new application and of the updated scientific and medical literature, the CSS scientific review and recommendations for labeling changes provided in the consult review, dated August 19, 2009, remain the same.

Background

The CSS review dated August 19, 2009, focused on the Sponsor's proposed draft label for AndroGel (testosterone gel) 1.62% under "9. DRUG ABUSE AND DEPENDENCE" which originally read as follows:

(b) (4)

(b) (4)

Along with the recommendation, CSS in its review provided a scientific rationale for the change in labeling.

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/s/

JAMES M TOLLIVER
04/04/2011

MICHAEL KLEIN
04/04/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 12, 2010
To:	Scott Monroe, MD, Director Division of Reproductive and Urologic Products
Through:	Kristina Arnwine, PharmD, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Division Director Division of Medication Error Prevention and Analysis
From:	Lori Cantin, RPh, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	AndroGel (Testosterone Gel), 1.62%
Application Type/Number:	NDA 22309
Submission Number:	N-000
Applicant:	Solvay Pharmaceuticals, Inc.
OSE RCM #:	2009-334

CONTENTS

EXECUTIVE SUMMARY

AndroGel 1.62% gel is a product line extension of AndroGel which is currently marketed as a 1% gel. AndroGel 1% has been marketed as a single-strength product since the year 2000. The introduction of a new concentration (1.62%) of AndroGel may result in increased confusion between the two AndroGel products (1% and 1.62%) if the labels and labeling do not adequately differentiate the two products. The Applicant has designed the labels to provide this differentiation, however, DMEPA has identified areas of needed improvement and has recommended additional revisions to the labels and labeling in order to minimize confusion and the risk of medication error.

Additionally, confusion may result if physicians, pharmacists, and other healthcare providers are not educated with respect to the availability of the co-marketing of the currently marketed AndroGel 1% product with the AndroGel 1.62% product, and the differences between the two products. In order to address the potential for confusion, the Applicant has included information in the launch plan which is intended to help mitigate potential risks to patients which might result from confusion on the part of physicians, pharmacists, or other healthcare providers with respect to the co-marketing of the currently marketed AndroGel 1% product with the AndroGel 1.62% product. DMEPA has reviewed the Applicant's proposed education and communication plan, and finds the plan acceptable with the revisions recommended based on new information submitted by the Applicant on November 6, 2009.

1 INTRODUCTION

The proposed product, AndroGel (Testosterone) Gel 1.62%, is a new strength in the AndroGel product line. AndroGel is currently marketed as a 1% Gel. AndroGel 1.62% has been formulated to be of a (b) (4), a reduced volume for application, and (b) (4) compared to the AndroGel 1% Gel.

1.1 PRODUCT INFORMATION

AndroGel 1% and 1.62% will have the same dosage form (topical gel) and indication (replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone). Both the 1% and 1.62% products will utilize the proprietary name, AndroGel. The two products will be differentiated by their packaging and each will have its own separate package insert.

The AndroGel 1.62% product has a (b) (4), a reduced volume for application, and (b) (4) (b) (4) as compared to the AndroGel 1% product. The two different concentrations will not be capable of delivering equivalent doses. For example, a 5 gm dose (4 pumps) of the 1% product will deliver 50 mg of testosterone, whereas a 5 gm dose (4 pumps) of the 1.62% product will deliver 81 mg of testosterone. The recommended doses for both AndroGel products are as follows:

ANDROGEL 1%		**ANDROGEL 1.62%**	
Daily Dose	**#of pump depressions**	**Daily Dose**	**#of pump depressions**
2.5 g (*25 mg)	2 (once daily)	1.25 g (*20.25 mg)	1 (once daily)
5 g (*50 mg)	4 (once daily)	2.5 g (*40.5 mg)	2 (once daily)
7.5 g (*75 mg)	6 (once daily)	3.75 g (*60.75 mg)	3 (once daily)
10 g (*100 mg)	8 (once daily)	5 g (*81 mg)	4 (once daily)

*****Amount of testosterone

The daily dose is to be applied to clean, dry, healthy, intact skin of either the shoulders/upper arms or abdomen. The dose should be adjusted to achieve and maintain serum testosterone levels in the normal range. Both strengths of AndroGel will be available in 75 g multi-dose pump capable of dispensing 60 metered 1.25 g doses. The AndroGel 1% product is also available in 2.5 g (25 mg of testosterone) and 5 g (50 mg of testosterone) unit-dose foil packets in cartons of 30.

New dosage and administration information was submitted by the Applicant on November 6, 2009, and provided for a dose-dependent number of application sites for administration. The proposed dosing and administration information is as follows:

(b) (4)

1.2 REGULATORY BACKGROUND

A pre-NDA meeting between the Applicant and FDA was held on January 22, 2008. FDA stated that there was no objection to co-marketing two strengths of AndroGel (1% and 1.62%). However, FDA did request that the applicant submit a plan to minimize dispensing and administration errors when the new 1.62% strength is introduced to the market.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) use Failure Mode and Effects Analysis[1] (FMEA) to evaluate the labels and labeling submitted as part of the February 11, 2009, submission. We also evaluated the revisions to the package insert labeling and medication guide that were submitted on November 6, 2009. Additionally, a search of the Adverse Events Reporting System (AERS) database was conducted to determine if medication errors related to the use of the currently marketed Angrogel 1% gel product have been reported, and the Applicant's proposed Education and Communication Plan was evaluated.

