

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203098Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

| Application Information | | |
|---|--|------------------------------|
| NDA # 203098 | NDA Supplement #: S- | Efficacy Supplement Type SE- |
| Proprietary Name: N/A Established/Proper Name: testosterone gel Dosage Form: gel Strengths: Packets containing 25 mg of testosterone per packet Packets containing 50 mg of testosterone per packet Pump that dispenses 60 metered 12.5 mg doses of testosterone | | |
| Applicant: Perrigo Israel Pharmaceuticals Ltd | | |
| Date of Receipt: Resubmission received August 1, 2012 (Original submission was received on July 5, 2011 and a CR letter sent on May 3, 2012). | | |
| PDUFA Goal Date: February 1, 2013 | Action Goal Date (if different): January 31, 2013 | |
| Proposed Indication(s): Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: | | |

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

| Source of information* (e.g., published literature, name of referenced product) | Information provided (e.g., pharmacokinetic data, or specific sections of labeling) |
|---|---|
| Published Literature | Non-Clinical Labeling |
| Androgel 1% (NDA 21015) | Efficacy and some safety. The Applicant did their own transfer, washing and |

| | |
|--|--|
| | application site studies which will be reflected in their label. |
| | |

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

A single-dose, three way-crossover BE study was conducted in 24 hypogonadal men to compare the Sponsor’s Testosterone gel product and the reference listed drug (AndroGel® 1%). The Office of Clinical Pharmacology concludes that the Sponsor has adequately bridged the proposed product to the referenced product.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If “NO,” proceed to question #5.

If “YES”, list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If “NO,” proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

| Name of Drug | NDA/ANDA # | Did applicant specify reliance on the product? (Y/N) |
|--------------|------------|--|
| Androgel 1% | 021015 | Y |
| | | |

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

- d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

- i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If

a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

- 9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

It is understood from the Citizen’s Petitions in 2009 and 2010 that a testosterone transdermal gel product in which the formulation uses different inactive ingredients, including but not limited to different (b) (4) (see below), from those in the reference listed drug (RLD) can not be submitted as an ANDA. The active ingredients, the route of administration, the dosage form and strength of the proposed drug product are the same as those of the RLD. Information provided by the applicant demonstrates that the proposed drug product provides sufficiently comparable exposures to the RLD drug is provided in the application. In addition, transfer and hand-washing studies have been required and completed and demonstrate acceptable safety. According to CDER’s responses to the Citizen’s Petitions in 2009 and 2010, this application must be submitted as a (b)(2) application.

Because transfer and washing studies were necessary for approval, it became a 505 b2. In addition, the Sponsor used a different penetration enhancer.

The only difference between Perrigo’s formulation and that of the RLD is that the RLD contains isopropyl myristate and the Perrigo formulation contains isotearic acid.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

- 10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s): Pharmaceutical equivalent(s):
NDA 021454, Testim 1% transdermal gel, Auxilium Pharmaceuticals
NDA 202763, testosterone gel, Teva Pharmaceuticals

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): 6503894 (expires 8/30/20)
6503894*PED (expires 3/31/21)

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

- No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the

NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s): 6503894 and 6503894*PEDS
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO
If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO
If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):
*Proof of notification was submitted to this NDA on 11/21/11.
The proof of notification dates are: 9/21/11, 9/22/11, 9/23/11, 9/26/11, and 9/27/11*

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

The patent infringement lawsuit was dismissed on December 22, 2011, in the US District Court of New Jersey.

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

/s/

JEANNIE M ROULE
01/31/2013

**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**

Labeling Memo

Date: January 31, 2013

Reviewer: 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

Drug Name: Testosterone Gel
12.5 mg per actuation Metered-Dose Pump,
25 mg Unit-Dose Packet, and 50 mg Unit-Dose Packet

Application Type/Number: NDA 203098

Applicant: Perrigo

OSE RCM #: 2012-2211

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

1 INTRODUCTION

This memo responds to a request from the Division of Reproductive and Urologic Products (DRUP) for a review of the revised labels and labeling for Testosterone by Perrigo. DMEPA initially reviewed the labels and labeling submitted on August 1, 2012 and September 20, 2012 and provided comments to the Division for the applicant via email on December 11, 2012 (see Appendix A for recommendations) . The Applicant responded to the recommendations and submitted revised carton labeling, container labels, insert labeling, and medication guide labeling on January 25, 2013.

2 MATERIAL REVIEWED

DMEPA reviewed the labels and labeling submitted on January 25, 2013 (see Appendix B).

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised labels and labeling show that they Applicant implemented all of DMEPA's previous recommendations and we find the revisions acceptable. We have no additional recommendations at this time.

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 on this review, please contact the OSE Regulatory Project Manager, Shawnetta Jackson at 301-796-4952.

Appendix A: Label and labeling comments provided to the Division of Reproductive and Urologic Products via e-mail on December 11, 2012

A. Container Label for the Metered-Dose Pump

1. Delete (b) (4) from the principal display panel. Retain the smaller net quantity statement on the back panel.
2. Incorporate the statement to read "Multi-dose pump capable of dispensing 60 metered pump activations" on the principal display panel, so healthcare personnel can calculate the number of days supply a pump can provide based upon the daily dose.

B. Carton Labeling for the Metered-Dose Pump

Incorporate the statement "Multi-dose pump capable of dispensing 60 metered pump activations" on the principal display panel, back panel, and side panel with the dosing chart so healthcare personnel can calculate the number of days supply a pump can provide based upon the daily dose.

5 Pages of Draft Labeling have been
Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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

/s/

ZACHARY A OLESZCZUK on behalf of TERRI WOOD-CUMMINGS
01/31/2013

ZACHARY A OLESZCZUK
01/31/2013

ADDENDUM

FOOD AND DRUG ADMINISTRATION

Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research

Date: January 25, 2013

From: Jeffrey Bray, Ph.D., Pharmacologist

To: NDA 203098

Subject: Final Labeling

Pharm/Tox has reviewed the final submitted labeling and finds it acceptable.

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

/s/

JEFFREY D BRAY
01/25/2013

LYNNDA L REID
01/28/2013
I concur

SEALD Director Sign-Off Review of the End-of-Cycle Prescribing Information: Outstanding Format Deficiencies

| | |
|--|---|
| Product Title | TESTOSTERONE gel, for topical use, CIII |
| Applicant | Perrigo-Israel Pharmaceuticals Ltd. |
| Application/Supplement Number | NDA 203098, (b) (4) |
| Type of Application | Resubmission Class 2 |
| Indication(s) | For replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: <ul style="list-style-type: none"> • Primary Hypogonadism (Congenital or Acquired) • Hypogonadotropic Hypogonadism (Congenital or Acquired) |
| Established Pharmacologic Class ¹ | Androgen |
| Office/Division | ODE III/DRUP |
| Division Project Manager | Jeannie Roule |
| Date FDA Received Application | August 1, 2012 |
| Goal Date | February 1, 2013 |
| Date PI Received by SEALD | January 9, 2013 |
| SEALD Review Date | January 22, 2013 |
| SEALD Labeling Reviewer | Abimbola Adebowale |
| SEALD Division Director | Laurie Burke |

PI = prescribing information

¹ The established pharmacologic class (EPC) that appears in the final draft PI.

This Study Endpoints and Labeling Development (SEALD) Director Sign-Off review of the end-of-cycle, draft prescribing information (PI) for critical format elements reveals **outstanding labeling format deficiencies that must be corrected** before the final PI is approved. After these outstanding labeling format deficiencies are corrected, the SEALD Director will have no objection to the approval of this PI.

The critical format elements include labeling regulation (21 CFR 201.56 and 201.57), labeling guidance, and best labeling practices (see list below). This review does not include every regulation or guidance that pertains to PI format.

Guide to the Selected Requirements of Prescribing Information (SRPI) Checklist: For each SRPI item, one of the following 3 response options is selected:

- **NO:** The PI **does not meet** the requirement for this item (**deficiency**).
- **YES:** The PI **meets** the requirement for this item (**not a deficiency**).
- **N/A** (not applicable): This item does not apply to the specific PI under review.

Selected Requirements of Prescribing Information

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment: RPM confirmed that waiver for ½ page requirement has been granted by DRUP.