2.1 FDA'S ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE SEARCH

Because AndroGel is currently marketed in a 1% concentration, DMEPA conducted a search of the Adverse Events Reporting System (AERS) database to determine if medication errors related to the use of this product have been reported. The search was conducted on May 27, 2009 using the following terms: Trade Name "AndroGel" and Verbatim Name "Testoster%" (only gel products selected), and the MedDRA reactions "Medication Errors" (HLGT) and "Pharmaceutical Product Complaint" (PT).

The reports were manually reviewed to determine if a medication error occurred. Those reports that did not describe a medication error with AndroGel were excluded from further analysis. If an error occurred, the staff reviewed the case to determine if the root cause could be associated with the labels or labeling of the product, and thus pertinent to this review. The cases that described a medication error possibly relevant to this review of this product were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

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

2.2 EDUCATION AND COMMUNICATION PLAN

DMEPA reviewed the Applicant's proposed Education and Communication Plan, which is intended to help mitigate potential risks to patients which might result from confusion on the part of physicians, pharmacists, or other healthcare providers with respect to the co-marketing of the currently marketed AndroGel 1% product with the AndroGel 1.62% product.

3 RESULTS

3.1 AERS RESULTS

The FDA Adverse Event Reporting System (AERS) search retrieved a total of 11 reports involving AndroGel. Eight (8) of these reports were excluded from further analysis because these cases described adverse events or product quality issues that resulted in lack of therapeutic effect.

The remaining 3 reports involved postmarketing medication errors related to AndroGel. Two (n=2) reports were complaints concerning the product labeling for the AndroGel 1%, 2.5 g and 5 g packets, and one (n=1) report describes a wrong route of administration.

3.1.1 Complaints Due To Product Labels and Labeling (n=2)

Two (n=2) cases describing confusing labeling were reported in 2000 and 2004. In the first case, the reporter stated that both the 2.5 g and 5 g packets are labeled as AndroGel 1%, which could lead to confusion. The 2.5 g and 5 gm unit dose packets are, in fact, both labeled as AndroGel 1%, but the carton labeling and container labels indicate that the unit dose packets contain 2.5 g and 5 g, respectively. Additionally, the two sizes are differentiated with different colored packaging.

In the second case, the reporter cited that there was a potential for confusion between the AndroGel 1% Gel 5 g unit dose packet,and the Testim (Testosterone) 1% gel, single-use tube because the AndroGel 1% product is labeled according to the total weight of the product (5 g), while the Testim 1% product is labeled according to weight of the active ingredient (50 mg). Both products have a total weight of 5 g and are labeled 1%.

3.1.2 Wrong Route of Administration (n=1)

One case was reported in 2004, and involved a patient who administered AndroGel 1% subcutaneously into his penis and testicles. The patient had been receiving AndroGel 1% Gel topically prior to this event, but this product was discontinued after the patient experienced a skin reaction and the patient was started on testosterone injections. The patient developed a wound at the site of the subcutaneous injection of AndroGel, which required hospitalization and intravenous antibiotics. The case report does not provide any information as to why the patient injected the AndroGel 1% product subcutaneously.

3.2 EDUCATION AND COMMUNICATION PLAN

The Applicant proposes to use the proprietary name 'AndroGel' for both the currently marketed 1% gel product and the proposed 1.62% gel product. To minimize confusion between these strengths, the Applicant proposed including information in the Education and Communication Plan. This multi-pronged, education plan that is aimed at providing targeted healthcare providers with the necessary information to understand the addition of the new, low volume AndroGel 1.62% formulation, as well as the differences between this new product and the currently marketed AndroGel 1% gel product.

The plan consists of 3 components: A communication strategy, labeling and packaging differentiation, and an assessment of the effectiveness of education and communication plan.

3.2.1 Communication Strategy

The goal of the proposed communication strategy is to target healthcare professionals including physicians, pharmacists, and other healthcare practitioners. Specific messages will be designed to educate physicians and pharmacists on how to correctly prescribe and dispense the two strengths of AndroGel. Ongoing personal communication between healthcare providers that are directly and indirectly involved with the prescribing and dispensing of AndroGel and the Solvay sales force is planned. The proposed elements of the plan were described by the Applicant, however, the actual communication materials were not submitted. The specific elements of this plan include an MD-Alert Mailer, an MD-Alert Fax Blast, Professional Journal Advertising, Pre-scripted Script Pads, Physician Office Shelf-Talkers, Pharmacist-Alert Mailer, Pharmacist-Alert Fax Blast, Pharmacy Journal Advertising, Pharmacy Ordering System Advertisement, Pharmacy Shelf Talkers, Pharmacy Wholesaler Website & Software Updates, an AndroGel 1% and AndroGel 1.62% Visual Comparison Chart, AndroGel.com Website Updates, Journal Belly Bands, ePocrates Electronic DocAlerts, and Physician Web Banners. The details of the proposed communication strategy are provided in the NDA submission dated February 11, 2009.