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

- YES** 6. Section headings are presented in the following order in HL:

| Section | Required/Optional |
|--|---|
| • Highlights Heading | Required |
| • Highlights Limitation Statement | Required |
| • Product Title | Required |
| • Initial U.S. Approval | Required |
| • Boxed Warning | Required if a Boxed Warning is in the FPI |
| • Recent Major Changes | Required for only certain changes to PI* |

Selected Requirements of Prescribing Information

| | |
|---|---|
| • Indications and Usage | Required |
| • Dosage and Administration | Required |
| • Dosage Forms and Strengths | Required |
| • Contraindications | Required (if no contraindications must state “None.”) |
| • Warnings and Precautions | Not required by regulation, but should be present |
| • Adverse Reactions | Required |
| • Drug Interactions | Optional |
| • Use in Specific Populations | Optional |
| • Patient Counseling Information Statement | Required |
| • Revision Date | Required |

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**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).**”

Comment:

Product Title

YES

10. Product title in HL must be **bolded**.

Comment: *Include commas after the words “gel” and “use” in Product Title.*

Initial U.S. Approval

YES

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning

YES

12. All text must be **bolded**.

Comment:

NO

13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Selected Requirements of Prescribing Information

Comment: Center the heading “**WARNING: SECONDARY EXPOSURE TO TESTOSTERONE.**”

- NO** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” in *italics* and centered immediately beneath the heading.

Comment: Center the verbatim statement “*See full prescribing information for complete boxed warning.*”

- YES** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

- YES** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

- N/A** 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

Selected Requirements of Prescribing Information

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product does not have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product has FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment:

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: Change revision date from “xx/2013” to actual revision date (i.e. 01/2013 or 02/2013) prior to approval action.

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

- YES** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Selected Requirements of Prescribing Information

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) 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.”

Comment: *The statement “*Sections or subsections omitted from the full Prescribing Information are not listed” should not be bolded in the TOC. Unbold.*

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

YES 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

| |
|--------------------------------------|
| Boxed Warning |
| 1 INDICATIONS AND USAGE |
| 2 DOSAGE AND ADMINISTRATION |
| 3 DOSAGE FORMS AND STRENGTHS |
| 4 CONTRAINDICATIONS |
| 5 WARNINGS AND PRECAUTIONS |
| 6 ADVERSE REACTIONS |
| 7 DRUG INTERACTIONS |
| 8 USE IN SPECIFIC POPULATIONS |
| 8.1 Pregnancy |
| 8.2 Labor and Delivery |
| 8.3 Nursing Mothers |
| 8.4 Pediatric Use |
| 8.5 Geriatric Use |
| 9 DRUG ABUSE AND DEPENDENCE |
| 9.1 Controlled Substance |
| 9.2 Abuse |
| 9.3 Dependence |

Selected Requirements of Prescribing Information

| |
|---|
| 10 OVERDOSAGE |
| 11 DESCRIPTION |
| 12 CLINICAL PHARMACOLOGY |
| 12.1 Mechanism of Action |
| 12.2 Pharmacodynamics |
| 12.3 Pharmacokinetics |
| 12.4 Microbiology (by guidance) |
| 12.5 Pharmacogenomics (by guidance) |
| 13 NONCLINICAL TOXICOLOGY |
| 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility |
| 13.2 Animal Toxicology and/or Pharmacology |
| 14 CLINICAL STUDIES |
| 15 REFERENCES |
| 16 HOW SUPPLIED/STORAGE AND HANDLING |
| 17 PATIENT COUNSELING INFORMATION |

Comment:

YES

39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

NO

40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, “[see *Warnings and Precautions (5.2)*]”.

Comment: *In subsection 17.2:*



For the cross-reference in the 4th sub-bullet of the last bulleted item, change the “p” in precautions to uppercase “P.”

N/A

41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

YES

42. All text is **bolded**.

Comment:

YES

43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

YES

44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

Selected Requirements of Prescribing Information

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), 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.”

Comment:

- YES** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“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.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “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)”

Comment: *The statement “See FDA-approved patient labeling (Medication Guide)” should not be bolded in the FPI. Unbold.*

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/s/

ABIMBOLA O ADEBOWALE
01/23/2013

LAURIE B BURKE
01/24/2013



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 2, 2013
To: Hylton V. Joffe, M.D., Director
Division of Reproductive and Urologic Products
Through: Michael Klein, Ph.D., Director
Silvia Calderon, Ph.D., Team Leader
Controlled Substance Staff
From: James M. Tolliver, Ph.D., Pharmacologist
Controlled Substance Staff
Subject: NDA 203-098 Testosterone Gel (b) (4)
Indication: Testosterone replacement therapy in males for conditions associated with deficiency or absence of endogenous testosterone: Primary hypogonadism (congenital or acquired); Hypogonadotropic hypogonadism (congenital or acquired).
Dosages: Transdermal Gel, 5 mg, 7.5 mg, and 10 mg strengths
Sponsor: Perrigo Israel Pharmaceuticals Ltd.
Materials reviewed: Proposed Labeling for Testosterone Gel (b) (4) submitted on November 4, 2012 under NDA 203-098

Table of Contents

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I. Summary

A. Background

This memorandum is in response to a consult request dated August 6, 2012, from the Division of Reproductive and Urologic Products (DRUP) for CSS to review the "9. DRUG ABUSE AND DEPENDENCE" section of the proposed label for Testosterone Gel (b) (4) under the second review

cycle for NDA 203-098 by Perrigo Israel Pharmaceuticals. In a memorandum dated April 9, 2012, CSS recommended language for Section 9 of the label for NDA 203-098 under the first review cycle. In a communication dated November 4, 2012, the Sponsor provided to the Division proposed language of the label for Testosterone Gel (b) (4) under the second review cycle. CSS has reviewed the proposed language under Section 9 of the label.

B. Conclusions:

1. This proposed language is identical to that recommended by CSS to the Division in April 2012, for Testosterone Gel (b) (4) under NDA 203-098 (DAARTS, NDA 203-098, April 9, 2012, Author: James M. Tolliver, Ph.D.).

C. Recommendations:

1. Until such time as class labeling language is implemented for testosterone products, CSS continues to support the language of Section 9 of the label for Testosterone Gel (b) (4) under NDA 203-098 as set forth in the CSS April 9, 2012, memorandum and as currently proposed by the Sponsor.

II. Discussion

A. Chemistry

1. Product information

Testosterone Gel (b) (4) is a transdermal testosterone formulation indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The product is a clear, colorless hydroalcoholic gel containing (b) (4) testosterone. Inactive ingredients include carbomer 980, ethanol 67.0%, isostearic acid, purified water, and sodium hydroxide. Topical administration of Testosterone Gel (b) (4) 5 g, 7.5 g or 10 g contains 50 mg, 75 mg, or 100 mg testosterone, respectively. The product would be available as: 1) 2 x 75 g pumps with each pump dispensing 60 metered 1.25 g testosterone doses; and 2) individual 2.5 g testosterone packets or 5 g testosterone packets. The recommended starting dose is 5 grams for adult males, applied topically once daily to the shoulders, upper arms or abdomen. If the serum testosterone level remains below the normal range with the recommended starting dose, the dose may be appropriately increased from 5 g to 7.5 g and from 7.5 g to 10 g.

B. Integrated assessment

1. Labeling issues

The specific language of Section 9 of the proposed labeling for Testosterone Gel (b) (4) dated November 4, 2012, is provided below in italics.

DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Testosterone gel 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.*

This proposed language is identical to that recommended by CSS to the Division in April 2012, for Testosterone Gel (b) (4) under NDA 203-098 (DAARTS, NDA 203-098, April 9, 2012, Author: James M. Tolliver, Ph.D.). In that memorandum, it was noted that the scientific and medical justification for the label language was provided in a prior memorandum concerning the CSS review (b) (4). Until such time as class labeling language is implemented for testosterone products, CSS continues to support the language of Section 9 of the label for Testosterone Gel (b) (4) under NDA 203-098 as set forth in the CSS April 9, 2012, memorandum and as currently proposed by the Sponsor.

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/s/

JAMES M TOLLIVER
01/02/2013

SILVIA N CALDERON
01/02/2013

MICHAEL KLEIN
01/02/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
[Division of Professional Drug Promotion/Division of Consumer Drug
Promotion]

*****Pre-decisional Agency Information*****

Memorandum

Date: December 19, 2012

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

From: Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer
Division of Prescription Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Jina Kwak, PharmD
Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
OPDP

Through: Mathilda Fienkeng, PharmD, Acting Group Leader (DPDP)

CC: Twyla Thompson, PharmD, Group Leader (DCDP)
Jessica Cleck-Derenick, PhD, Regulatory Review Officer (DPDP)

Subject: **NDA 203098**
OPDP labeling comments for TESTOSTERONE gel for topical use
CIII

Background

On August 6, 2012, DRUP consulted OPDP to review the proposed package insert (PI), Medication Guide, and carton/container labeling for TESTOSTERONE gel for topical use CIII (Testosterone Gel).

DPDP reviewed the PI from the proposed substantially complete version retrieved from the eRoom on December 4, 2012. Our comments are provided below.

DPDP also reviewed the carton/container labeling submitted to the electronic document room on February 21, 2012 and we have no comments.

Please note that the Division of Medical Policy Programs (DMPP) provided comments on the Testosterone Gel medication guide on December 07, 2012 and DCDP has additional comments on this version of the Medication Guide.

OPDP appreciates the opportunity to provide comments on these materials. If you have any questions on the PI, please contact Melinda McLawhorn at 6-7559 or at Melinda.McLawhorn@fda.hhs.gov. If you have any questions on the Medication Guide, please contact Jina Kwak at 6-4809 or at Jina.kwak@fda.hhs.gov.

21 Pages of Draft Labeling have been
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/s/

MELINDA W MCLAWHORN
12/19/2012

**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: **December 07, 2012**

To: Hylton Joffe, 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): testosterone gel

Dosage Form and Route: For Topical Use

Application Type/Number: NDA 203-098

Tracked Safety Issue Number: **585**

Applicant: **Perrigo Israel Pharmaceuticals**

1 INTRODUCTION

On August 01, 2012 Perrigo Israel Pharmaceuticals re-submitted a New Drug Application (NDA 203-098) for testosterone gel, indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. This NDA was originally submitted on July 04, 2011 and on May 03, 2012 the Applicant received a Complete Response (CR) letter from the FDA citing clinical pharmacology and safety deficiencies.

This review is written in response to a request by the Division of Reproductive and Urologic (DRUP) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for testosterone gel.

The REMS is being reviewed by DRISK and will be provided to DRUP under separate cover.

2 MATERIAL REVIEWED

- Draft testosterone gel Medication Guide (MG), received on August 01, 2012 and received by DMPP on December 04, 2012.
- Draft testosterone gel Prescribing Information (PI) received August 01, 2012, revised by the Review Division throughout the current review cycle, and received by DMPP on December 04, 2012.
- Approved ANDROGEL 1% (testosterone gel) comparator labeling approved September 20, 2012.

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 APFont 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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Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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/s/

SHAWNA L HUTCHINS
12/07/2012

MELISSA I HULETT
12/07/2012

LASHAWN M GRIFFITHS
12/07/2012

MEMORANDUM

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

DATE: November 28, 2012

TO: Audrey L. Gassman, M.D.
Deputy Director, Division of Reproductive and Urologic
Products (DRUP)

Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology 3 (DCP3)
Office of Clinical Pharmacology (OCP)

FROM: Gopa Biswas, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

THROUGH: Sam H. Haidar, Ph.D., RPh
Chief, Bioequivalence Branch,
Division of Bioequivalence and GLP Compliance (DBGLPC)
Office of Scientific Investigations (OSI)

William H. Taylor, Ph.D.
Director
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Addendum to Review of EIRs Covering NDA 203-098,
Testosterone Gel (b) (4) sponsored by Perrigo Israel
Pharmaceuticals

At the request of DRUP and DCP3, Division of Bioequivalence and GLP Compliance (DBGLPC) conducted inspection of the clinical and analytical portions of the following bioequivalence study:

Study Number: 03-0415-001
Study Title: "A Randomized, Single-Dose, Three-Way Crossover
Relative Bioavailability Study of Testosterone Gel
Formulations in Hypogonadal Men"

The inspections of the clinical portion were conducted by Gene R. Gunn and Brian Keefer (ORA) (b) (4), and analytical portions by Gopa

Biswas, Ph.D. (DBGLPC) and Tonia L. Sawyer (ORA) (b) (4)

DBGLPC provided an initial review of inspectional findings at the clinical and analytical sites for this study on April 4, 2012.

A first addendum review for the clinical portion was provided on April 20, 2012. DBGLPC concluded that the dosing during the period 3 could not be assured due to lack of actual dosing records.

A complete response letter was issued to the sponsor, Perrigo on May 3, 2012 (**Attachment 1**). The sponsor provided period 3 dosing log in a response dated May 18, 2012 (**Attachment 2**).

A second addendum review was provided on May 2, 2012 for the response received for observations related to the analytical portion of the inspection. DBGLPC concluded that the concentrations of testosterone in study samples should be recalculated using the extrapolated value, 0.128 ng/mL for endogenous testosterone.

A teleconference was held by DRUP, DCP3 and OSI with the Sponsor on June 11, 2012, and the sponsor was advised to recalculate the concentrations to include the value of endogenous testosterone and submit the new data. A response with the recalculated data was received from the analytical site (b) (4) on June 20, 2012 (**Attachment 3**).

This third addendum provides our evaluation of the responses for clinical observation 3 and analytical observation 1:

Clinical Site: (b) (4)

Observation 3. Investigational drug disposition records are not adequate with respect to dates. Specifically, the drug administration records for Period 3 do not indicate the date and time at which the drug was administered.

Perrigo Response:

In their response to the complete response letter relating to observation 3 of Form FDA-483, Perrigo submitted the dosing logs for period 3. Perrigo acknowledged that the CRF data was not entered electronically as claimed in the original response received on April 13, 2012. Perrigo stated that period 3 dosing

logs were found in a "study document binder" where they were "improperly" filed in a section that contained records for laboratory certification (see **Attachment 2**).

DBGLPC's assessment of response:

In the opinion of this reviewer, documents provided in the response containing missing information appear to be authentic and thus resolved the main concern with the study. The response is complete and acceptable.

Analytical site: (b) (4)

Observation 1. Failure to adjust calibrator and QC samples concentrations for endogenous testosterone in blank plasma matrix used for preparing them.

(b) (4) **Response:**

In response to this observation, (b) (4) recalculated the testosterone concentration in subject samples by adding the concentration of endogenous testosterone, 0.128 ng/mL obtained by extrapolation of calibration lines from 25 analytical runs. The response also provided the calculation of difference between the original and the recalculated testosterone concentrations in subject samples.

DBGLPC's assessment of response:

In the opinion of this reviewer, the recalculated concentrations of testosterone in subject samples (after adjustment with endogenous levels) did not differ significantly from the original values. As a result, observation 1 does not appear to have an impact on study outcome. The response is acceptable.

Conclusions:

Following evaluation of the response to Form FDA-483, this reviewer recommends that the data for the clinical and analytical portions of study 03-0415-001 should be accepted for Agency review.

Gopa Biswas, Ph.D.

Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

VAI-

VAI:

(b) (4)

cc:

OSI/Moreno

OSI/DBGC/Taylor/Dejernet

OSI/DBGC/BB/Haidar/Biswas/Mada

OTS/OCP/DCPIII/Bashaw/Li/Hyunjin Kim

OND/ODE3/DRUP/Kaul/Roule/Gassman

SE-FO/FLA-DO/FIB/Torres/Sinninger

ORA/CE-FO/PHI-DO/PHI-IB/Keefer

ORA/SE-FO/FLA-DO/FIB/TAM-FL/Gunn

ORA/P-FO/LOS-DO/LADIB/PHO-AZ/Sawyer

Draft: GB 10/2/2012

Edit: SRM 10/24/2012; SHH 11/28/12; WHT 11/29/12

DSI: 6306; O:\BE\eircover\203098per.tes.addendum-III.doc

FACTS: 1378734

ATTACHMENT 1

APPEARS THIS WAY ON
ORIGINAL



NDA 203098

COMPLETE RESPONSE

Perrigo Company
Attention: Valerie Gallagher
U.S. Agent for Perrigo Israel Pharmaceuticals Ltd.
502 Eastern Avenue
Plant 6
Allegan, MI 49010

Dear Ms. Gallagher:

Please refer to your New Drug Application (NDA) dated July 4, 2011, received, July 5, 2011, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for testosterone gel.