3.2.2 Labeling and Packaging Differentiation

The Applicant has proposed container labels and carton labeling intended to provide visual differentiation of the new AndroGel 1.62% product from the currently marketed AndroGel 1% product. Additionally, each product will have its own individual package insert (see Appendix A for a comparison of the AndroGel 1% and AndroGel 1.62% container labels and carton labeling). The results of DMEPA's review of the proposed container labels and carton labeling are contained in Section 3.3.

3.2.2.1 Container Labels and Carton Labeling

The product strengths (1% and 1.62%) are not displayed with sufficient prominence, particularly for the 1% product. The prominence of the strength becomes more important with the availability of a second strength of AndroGel on the market.

The intended space for the bearing of the required expiration date is not specified on the proposed labels and labeling. 21 CFR 201.17 requires that the expiration date appear on the immediate container and carton label.

The NDC number is displayed at the bottom of the principal display panel of the carton labeling and is not displayed on the immediate container label's principal display panel. Per 21CFR 207.35(b)(3)(i), if the NDC number is shown on a drug label, it shall be placed in the top third of the principal display panel of the immediate container and of any outside container or wrapper. The NDC number is also displayed as part of the bar-code symbol. If the NDC number is to appear as part of the bar-code symbol, it must be displayed prominently on both the immediate container and on any outside container or wrapper, as required by regulation.

Based on the new information submitted in an amendment on November 6, 2009, the dosing table on the container label and carton labeling should be revised to reflect the number of application sites required for each dose.

3.2.2.2 Package Insert Labeling

In Section 2 (DOSAGE AND ADMINISTRATION) of the Full Prescribing Information, Table 2 does not specify that the dosing information is for the 1.62% product. Although the package insert is specific to the AndroGel 1.62% product, adding the strength of the product to the table header will increase clarity and decrease the potential for errors when prescribing, particularly if the package insert labeling is accessed via the internet (e.g., the prescriber intended to select the labeling for AndroGel 1%, but had selected the labeling for the AndroGel 1.62% product in error).

3.2.3 Assessment of Education and Communication Plan Effectiveness

The Applicant proposes to monitor the effectiveness of the targeted interventions through the use of spontaneous medication error reports submitted to Solvay's Global Drug Safety and Surveillance system. The results of the interventions will be assessed on an ongoing basis, evaluated at the end of six months, and adjusted as needed.

4 DISCUSSION

The Applicant proposes to market a new 1.62% strength of AndroGel (testosterone gel). Currently the Applicant markets AndroGel in a 1% strength, and is proposing to market both concentrations of testosterone gel using the same proprietary name, AndroGel. In order to minimize confusion between the 1% and 1.62% strengths, the Applicant proposes an education and communication plan, as well as differentiating the labeling and packaging for the two strengths.

4.1 PROPRIETARY NAME

AndroGel 1.62% is an extension of the existing AndroGel product line. The two products will be differentiated by the different strengths (1% and 1.62%). In evaluating the proposed proprietary name, AndroGel, for the 1.62% product, we have considered whether the product line could be safely managed using the same proprietary name, and have assessed the risk of medication error due to confusion between the two AndroGel products.

One important difference between AndroGel 1% and AndroGel 1.62% relates to the risk of transfer to other individuals. For the currently marketed AndroGel 1% product, patients can minimize the transfer of testosterone to others (including women and children) by washing their hands with soap and water after application of AndroGel 1% and by covering the application site with clothing after the application site dries. However, during the review of this application, the Division of Reproductive and Urology Products (DRUP) noted that transfer of testosterone to others was not adequately blocked by wearing a T-shirt with doses of AndroGel 1.62% greater than 2.5 g. Data submitted by the Applicant showed that transfer could, however, be prevented by washing the site(s) in a shower prior to physical contact with others. As patient compliance with thorough washing is considered to be an issue, DRUP does not believe that washing in a shower is a feasible means of preventing product transfer, and that patients are unlikely to comply.

In response to DRUP's concerns regarding this new step, the Applicant conducted a study (protocol S176.1.009) and submitted these results on November 6, 2009. The data from this study showed that application of doses to a greater number of application sites (three sites for a 3.75 g dose and four sites for a 5 g dose) successfully mitigated transfer through a T-shirt, without the need to wash the application site. The Applicant also submitted revisions to the sections of the labeling, (b) (4) Based on this information, DMEPA agrees that the use of the proprietary name 'AndroGel' is acceptable for the 1.62% product. However, if the Dosage and Administration section or other product characteristics change, we rescind this finding and would have to re-evaluate the acceptability of the AndroGel name for the 1.62% product.

4.2 LABELS AND LABELING

With respect to the container labels and carton labeling for the AndroGel products, DMEPA believes that the proposed design of the trade dress aimed at distinguishing these products is not adequate. A more distinctive trade dress is needed in order to minimize anticipated selection errors. Increasing the prominence of the product strength for the AndroGel 1.62% product would highlight this information and further differentiate the proposed 1.62% product from the currently marketed 1% product. A statement

indicating the amount of testosterone per each pump actuation would also help to highlight the difference between the two different strengths of AndroGel.

Upon review of the AndroGel 1% labeling, DMEPA noted that the number of application sites is not correlated with the dose. DMEPA recommends that the Applicant revise the labeling for AndroGel 1% to specify the number of application sites that would be required for each dose, as was done for AndroGel 1.62% in the labeling revisions submitted on November 6, 2009. Also, we would recommend a statement be included in the Highlights, Dosage and Administration, and FDA-Approved Medication Guide sections of the package insert labeling for the 1% and 1.62% products stating that the number of application sites depends on the strength of product to be administered. By including such a statement, errors in administration can be prevented if a patient or healthcare practitioner is consulting electronic or other sources of drug information for the administration of AndroGel 1% product when the AndroGel 1.62% product is prescribed, and vice versa.