We acknowledge receipt of your amendments received July 28, August 4, 8, 11, and 25, September 14, November 8, 21 (2), and 22, December 1, and 12, 2011; January 19, February 1, 6, 21, and 29, March 5, 7, 22, and 26, and April 13, 2012.

We have completed our review of this 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.

CLINICAL PHARMACOLOGY

Your Bioequivalence (BE) study between the proposed product (testosterone gel) and the reference listed drug (RLD; AndroGel® 1%) cannot be adequately evaluated. As outlined in Form 483s (dated March 1 and 30, 2012), there are unresolved clinical and bioanalytical site inspection deficiencies. Specifically, a major deficiency of missing dosing records for study period 3 was reported in FDA Form 483. As a result, data from study period 3 were excluded from statistical evaluation. The resultant small sample size makes it unfeasible to do any meaningful statistical analysis for the BE evaluation.

In addition, as reported in Form 483 from the bioanalytical site inspection, the measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and quality control samples. To date, you have not adequately addressed these deficiencies.

Information Needed to Address the Clinical Pharmacology Deficiency

A study demonstrating the safety and efficacy of the proposed product (testosterone gel) needs to be conducted. This can be done by conducting a pivotal BE study using an approved testosterone

product as a RLD or a new clinical trial to assess the efficacy and safety of the proposed product. This should be submitted as a part of the NDA re-submission. We recommend that you submit the study protocol to the Agency before initiation of the study.

Alternatively, you may provide an adequate response to the outstanding deficiencies listed in Form 483s. If you choose to submit a response to these deficiencies, you should also submit a letter to your NDA notifying the Division that you have done so.

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

We acknowledge the submission of your proposed REMS on December 12, 2011, which contains a Medication Guide and a timetable for submission of assessments of the REMS. We will continue discussion of your proposed REMS after your complete response to this action letter has been submitted.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously 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 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>.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jeannie Roule, Regulatory 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/

GOPA BISWAS

12/28/2012

Gopa Biswas also signing on behalf of Dr. Sam H. Haidar and Dr. William H. Taylor

**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: May 10, 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): Testosterone Gel ^{(b) (4)}
12.5 mg per actuation Metered-Dose Pump,
25 mg Unit-Dose Packet, and 50 mg Unit-Dose Packet

Application Type/Number: NDA 203098/S-001

Applicant/sponsor: Perrigo

OSE RCM #: 2011-2506

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

1 INTRODUCTION

This review evaluates the proposed container labels and carton labeling submitted by the Applicant, Perrigo, on February 21, 2012, for the product, Testosterone gel, (NDA 203098) for areas of vulnerability that can lead to medication error.

Additionally, this review evaluates the prescribing information submitted on December 1, 2011 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND

Topical testosterone is currently marketed in the United States in three dose forms (gel, solution, and transdermal patch). The testosterone gels are available in metered-dose pumps and unit-dose packets in various strengths. Additionally, even those testosterone gel products that are the same strength are not equivalent because the amount of testosterone delivered to the patient varies based on the inactive ingredients for each gel.

The Agency recently revised the strength presentation of topical testosterone gel products from the use of percentage to the use of milligrams of testosterone per packet for unit-dose packets and the use of milligrams of testosterone per pump actuation for metered-dose pumps.

Perrigo submitted the New Drug Application (NDA) for Testosterone gel on July 4, 2011 as a 505(b)(2) based on AndroGel (Testosterone Gel) 1% (NDA 021015) as the reference listed drug. AndroGel 1% was approved February 28, 2000. Perrigo resubmitted the labeling section of the NDA for Testosterone gel on December 1, 2011 in response to filing issues identified by the Agency on September 15, 2011. For this application, the Applicant proposes to market the product, Testosterone gel, under the established name, Testosterone Gel.

Requests for Information were sent to the Applicant on December 27, 2011, February 9, 2012, February 24, 2012, and March 22, 2012, after the Division of Reproductive and Urologic Products (DRUP) and the Division of Medication Error Prevention and Analysis (DMEPA) completed collaborative preliminary reviews of the proposed container labels and carton labeling (see Appendices B, and D for proposed labels and labeling and Appendices C and E for our recommendations). In response to these requests, the Applicant submitted revisions to the proposed container labels and carton labeling on February 6, 2012 and on February 21, 2012. The February 21, 2012 submissions are the primary subject of this review. The Applicant additionally submitted a request for advice via email pertaining to the proposed carton labeling and container labels submitted on February 24, 2012 which may be found in Appendix F. DMEPA's response to the request for advice may be found in section 4.2 Comments to the Applicant.

1.2 PRODUCT INFORMATION

The proposed indication for Testosterone gel is for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone such as primary hypergonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired). The recommended starting dose of Testosterone gel is 50 mg of testosterone once daily (preferably in the morning) applied to the clean, dry, intact skin of the shoulders and upper

arms and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt). After applying the gel, the application site should be allowed to dry for a few minutes prior to dressing. Hands should be washed with soap and water after Testosterone gel has been applied. Testosterone gel will be supplied in non-aerosol, metered-dose pumps in cartons containing two pumps. Each pump is capable of dispensing 1215 mg of testosterone in 75 g of gel or 60 metered 1.25g doses containing 20.25 mg testosterone per dose. Additionally, Testosterone gel will be supplied in unit-dose aluminum foil packets in cartons of 30. Each packet of 2.5 g or 5 g of gel contains 25 mg or 50 mg of testosterone, respectively.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹, the principals of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Insert Labeling submitted December 1, 2011 (no image)
- Container Labels and Carton Labeling submitted February 21, 2012 (Appendix A)

Additionally, since similar topical testosterone gel products, such as AndroGel, are currently marketed, DMEPA would typically search the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving topical testosterone gel products. However, three previous AERS searches for currently marketed AndroGel products were conducted on May 27, 2009 (OSE Review #2009-334 dated March 12, 2010), January 14, 2011 (OSE Review #2010-2433 dated March 2, 2011), and January 11, 2012 (OSE Review #2011-4304, dated pending). Thus, the results of these AERS searches were used instead of conducting a new search.

The three searches combined reference the time from the introduction of AndroGel products in 2000 to January 11, 2012. 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 topical testosterone gel products were deemed not applicable to this review and were excluded from further analysis.

3 RESULTS AND DISCUSSION

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

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

3.1 ADVERSE EVENTS REPORTING SYSTEM SEARCH RESULTS

The previous AERS searches identified 45 cases relevant to this review. Six cases described thirteen medication errors (two or more errors per case). Thus, the number of medication errors reported (n=52) is more than the number of cases. The medication errors were categorized as, accidental transfers (n= 19), wrong route of administration (n=15), wrong dose (n= 9), dose omission (n=4), complaints due to product labels and labeling (n=2), dispensing errors (n= 2), and wrong technique (n=1). The medication error cases are described in the following subsections.

3.1.1 Accidental Transfer (n=19)

Nineteen cases described secondary exposure to Androgel or other topical testosterone products either by transfer from the actual user or by suspected transfer from objects contacted by the actual user. One case also involved a second medication error discussed in section 3.1.3. These cases, which led to adverse outcomes, occurred between 2003 and 2011 and involved children and adults. A REMS was implemented for AndroGel and Testim 1% in 2009 that utilizes a medication guide which specifically warns about accidental exposure. This proposed product will also have a medication guide that warns about accidental exposure and how to minimize the risk.

3.1.2 Wrong Route of Administration (n=15)

Fifteen cases involved patients applying Androgel or other topical testosterone products to the wrong application sites including the chest, abdomen, underarms, forearms, legs. Androgel is only to be applied topically to the upper arms and shoulders. Four of the cases also involved other medication errors described in sections 3.1.3, 3.1.4, and 3.1.6. 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 pharmacist neglected to explain the application sites for Androgel so the patient applied it to the wrong site. In a sixth case a patient injected Androgel subcutaneously into the penis and testicles after the pharmacist informed the patient that this route of administration would cause no harm. No specific causality was given for the other nine cases, nor could we determine the root cause based on the limited information contained in the narratives.

The proposed product is packaged in unit-dose packets and metered-dose pumps which are appropriate for topical products, and it will be applied to the shoulders, upper arms, and stomach. Additionally, the route of administration for the proposed product is clearly labeled on the container labels and carton labeling and in the full prescribing information where it is also accompanied by a diagram identifying which parts of the body to which Testosterone gel can be applied. These methods to distinguish the route of administration should minimize the types of errors described here.

3.1.3 Wrong Dose (n=9)

Seven cases involved overdoses, and four of these seven cases also involved other medication errors discussed in sections 3.1.1, 3.1.2, 3.1.4, and 3.1.6. In five cases, patients used more than

their prescribed dose due to their perception of no improvement in their baseline symptoms. In two cases, the patient was prescribed more than the recommended maximum daily dose.

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, and two of these cases also involved other medication errors discussed in sections 3.1.2 and 3.1.3. 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 fourth case and could not be determined from the narrative.

3.1.5 Complaints Due to Product Labels and Labeling (n=2)

Two 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 were labeled as AndroGel 1 %, which could lead to confusion. The 2.5 g and 5 g 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 of gel, respectively. Additionally, the two sizes are differentiated with different colored packaging. The proposed product also has two sizes, however the presentation of strength includes the amount of testosterone in milligrams in each packet, and each size packet will be a different color to help differentiate the different sizes.

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 was labeled according to the total weight of the product (5 g), while the Testim 1 % product was labeled according to the weight of the active ingredient (50 mg). The products were mistakenly being stored in the same Pyxis drawer. A nurse believed the products were interchangeable and attempted to administer the testosterone dose using both products. The error did not reach the patient.

The concern regarding product interchangeability will be on going because these products contain the same active ingredient and same numerical strength even though the amount that is delivered to each patient will be different based on the different inactive ingredients in the products. We recommend labeling these products to warn healthcare practitioners that testosterone products are not equivalent.

3.1.6 Dispensing Errors (n=2)

Two cases described dispensing errors. In one case, also described in Sections 3.1.2 and 3.1.3 above, the wrong medication was dispensed when the patient was given AndroGel 1.62% instead of the prescribed AndroGel 1%. Although the identity of the topical testosterone product could not be determined from the Medwatch report in the second case, the narrative states that the

patient was given the wrong strength of drug, 100 mg/mL instead of the prescribed 200 mg/mL. No root cause analysis was performed for either case, nor could we determine a root cause from the information provided in the narratives.

3.1.7 Wrong Technique (n=1)

In one case a patient used “one half pump daily” and complained of lack of therapeutic effect compared to previous use. The Dosage and Administration section of the proposed insert labeling clearly states that patients should completely depress the pump one time for every 12.5 mg of testosterone required.

3.2 LABELS AND LABELING

DMEPA reviewed the prescribing information and medication guide submitted on December 1, 2011, and the container labels and carton labeling submitted on February 21, 2012. We note that most of DMEPA’s previous recommendations provided by email were implemented as requested. However, we have additional concerns as discussed below, including possible inappropriate interchanging of topical testosterone products as described above in Section 3.1.5 (AERS) Complaints Due to Product Labels and Labeling. We identified the following deficiencies:

3.2.1 All Container Labels and Carton Labeling

- We note that there are no statements on the container labels and carton labeling warning prescribers not to interchange these products.
- All container labels and carton labeling lack the statement, “*For Topical Use Only*” on the principal display panel.
- All container labels and carton labeling lack the lot number and expiration date.

3.2.2 Insert Labeling

- The strength and dosage of Testosterone gel are expressed (b) (4) rather than milligrams of testosterone throughout the insert labeling for Testosterone Gel. This may cause confusion of strength which can lead to medication errors in dosing as well as inappropriate interchange of one topical testosterone product for another.
- 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 “Safety and effectiveness of Testosterone Gel, (b) (4) in males < 18 years old has not been established” uses the abbreviation “<.” This abbreviation has been identified by the Institute of Safe Medication Practices (ISMP) as an error-prone because it has been confused with the greater than sign (i.e. >).
- The insert labeling does not clearly state that the exposure level for testosterone may differ for Testosterone gel compared to other topical testosterone products.

3.2.3 Medication Guide Labeling

- The graphic figure which illustrates the sites for Testosterone gel application the body has different shading for different sites which may lead to confusion about which sites are appropriate for Testosterone gel application.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling introduce vulnerability that can lead to medication errors because the strength presentation, lack of statement concerning different testosterone exposures with different topical testosterone products, and similarity of labels and labeling for the two unit-dose packet strengths increase the potential for inappropriate product substitution and increase the potential for confusion which may lead to medication errors. We provide recommendations for the professional labeling in section 4.1, *Comments to the Division*. Section 4.2, *Comments to the Applicant*, contains our recommendations for the container labels and carton labeling.

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, project manager, at 301-796-5413.

4.1 COMMENTS TO THE DIVISION

4.1.1 Insert Labeling

A. General Comments

Replace [REDACTED] ^{(b) (4)} with the revised strength presentations of 12.5 mg of testosterone per pump actuation, 25 mg testosterone per packet, and 50 mg testosterone per packet where appropriate.

B. 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 the symbol “<” to “less than.” This abbreviation has been identified by the Institute of Safe Medication Practices (ISMP) as an error-prone because it has been confused with the greater than sign (i.e. >).

C. Revise the Indications and Usage section of the Highlights 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.”

D. Revise the Dosage and Administration section of the Highlights and Full Prescribing Information and Section 2 Dosage and Administration in the Full Prescribing Information to use milligrams of testosterone [REDACTED] ^{(b) (4)} when referring to strengths or doses of your product.

E. Section 2 Dosage and Administration, Full Prescribing Information

Table 1 in Section 2.2 Administration Instructions uses (b) (4) rather than milligrams of testosterone to indicate prescribed daily doses.

1. Revise the prescribed daily doses (b) (4) to read as “50 mg,” “75 mg,” and “100 mg.”
2. Revise your Administration Instructions to include a diagram of appropriate application sites similar to the one found in the Medication Guide.

F. Dosage Forms and Strengths section, Highlights of Prescribing Information and Section 3 Dosage Forms and Strengths, Full Prescribing Information

1. The current strength statements in the Highlights of Prescribing Information refer to (b) (4) rather than milligrams of testosterone. Revise these statements to read as follows:

Testosterone gel for topical use only is available as:

- 25 mg of testosterone per packet
- 50 mg of testosterone per packet (3)
- 2 x 750 mg pumps (each pump dispenses 60 metered 12.5 mg doses of testosterone)

2. The current strength statements in Section 3 Dosage Forms and Strengths of the Full Prescribing Information refer to (b) (4) rather than milligrams of testosterone. Revise the statements to read as follows:

“Testosterone gel for topical use only is available as:

- 25 mg of testosterone per packet
- 50 mg of testosterone per packet
- 2 x 750 mg pumps (each pump dispenses 60 metered 12.5 mg doses of testosterone)

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

The statements on strength of Testosterone gel refer to (b) (4) rather than milligrams of testosterone. Revise the statements to read as follows:

1. Testosterone gel is supplied in non-aerosol metered-dose pumps. The pump is composed of plastic and stainless steel and an LDPE/aluminum foil inner liner encased in rigid plastic with a polypropylene cap. Each 88 g Testosterone gel pump in the twin package is capable of dispensing 75 g of gel containing 750 mg of testosterone (60 metered 1.25 g doses of gel containing 12.5 mg of testosterone per dose).

- 2 pumps each pump delivering 750 mg of testosterone as 60 metered doses of 12.5 mg. NDC 45802-116-02
2. Testosterone gel is also supplied in unit-dose foil packets in cartons of 30.
 - 25 mg of testosterone per packet. Each packet contains 2.5 g of gel. NDC 45802-116-65
 - 50 mg of testosterone per packet. Each packet contains 5 g of gel. NDC 45802-116-39

4.1.2 Medication Guide Labeling

The graphic figure which illustrates the sites for Testosterone gel application the body has different shading for different sites which may lead to confusion about which sites are appropriate for Testosterone gel application.

Revise the graphic picture so that the illustrated areas for Testosterone gel application are one shade of gray.

4.2 COMMENTS TO THE APPLICANT

A. All Container Labels and Carton Labeling

1. We note that there are no statements on the container labels and carton labeling warning prescribers not to interchange these products.

Please 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.”

2. All container labels and carton labeling lack the statement, “*For Topical Use Only*” on the principal display panel.
3. All container labels and carton labeling lack the lot number and expiration date.