Although the Education and Communication Plan appears to be comprehensive to introduce the AndroGel 1.62% product overall, DMEPA would recommend revisions to the education and communication plan to inform practitioners that the dose of AndroGel 1% or 1.62% will determine the number of application sites. We have provided recommendations as to how to improve the proposed design of the labels and labeling in order to better differentiate these two products in Section 5.3.

4.3 EDUCATION AND COMMUNICATION PLAN

To minimize dispensing and administration errors when the new 1.62% strength is introduced to the market, the Applicant has submitted an education and communication plan that is aimed at educating physicians and pharmacists as to the differences between AndroGel 1% and AndroGel 1.62% in order to minimize the risk of medication errors within the AndroGel product line. The new 1.62% strength provides for delivery of a higher concentration, and therefore a higher dose, of testosterone per each pump actuation. For example, a 5 gm dose (4 pumps) of the 1% product will deliver 50 mg of testosterone, whereas a 5 gm dose (4 pumps) of the 1.62% product will deliver 81 mg of testosterone. Since both products will be marketed concurrently, there is a need to educate healthcare providers about these product differences, and to minimize selection error that may occur within this product line. The Applicant proposes to utilize several different tools, including MD and Pharmacist Alert Mailers and Alert Fax Blasts, professional journal advertising, pre-printed script pads, physician and pharmacy shelf-talkers, pharmacy ordering system advertising, pharmacy wholesaler website and software updates, AndroGel.com website updates, and ePocrates DocAlerts to communicate this information to healthcare providers. DMEPA thinks this plan should help to increase practitioner awareness of the products, which may help to achieve the sponsor's goal of reducing the risk of medication errors.

5 CONCLUSIONS AND RECOMMENDATIONS

The proposed labels and labeling require improvement to minimize the risk of confusion within the AndroGel product line. If these changes are implemented and the launch plan is implemented, we are satisfied that the risk of confusion between AndroGel 1% and 1.62% should be minimized. We provide recommendations on the insert labeling in Section 5.1 *Comments to the Division* and in Section 5.2 *Comments to the Office of New Drug Quality Assessment.* Section 5.3 *Comments to the Applicant* contains our recommendations for the container labels and carton labeling. We request the recommendations in Section 5.3 be communicated to the Applicant.

We would be willing to meet with the Division for further discussion, if needed. 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 the please contact Maria Wasilik, OSE Project Manager, at 301-796-0567.

5.1 COMMENTS TO THE DIVISION

5.1.1 Insert Labeling for AndroGel 1.62%

1. DMEPA recommends that the header for the Table titled "Dosing Information for the 75 g Multi-Dose Pump" in the Highlights, Dosage and Administration, and FDA-Approved Medication Guide sections include the strength of the product in order to improve clarity and minimize the potential for errors when prescribing.

2. In addition to the proposed table referred to in number 1 above, DMEPA recommends a statement be included in the Highlights, Dosage and Administration, and FDA-Approved Medication Guide sections stating that the number of application sites is also dependent on the strength of AndroGel product to be administered.

5.1.2 Labels and Labeling for the AndroGel 1% Product

The Applicant plans to manage both 1% and 1.62% products under the proprietary name "AndroGel", thus it is important to differentiate the proposed labels for the 1.62% product from the currently marketed labels for the 1% product. Revisions to the labels and labeling for the currently marketed product (AndroGel 1%) will be needed in order to inform healthcare providers of the differences in the amount of testosterone between the two AndroGel products, and to adequately differentiate the two different product strengths. We request that the Applicant submit a prior approval labeling supplement to NDA 21-015 to address this issue. This prior approval supplement for AndroGel 1% should be approved at the same time as the NDA for AndroGel 1.62%. The following revisions are requested:

1. Increase the prominence of the product strength for the AndroGel 1% product on the container label and carton labeling in order to highlight this information and further differentiate the 1% and 1.62% products. The prominence of the product strength on the labels and labeling will become more important with the availability of a second strength of AndroGel on the market.

2. Add a statement the container label and carton labeling to inform healthcare providers of the actual amount of testosterone delivered for each actuation. For example, "Each actuation delivers XXXX of testosterone." This information is necessary to show that the actual amount of testosterone per each pump actuation of 1.25 grams delivers a different amount of testosterone for the 1% and 1.62% products.

3. Based on the new information submitted by the Applicant on November 6, 2009, DMEPA recommends that the dosing table on the container label and carton labeling be revised to reflect the number of application sites required for each dose of AndroGel 1%.

4. DMEPA recommends that the Highlights, Dosage and Administration, and FDA-Approved Medication Guide sections of the package insert labeling for the AndroGel 1% product be revised to include a table similar to the "Dosing Information for the 75 g Multi-Dose Pump" Table proposed for AndroGel 1.62%, that specifies the number of administration sites for each prescribed dose.