Please revise all container labels and carton labeling to include a lot number and expiration date per 21 CFR 201.17 and 21 CFR 201.18.

B. Container Labels for the Unit-Dose Packets

1. For the 25 mg packet principal display panel, please clarify what the "CODE AREA" within the color bar is for. For both the 25 mg and 50 mg packet principal display panels, the size of the color bar may be reduced to create more text space.
2. The statements (b) (4) on the right lower corner of both principal display panels is redundant and may be deleted.
3. The US distributor address on the back panels of both packets is sufficient for regulation 21 CFR 201.1(h)(5). (b) (4).
4. To further increase space on both principal display panels move the statements "Use complete contents of foil packet. Used packets should be discarded safely. Patient:

please read patient leaflet." from the principal display panels to the back panels of both packets and place them underneath the warning statements regarding keeping out of the reach of children and the non-child resistant container.

5. These changes should allow enough space on both principal display panels to include the statement:

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

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

7. Thus, the following text would appear on the front display panel:

Testosterone Gel

25 mg of testosterone per packet or 50 mg of testosterone per packet

Topical testosterone product may have different doses, strengths, or application instructions that may result in different systemic exposure. See prescribing information.

Dispense the enclosed Medication Guide to each patient.

The following text would appear on the back display panel:

Warnings

Keep out of reach of Children;

this packet is not child-resistant.

ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME, OR SMOKING UNTIL THE GEL HAS DRIED.

Use complete contents of foil packet.

Used packets should be discarded safely.

Patient: please read patient leaflet.

C. Carton Labeling for the Unit-Dose Packets

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

D. Container Labels and Carton Labeling for the Metered-Dose Pump

1. Relocate the statement, *For Topical Use Only*, from the back panel of the pump label and the side panel of the carton labeling to the principal display panel.
2. The size of the text should remain similar to the current proposal.
3. We have the following comment for the pump label and carton labeling to be consistent with language used in the prescribing information:

The language used within the dosing table on the principal display panel of the pump label and on the side panel of the pump carton labeling (b) (4) is not consistent with the language within the equivalent table in Section 2.2 Administration Instructions of the Full Prescribing Information which refers to "*Number of 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 on the pump label and carton labeling to read "*Number of Pump Actuations*" to maintain consistency.

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.
3. OSE Review # 2011-4304, Label and Labeling Review for AndroGel (Testosterone) 1.62%, pending, Wood-Cummings, T.

Pages of Draft Labeling have been Withheld in Full as
B4 (CCI/TS) Immediately Following this Page

Appendix C: Comments for February 6, 2012 labeling submissions sent to the Applicant via email on February 9, 2012

The CMC and DMEPA reviewers have reviewed your latest versions of your carton and containers and have the following comments:

The container labels and carton labeling for your 2.5 gram and 5 gram packets utilize two colors, (b) (4) formatted into a reverse color scheme to differentiate the two strengths.

The appearance of both colors in similar formats on the labels and labeling for both strengths makes them appear similar and difficult to differentiate, especially for people who are color blind.

DMEPA and CMC recommend using color schemes which do not overlap to differentiate between the two strengths. For instance, the 25 mg strength could use (b) (4) and the 50 mg strength could use (b) (4)

Appendix D: Contain Labels and Carton Labeling submitted July 4, 2011 (and re-submitted December 1, 2011)



Appendix E: Comments for July 4, 2011 (December 1, 2011) labeling submission Sent to the Applicant on December 27, 2011

1. The strength of the product in the packets should be changed (b) (4) to “25 mg (or 50 mg) of testosterone per packet.” The name, dosage form, and strengths on the labels should be displayed as follows:

TESTOSTERONE GEL

*25 mg (or 50 mg) of testosterone per packet**

For immediate container labels, the total content should be displayed as follows:

**Each packet contains 2.5 grams (or 5 grams) of gel*

For carton labeling, the total content should be displayed as follows:

30 unit-dose packets (2.5 grams [or 5 grams] of gel each packet)

2. Revise the container labels and carton labeling of your 2.5 gram and 5 gram packets to provide more differentiation between the two packet sizes. As currently presented with the identical layout and color schemes, the labels and labeling of the two sizes appear identical and could lead to selection of the wrong packet. You can increase the differentiation between the two products by using different colors on the labels and labeling of one of the packet sizes.
3. The Bar code should be provided on all container closure labels.
4. Provide “Net Quantity 88 g” on the metered-dose pump label.
5. The strength of the product in the metered-dose pump should be changed (b) (4) to “12.5 mg testosterone per pump actuation.” The name, dosage form, and strengths on the labels should be displayed as following:

TESTOSTERONE GEL

*12.5 mg of testosterone per pump actuation**

For immediate container labels and carton labeling, the following should be displayed:

**Each pump actuation dispenses 1.25 grams of gel*

6.  (b) (4)

8. The word “Pump” on the pump label and pump carton labeling matches the prominence of the established name and thus appears to be part of the name. Decrease the prominence of the word "Pump" by decreasing the size of the font, using unbolded font, and locating the word away from the established name.

9. Include the statement "Dispense the enclosed Medication Guide to each patient" on the principal display panel of all labels and labeling per 21 CFR 208.24 (d) which states:

The label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear on the label in a prominent and conspicuous manner.

10. We recommend revising the dosing chart on the principal display panel of the gel pump label to specify the dose in milligrams of testosterone (b) (4). The dosing of testosterone products should be based on the amount of testosterone that is applied. We recommend revising the table from:

 (b) (4)

To:

| Prescribed Daily Dose | Number of Pump Depressions |
|-----------------------|----------------------------|
| 50 mg | 4 (once daily) |
| 75 mg | 6 (once daily) |
| 100 mg | 8 (once daily) |

Appendix F: Excluded AERS Search Results

The three previous AERS searches conducted for AndroGel products on May 27, 2009, January 14, 2011, and January 18, 2012 yielded 78 cases. Of these cases, 33 were excluded from further evaluation for the reasons listed below.

- Adverse events or product quality issues not related to medication errors. (n= 24)
- Medication errors not associated with topical testosterone products (n= 5)
- Duplicated case (n=1)
- Drug dispensing error with no details of an error not relating to labels/labeling (n=1)
- Accidental exposure; patient accidentally splashed AndroGel into eye during application process and child playing in father’s medicine cabinet and smeared AndroGel all over the body (n=2)

Non-Relevant AERS search results

| | ISR # | | ISR # | | ISR # | | ISR # | | ISR # |
|---|---------|----|---------|----|---------|----|---------|----|---------|
| 1 | 7599973 | 8 | 7718405 | 15 | 7718516 | 22 | 4565209 | 39 | 6233792 |
| 2 | 7749125 | 9 | 7927850 | 16 | 7483439 | 23 | 4909101 | 30 | 6687485 |
| 3 | 7989240 | 10 | 7883869 | 17 | 7408011 | 24 | 4130579 | 31 | 6543831 |
| 4 | 7698566 | 11 | 7327766 | 18 | 7478995 | 25 | 5833554 | 32 | 6480547 |
| 5 | 7942282 | 12 | 7648201 | 19 | 7903573 | 26 | 5726593 | 33 | 7055472 |
| 6 | 7945118 | 13 | 8011241 | 20 | 4483668 | 27 | 5117213 | | |
| 7 | 7456113 | 14 | 7457216 | 21 | 6010900 | 28 | 6338276 | | |

Appendix G: 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: - manufacturer: 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 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 (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, fluoxetine (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 |

| ISR # | Recv Date | Narratives |
|---------|-----------|---|
| | | unknown. No further information was available at this time. The patient refused permission to contact his physician regarding the events. |
| 7508177 | 19-May-11 | <p>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.</p> |
| 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 | <p>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 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.</p> |
| 7516718 | 23-May-11 | <p>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 sulfated) 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</p> |

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| | | <p>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.</p> |
| 7516707 | 23-May-11 | <p>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 (b) (6), weight as 122.5 and not pregnant. She added that the father (reporter) claims sideburn hair on daughter started after on Testim. She added that she saw her only once (b) (6) 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.</p> |
| 7403662 | 31-Mar-11 | <p>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 10-Mar-2011, the wife reported she had a miscarriage. She stated she was in her second trimester, (b) (6). 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 additional 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</p> |