5. In addition to the table referred to in number 4 above, DMEPA recommends a statement be included in the Highlights, Dosage and Administration, and FDA-Approved Medication Guide sections stating that the number of application sites is also dependent on the strength of AndroGel product to be administered.

5.2 COMMENTS TO THE APPLICANT FOR THE ANDROGEL 1.62% PRODUCT

1. The placement of the NDC number on the drug labels is not in accordance with 21 CFR 207.35(b)(3). Revise these labels accordingly.

2. Increase the prominence of the product strength for the AndroGel 1.62% product in order to highlight this information and further differentiate the proposed 1.62% product from the currently marketed 1% product. It is important to highlight this difference in strength so selection errors are minimized during the co-marketing of these two products. The prominence of the product strength on the labels and labeling will become more important with the availability of a second strength of AndroGel on the market.

3. Add a statement to inform healthcare providers of the actual amount of testosterone delivered for each actuation. For example, "Each actuation delivers XXXX of testosterone." This information is necessary to show that the actual amount of testosterone per each pump actuation of 1.25 grams delivers a different amount of testosterone for the 1% and 1.62% products.

4. Ensure that the expiration date appears on the immediate container label and carton labeling as required by 21 CFR 201.17. The intended space for the bearing of the required expiration date is not specified on the proposed labels and labeling.

5. Based on the new information submitted in your amendment dated November 6, 2009, revise the dosing table on the container label and carton labeling to reflect the number of application sites required for each dose of AndroGel 1.62%, or alternatively (if space is an issue), eliminate the chart and refer the user to the package insert for complete dosing information.

6. Revise the originally submitted education and communication plan to include the new information regarding the recommended number of application sites for each prescribed dose of AndroGel.

6 REFERENCES

ADVERSE EVENTS REPORTING SYSTEM (AERS)

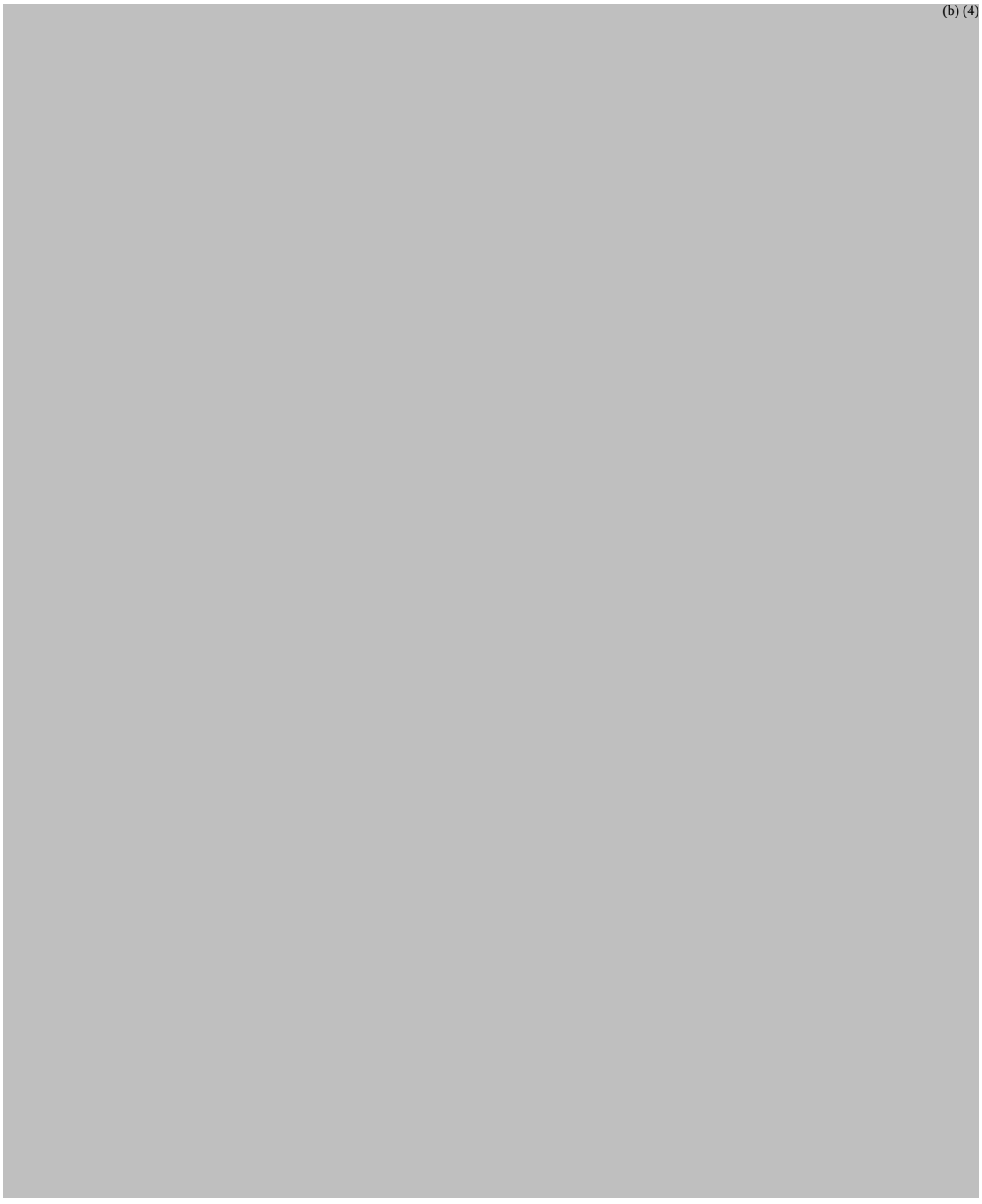
AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

7 APPENDICES

Appendix A: Comparison of Labels and Labeling for AndroGel 1% and AndroGel 1.62%

Front and Back Container Labels

(b) (4)



5 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS b4 (TS/ CCI) IMMEDIATELY FOLLOWING THIS PAGE

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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

/s/

LORI G CANTIN
03/12/2010

KRISTINA C ARNWINE
03/12/2010

DENISE P TOYER
03/12/2010

CAROL A HOLQUIST
03/12/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 26, 2010
To:	Scott Monroe, M.D., Division Director **Division of Reproductive and Urologic Products (DRUP)**
Through:	Mary Willy, PhD, Deputy Division Director **Division of Risk Management (DRISK)**
From:	LaShawn Griffiths, MSHS-PH, BSN, RN Patient Product Information Reviewer, Acting Team Leader **Division of Risk Management (DRISK)** Melissa Hulett, MSBA, BSN, RN Patient Product Information Reviewer **Division of Risk Management (DRISK)**
Subject:	Memo to File re: Review of Patient Labeling (Medication Guide)
Drug Name(s):	ANDROGEL 1.62% (testosterone gel)
Application Type/Number:	NDA 22-309
Applicant/sponsor:	Unimed Pharmaceuticals Inc.
OSE RCM #:	2009-334

The Division of Reproductive and Urologic Products (DRUP) requested that the Division of Risk Management review proposed patient labeling for New Drug Application (NDA) 22-309 submitted by Unimed Pharmaceuticals for ANDROGEL 1.62% (testosterone gel).

DRUP does not plan to address labeling during this review cycle; therefore, we will defer our review of the Medication Guide until such time as the review division plans to address labeling. Please send us a new consult request at that time. This memo serves to closeout the consult request for ANDROGEL 1.62% (testosterone gel).

Please let us know if you have any questions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

MELISSA I HULETT
02/26/2010

MARY E WILLY
02/26/2010
I concur

MEMORANDUM

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

DATE: November 9, 2009

TO: Scott Monroe, MD,
Director
Division of Reproductive and Urologic Products

Dennis Bashaw, Pharm.D.,
Director
Division of Clinical Pharmacology III

FROM: Xikui Chen, Ph.D.
Division of Scientific Investigations

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau 11/9/09
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-309 Testosterone Gel, 1.62%, Sponsored by Solvay Pharmaceuticals, Inc.

At the request of Division of Clinical Pharmacology III, the Division of Scientific Investigations audited the analytical portion of the following bioequivalence study:

> **Study# S176.3.104:** "A multi-center, randomized, double-blind, placebo-controlled efficacy and safety study of testosterone gel 1.62% for the treatment of hypogonadal men"

The analytical portion of the study was conducted at (b) (4) (b) (4) Following the inspection of (b) (4) (b) (4), Form FDA-483 was issued. Our evaluation of the objectionable findings is the following:

1. The same integration parameters were not applied to all the samples for assay of dihydrotestosterone in the bioanalytical runs 2SFT-A, 4SFT-A, 5SFT-B, 6SFT-A, 7SFT-A, 9SFT-A, 11SFT-A, 13SFT-A, 15SFT-A, and 56SFT-A.

The integration parameters for dihydrotestosterone were modified in a few samples in the runs 2SFT-A, 4SFT-A, 5SFT-B, 6SFT-A, 7SFT-A, 9SFT-A, 11SFT-A, 13SFT-A, 15SFT-A, and 56SFT-A. Although not applied consistently, DSI found that the modified integration parameters were used to adjust the baseline or select a proper integration for split peaks. As the quality control samples or calibration standards were not subjected to the modified integrations, it did not affect the run acceptability. No significant bias in data reporting was noted during the inspection.

2. No audit trail exists for run 33SFT-B and run 21SFT-A in Analyst. The audit trail for run 21SFT-B is named 21SFT-A.rdb. Modification of sample number SFT 4838 was not captured in the audit trail for run 11SFT-A. The audit trail in Analyst did not capture the change to sample number TFT 10866 in run 72TFT-A.

Although there was no audit trail in the 'Analyst' software for run 33SFT-B, the electronic data were available during the inspection. The audit trail for the re-injection run 21SFT-B was found under the original run 21SFT-A. Moreover, the audit trail in the 'Analyst' software did not capture the changes to sample numbers SFT 4838 for testosterone and TFT 10866 for estradiol. However, the changes were captured in the prints of the chromatograms in the study file. During the inspection, the firm was informed that the sources for these mistakes should be identified and corrected.

3. There was an error in Table 8 of the analytical report number S176.3.104.B1 for reported results of the samples SFT 460, SFT 532, SFT 620, and SFT 687.

The correct results for these samples were provided in the Table 20 of the analytical report. The firm should implement procedures to avoid such mistakes in their study reports.

Conclusion:

Following the above inspection, DSI recommends that the analytical portion of study S176.3.104 is acceptable for review.