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| | | <p>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.</p> |
| 7830644 | 21-Oct-11 | <p>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, the 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 (b) (6), 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 (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 (b) (6), 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 (b) (4). Laboratory Data: Selected laboratory results for son (approximately 10 months old) Laboratory results (2006) Hormone*Units I>Normal range May (b) (4) 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 .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</p> |

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| | | <p>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 ^{(b) (4)} 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.</p> |
| 7942270 | 28-Nov-11 | <p>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.</p> |
| 7272091 | 3-Feb-11 | <p>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 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</p> |

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| | | <p>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.</p> |
| 7941798 | 28-Nov-11 | <p>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 (b) (6) ***** 2011-11-28-10.47.38 ***** [USFDAMWVOLUTIONARY_196884_10154_20111126.xml Route To: AERS: Electronic</p> |
| 7942280 | 28-Nov-11 | <p>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 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.</p> |
| 7942288 | 28-Nov-11 | <p>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</p> |

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| | | 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 testosterone 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. |
| 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 |

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| | | <p>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's 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.</p> |
| 7942303 | 28-Nov-11 | <p>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.</p> |
| 7516097 | 1-Jun-11 | <p>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 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</p> |

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| | | <p>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".</p> |
| 7600504 | 11-Jul-11 | <p>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.</p> |
| 7716544 | 29-Aug-11 | <p>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 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.</p> |
| 7942285 | 28-Nov-11 | <p>Co-Marketer report from the USA of non-serious DECREASED TESTOSTERONE LEVELS and APPLYING MEDICATION TO THIGH with ANDROGEL 1.62% (TESTOSTERONE).</p> |

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| | | <p>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.</p> |
| 7942304 | 28-Nov-11 | <p>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.</p> |
| 7267519 | 21-Jan-11 | <p>On 14-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-2010, 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 (b) (6) and her estimated date of delivery is (b) (6). 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 previa. 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 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.</p> |
| 7979565 | 14-Dec-11 | <p>Solicited report from the USA of RIGHT HIP ARTHRITIS and non-serious ACNE,</p> |

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| | | <p>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 (b) (6) due to arthritis and was in the hospital for three days. In November 2011, the patient experienced THROMBOPHLEBITIS RIGHT FOOT. The patient had an uneventful recovery until he developed thrombophlebitis of his right foot (b) (6) 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.</p> |
| 7302410 | 18-Feb-11 | <p>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.</p> |
| 7637987 | 20-Jul-11 | <p>Franklin SL. Effects of unintentional exposure of children to compounded transdermal sex hormone therapy. <i>Pediatr Endocrinol Rev.</i> 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</p> |

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| | | <p>in children following dermal transfer: 2 case reports [abstract of Franklin SL. Effects of unintentional exposure of children to compounded transdermal sex hormone therapy. <i>Pediatr Endocrinol Rev.</i> 2011;8(3):208-212]. <i>React Wkly.</i> 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 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.</p> |
| 7637988 | 20-Jul-11 | <p>Franklin SL. Effects of unintentional exposure of children to compounded transdermal sex hormone therapy. <i>Pediatr Endocrinol Rev.</i> 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. <i>Pediatr Endocrinol Rev.</i> 2011;8(3):208-212]. <i>React Wkly.</i> 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 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: 2011AT000188 and 2011AT000190.</p> |
| 7656816 | 4-Aug-11 | <p>Case received from Besins-International, reference number BI-S-20110057. Case report received from MHRA. Patient became amenorrhoeic 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</p> |

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| | | partner was apparently applying Testogel carefully as per instructions 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. |
| 4390072 | 01-Jul-04 | I am reporting to comment on the packaging of the Testosterone (b) (4) gel. There is potential for confusion, two manufacturer have chosen different units of measure to prominently display and indicate the amount in the unit dose container. The Auxilium product, TESTIM, is packaged in single use tubes that state 'contains 50 mg testosterone per tube'. The product marketed by Unimed, ANDROGEL, is foiled packed in single use containers stating 'Contains 5 grams'. Although it seems unlikely that someone would use several packages to make a single dose, I do not believe it is outside the realm of possibility. It seems more likely that someone might try to use a portion of the container to make a dose. This labeling difference can be a source of confusion for the prescriber, pharmacist, and administrator of the medication. |
| 3574636 | 19-Sep-00 | THE PRODUCT COMES IN TWO PACKAGES, ONE CONTAINING 5G PER UNIT DOSE, THE OTHER 2.5G PER UNIT DOSE. THE LABELING DESIGNATIONS ARE CONFUSING. THE REPORTER FAXED IN HIS COMMENTS. MEDWATCH COMPLETED THIS COVER FORM. SEE ATTACHED DRUG MALADMINISTRATION |
| 4348709 | 23-Apr-04 | A physician report was received regarding a 49-year-old male patient on ANDROGEL therapy for a low testosterone level. The patient started ANDROGEL on an unknown date and experienced a skin reaction. ANDROGEL was discontinued and his skin reaction resolved. He was subsequently started on testosterone injections. In MAR 2004, the patient self-injected subcutaneous the ANDROGEL into his penis and his testicles. He did this only once. He developed an open wound at the injection site on his penis and scrotal edema within a few days of the injection. He was admitted to the hospital (b) (6) for intravenous antibiotics and a possible incision and drainage of the wound. The reporter's assessment of this case is "possible." ***UPDATED INFORMATION RECEIVED ON 16 APR 2004: The patient had no previous medical problems. On (b) (6), he was discharged from the hospital on oral antibiotics and psychiatric outpatient follow-up. His wound did not require incision and drainage and is healing. His scrotum edema has decreased. His adverse events are considered abating by the reporter. No additional information will be available on this adverse event since the reporter will not be following this patient after discharge. Corrective Therapy: IV antibiotics and possible incision and drainage. ***UPDATED INFORMATION RECEIVED ON 16 APR 2004: The patient did not require incision and drainage. He was discharged from the hospital on oral antibiotics and psychiatric outpatient follow-up. |
| | | A physician report concerning a female patient of unknown age who has had secondary exposure to ANDROGEL and experienced increased testosterone level while her male partner was being treated with ANDROGEL. The male partner of the female patient was on ANDROGEL pump (5 gm/day) since MAR 2009 for low testosterone. The physician reported that she talked with the female partner of the ANDROGEL user who stated that she had a testosterone level taken on an unknown date which showed a higher testosterone level. The physician learned of this event on |

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| 6296927 | 08-Apr-09 | <p>21 JUL 2009. As of 21 JUL 2009, the reported event was ongoing and the ANDROGEL user was still using the ANDROGEL. Outcome: Not yet recovered. The reporter assessed the causal relationship between ANDROGEL and the reported event as 'possible'. The reporter stated that the female partner was not sure how any testosterone was transferred to her as her partner showers each time before they have skin to skin contact. The female partner was aware of the precautions to use and prevent transfer. The reporter was not sure if the female partner had any testosterone level taken prior to this report. The female partner was not experiencing any adverse events, only the higher testosterone level. The female partner did not have any history of female problems that the reporter knew. This case is being submitted as an FDA 15 Day Report by Solvay Pharmaceuticals Inc. per request from the FDA that secondary exposure reports be submitted on an expedited basis until January 2010.</p> |
| | | <p>Date of initial report: 03-SEP-2009 A father reported that his 6-year-old daughter (Patient Initials: (b) (6)) experienced spike in growth (height) while the reporter used Androderm 5 mg and Androgel for low testosterone. In addition, the pediatric endocrinologist's notes reported she experienced premature adrenarche secondary to exogenous testosterone exposure, growth spurt, some increasing of her pubic hair growth/Tanner 1, slightly increased hair on her arms and legs, bone age 7 years 10 months at age 6 years 10 months. The reporter, who is 46 years old, indicated he had initially used Androgel from 2005 to 11/04/2008 then was switched to Androderm 5 mg for low testosterone on 11/05/2008. He was advised to switch from Androgel to Androderm by the pediatric endocrinologist. He reported his daughter experienced spike in growth about six months ago. He has family history significant for a niece growing one breast at the age of 6; once she was switched to organic milk it resolved. Her mother has a recessive gene for CAH (exact name unknown to reporter) which may cause symptoms of precocious puberty such as pubic hair growth. The reporter and his daughter were tested for the CAH gene, and they both tested negative. The reporter was concerned his daughter may be "getting testosterone somehow" and contemplated if it may be from his clothes, the sofa or carpet. He stated he applies a new patch in the morning after showering and his daughter does not have access to the patches. The reporter is divorced and moved out of the house that he shared with his daughter and ex-wife in June 2006; he only sees his daughter every other weekend. He confirmed his daughter's mother is not on any hormone replacement therapy and his daughter is not exposed to anyone at home or school who are on any kind of hormones. In addition, he reported his nine-year-old son experienced similar events while he was using Androderm and Androgel. Please refer to case 2009-07334 for this report. Additional information received 04-SEP-2009 via clinic notes from the pediatric endocrinologist (forwarded from the initial reporter, patient's father): "I was pleased to see --- in clinic for follow-up of her premature adrenarche secondary to exogenous exposure to testosterone. Since she was last seen, they have noted some increasing pubic hair development. No axillary hair, no body odor, no acne or other signs of puberty, no breast development. Dad is using a testosterone patch and had gone through his house and eliminated any known sources of the testosterone that he could find. Her last levels had normalize after he had done that task; however, there is some concern they have been spending more time with their Dad this summer, but he feels comfortable that he has eliminated the exposure from the environment. No other known exposures have occurred from other family members of other activities that they are aware. Mom has been very care(sic) to ask anyone they spent time with about this particular question. MEDICATIONS: None SOCIAL HISTORY: Unchanged. REVIEW OF SYSTEMS: Otherwise negative for all other general, eye, ear, nose throat, heart, lung, digestive, skin, urinary, neurological, muscle, bone, blood, allergy or other endocrine complaint not addressed above. PHYSICAL EXAMINATION: Weight 26.7 kg, 84th percentile, up 2.2 kg, height 124 cm, 72nd percentile. Growth velocity is 4.8 cm in 6 months. Pulse 100, blood pressure 116/70 (96/86</p> |