Please note that DSI has not yet received a response from (b)(4) to the Form FDA-483. We will update the review division if our recommendation is affected by the response.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Xikui Chen 11/9/09
Xikui Chen, Ph.D.

Final Classification:

VAI – (b) (4)

cc:
DSI/GLPBB/Rivera-Lopez/CF
DSI/Viswanathan/Chen/Yau
OND/ODE3/Jeannie Roule
OTS/OCP/DCP3/Sandhya Apparaju

By Email:
CDER DSI PM TRACK
HFR-CE2545/Dianne Milazzo

Draft: XC 11/4/09
Edit: MKY 11/5/09
DSI: 5951; O:\Bioequiv\EIRCover\22309sol.tes.doc
FACTS: 1045025

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22309	ORIG-1	UNIMED PHARMACEUTICALS INC	ANDROGEL

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/s/

XIKUI CHEN
11/09/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

PRE-DECISIONAL AGENCY MEMO

Date: October 6, 2009

To: Jeannie Roule
Regulatory Project Manager
Division of Reproductive and Urologic Products (DRUP)

From: Janice Maniwang, Pharm.D., M.B.A.
Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Carrie Newcomer, Pharm.D.
Regulatory Review Officer
DDMAC

Re: **NDA 22-309**
DDMAC labeling comments for AndroGel® (testosterone gel) 1.62%

DDMAC has reviewed the proposed product labeling (Package Insert (PI) and Medication Guide (Med Guide) for AndroGel 1.62%, submitted on February 11, 2009 by the sponsor.

The purpose of the proposed labeling is to reflect changes regarding a new strength and the addition of a boxed warning. Please note that our comments are based on the draft label sent to DDMAC on September 18, 2009 (**document title: PI from Sept 3.doc)**. In addition, we have considered the AndroGel 1% PI (approved September 18, 2009) and Testim 1% PI (approved September 18, 2009) in our review of the draft AndroGel 1.62% PI. DDMAC's comments are provided directly in the attached document (see below).

DDMAC appreciates the opportunity to provide comments on these materials. If you have any questions, please contact:

- Janice Maniwang (Professional directed materials)
  (301) 796-3821, or janice.maniwang@fda.hhs.gov

- Carrie Newcomer (Consumer directed materials)
  (301) 796-1233, or carrie.newcomer@fda.hhs.gov

DDMAC has reviewed the proposed Medication Guide for AndroGel (testosterone gel) 1.62%. Our comments are based on the version of the proposed Medication Guide received on September 22, 2009.

(b) (4)

Thank you. If you have any questions, please contact Carrie Newcomer at 301.796.1233 or Carrie.Newcomer@fda.hhs.gov

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/s/

JANICE L MANIWANG
10/06/2009

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: August 19, 2009

To: Scott Monroe, M.D., Director
Division of Reproductive and Urologic Products

Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff (CSS)

From: James M. Tolliver, Ph.D., Pharmacologist, CSS

Subject: Consult on NDA 22-309 - AndroGel (testosterone gel)1.62% - Indicated for testosterone replacement therapy in hypogonadal males.
Sponsor: Unimed Pharmaceuticals

Materials reviewed: All materials submitted and comprising NDA 22-309.

Background:

The Division of Reproductive and Urologic Products has submitted a consult concerning NDA 22-309 to CSS requesting verification on the scheduling status of AndroGel (testosterone gel) 1.62% and an assessment of the labeling for AndroGel (testosterone gel) 1.62% as it applies to abuse and dependence. NDA 22-309 was submitted to the FDA in February 2009 by Solvay Pharmaceuticals on behalf of Unimed Pharmaceuticals, LLC.

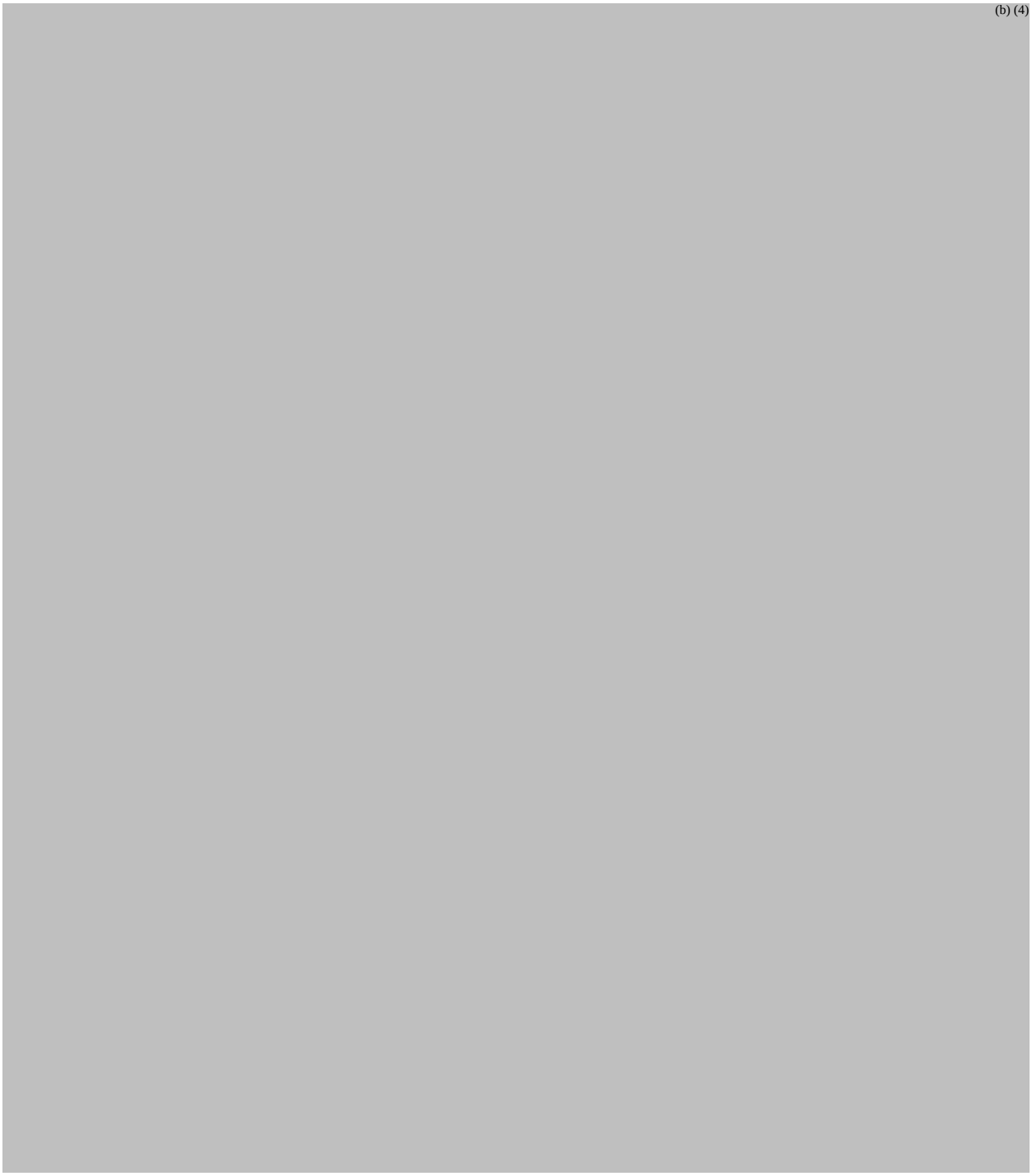
AndroGel 1.62% is a clear, colorless hydroalcoholic gel containing 1.62% testosterone. The AndroGel 1.62% doses 1.25 g, 2.5 g, 3.75 g or 5 g contain 20.25 mg, 40.5 mg, 60.75 mg or 81 mg of testosterone, respectively. It is intended for testosterone replacement therapy in males with a deficiency or absence of testosterone resulting from either primary or secondary hypogonadism (congenital or acquired). The recommended starting dose is 2.5 g applied once daily to dry, healthy, intact skin of either the shoulders/upper arms (b) (4). AndroGel 1.62% will be supplied in a non-aerosol, metered-dose pump containing (b) (4) of AndroGel 1.62% and capable of dispensing 75 g or 60 metered 1.25 doses.

CSS Review and Recommendations

Testosterone, and therefore the product AndroGel 1.62%, is in Schedule III of the Controlled Substances Act. Testosterone is specifically designated a Schedule III anabolic steroid under 21 U.S.C. 802(41)(A)(xlvii).

Labeling of AndroGel (testosterone gel)1.62%

(b) (4)



Discussion

With respect to scheduling status, we recommend that the label states that Androgel 1.62& is in Schedule III under the Controlled Substances Act, and not under the Anabolic Steroids Control Act. This latter legislation simply amended the Controlled Substances Act to place anabolic steroids, including testosterone and its esters into Schedule III.

(b) (4)

We recommend that some general class information regarding anabolic steroid abuse and dependence be added to the Abuse and Dependence section of the label. This information would at least alert the reader that abuse and dependence development is a possibility and should be considered when they store, dispense or use an anabolic steroid. Similar general information is recommended for the labeling of other products containing testosterone and other anabolic steroids.

Over the years, a considerable scientific and medical literature has accumulated documenting the abuse of anabolic steroids by athletes and bodybuilders; patterns of abuse and physical and psychiatric adverse effects are described. Several recent review articles on this topic include Brower (2002), Hartgens and Kuipers (2004), Trenton and Currier (2005), and Pope and Brower (2009). In addition, there is evidence that abuse of high doses of anabolic steroids can lead to dependence. A number of studies with athletes using high doses of anabolic steroids examine dependence according to the DSM diagnostic criteria for substance abuse dependence (Brower et al, 1991; Gridley and Hanrahan, 1994; Pope and Katz, 1994; Malone et al., 1995; Copeland et al., 1998; Midgley et. al., 1999; Perry et al, 2005; and Kanayama et al., 2009). In addition, a specific withdrawal syndrome upon termination of prolonged high dose anabolic steroids is identified. Recently, a group of researchers published a paper in the American Journal of Psychiatry suggesting the future addition in DSM-V of specific diagnostic criteria for dependence to anabolic-androgenic steroids (Kanayama et al., 2009). Recent review articles concerning dependence on anabolic steroids include Brower (2002), Pope and Brower (2009), Quaglio et al, 2009 and Wood (2008).

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/s/

JAMES M TOLLIVER
08/19/2009

SILVIA N CALDERON
08/19/2009

MICHAEL KLEIN
08/19/2009