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| 6454749 | 24-Nov-09 | <p>percentile). BMI 17.4 (the 85th percentile). In general, unchanged exam with the exception of . GEN: Alert, interactive HEENT: Normocephalic, atraumatic NECK: Supple, no LAD, no thyromegaly LUNGS: Clear to auscultation CV: RRR, no audible murmur ABD: Soft, ND, NABS BREAST: Tanner 1 G-U: Tanner 1, no virilization, some slight darkening of the pubic hair in the mons area, but it is not coarse and curly yet or long like true pubic hair. No axillary hair, no acne, no body odor NEURO: Normal speech, gait, affect, language and strength. DERM: No rashes, acanthosis nigricans, or lipohypertrophy. She has freckles. No cafe au lait spots or other unusual birthmarks except mark on her forehead, slightly increased hair on her arms and legs, but not in excess. MUSC: Normal hands and feet LABORATORY: Bone age study According to the standards set forth by Greulich and Pyle, the patient's bone is 7 years, 10 months. ASSESSMENT: Premature adrenarche secondary to exogenous exposure, small advancement in pubic hair changes and a growth spurt. RECOMMENDATIONS: 1. We will evaluate for exposure again and advancement of bone age. 2. We will see her back in 3 months, and if her levels are elevated, we will have Dad re-clean the environment, change the frequency of exposure, and repeat labs in 1 month. ADDENDUM: Labs are prepubertal and no evidence of current exposure to testosterone." Additional information received 18-NOV-2009 from the patient's pediatric endocrinologist via health care professional form and medical records: The pediatric endocrinologist stated that the patient's father, who is not her patient, was using Androderm for hypogonadism. She indicated that the patient was taking no other medications. She reported that the date of event onset was "unclear." She also stated that "the patient developed signs of early puberty including pubic hair, body odor, rapid growth and acne. He [sic] developed an advanced bone age and thus a shortened predicted adult height. Symptoms progressed despite switch from gel [AndroGel] to patch [Androderm] by father, although environmental contamination with gel [AndroGel] remaining cannot be ruled out as the cause." The pediatric endocrinologist also provided her clinic notes from the patient's previous visit on 02/03/2009: "AGE: 6 years 4 months. HISTORY OF PRESENT ILLNESS: --- is a lovely 6-year-4 -month old here for evaluation of premature adrenarche. I saw her brother earlier this year for a similar complaint. It was discovered that dad had been using a topical testosterone gel and there was evidence that elevated androgens in his blood with advanced bone age. Then the concern was raised that dad may also be exposing the sister, who has had some signs of pubertal development of pubic hair recently noted, no body odor, though acne, axillary or breast development. Primary care provider performed a number of tests to screen for this. They were similar to her brother's through ---. LH was less than 0.2, FSH 1.5, estrogen 146, CMP normal, 17-OHP 190, androstenedione 35, DHEA sulfate 48. TSH on her was elevated, however, at 7.0 (range of normal is 0.5-4.3). Free T4 was normal at 1.3. Total testosterone was 26. Dad has changed to testosterone patch approximately a few weeks to a few days after these labs were drawn, however. The brother's levels were normal when they were performed here. MEDICATIONS: None. BIRTH HISTORY: Mom had gestational diabetes, diet controlled. She was born at 39 weeks, 8 pounds, 20 inches, C-section (repeat). Was breastfed to 7 months. Developmental milestones were all early. SOCIAL HISTORY: She is in the first grade, doing very well. She worries a lot, however. She lives at home with her family. ALLERGIES: No allergies. PAST MEDICAL/SURGICAL HISTORY: She has had PE tubes at 6 months of age for recurrent infections, that is her only surgery, and no hospitalizations. She did knock her 2 teeth out at the age of 4 in a ballet fall. REVIEW OF SYSTEMS: Significant for average moods for girl. No hearing loss, but did have PE tubes, RC at 6 months, UTI 2 years ago. Some complaints of abdominal pain that are relieved by having a bowel movement. Review of systems is otherwise negative for all other general, eye, ear, nose, throat, heart, lung, digestive, skin, urinary, neurological, muscle, bone, blood, allergy or other endocrine complaint not addressed above. FAMILY HISTORY: Dad is 6 feet 2. Mom is 5 feet 3. Dad's and mom's pubertal onset was normal, with menarche at age 13 in mom. There are some anxiety and depression and hypertension in the family. History of kidney stones in dad. Maternal grandmother also has had hypothyroidism. Again, the 8-year-old brother was evaluated for concerns with regard to</p> |

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| | | <p>precocious puberty, which was found to be exogenous exposure. Other family history includes macroglobulinemia, multiple myeloma. CAH in 1 aunt and 1 uncle, nonclassical, in the maternal family. PHYSICAL EXAMINATION: Vital signs: Weight is 24.5 kg (75th percentile). Height is 119.3 cm (70th percentile). BMI is 17.2 (40th percentile). Pluse 95, blood pressure 105/63. GEN: Alert, interactive HEENT: Normocephalic, atraumatic NECK: Supple, no LAD, no thyromegaly LUNGS: Clear to auscultation CV: RRR, no audible murmur ABD: Soft, ND, NABS BREAST: Tanner 1 G-U: Tanner 1, few long curly pubic hairs in the labia majora only, no virilization NEURO: Normal speech, gait, affect, language and strength. DERM: No rashes, acanthosis nigricans, or lipohypertrophy. She has freckles. No cafe au lait spots or other unusual birthmarks expect mark on her forehead, slightly increased hair on her arms and legs, but not in excess, apocrine activity present in the axillas, but no axillary hair MUSC: Normal hands and feet LABORATORY: Bone age was normal, consistent with chronological age. ASSESSMENT: Premature adrenarche secondary to exogenous exposure, without stunting of the growth at this time. RECOMMENDATIONS: 1. Will repeat her labs to verify that her blood levels have all normalized now that her father is not longer using gel, and repeat the thryoid functions, as there are concerns that hypothyroidism in the family and the elevated TSH before. 2. We will consider treatment should those levels be abnormal on repeat. 3. We will see her back in 6 months. ADDENDUM: All labs are normal."</p> |
| | | <p>Date of initial report: 03-SEP-2009 A father reported that his son (Patient Initials: (b) (6)), who is currently nine years old, experienced pubic hair growth, testosterone levels were elevated, x-ray of hand indicated his bone growth was comparable to 12 & 1/2 year old/growth spurt, initially thought to grow up to be 6'2" and now estimated to grow to only 5'6" while the reporter used Androgel and Androderm 5 mg for low testosterone. In addition, the pediatric endocrinologist's notes reported he experienced premature adrenarche secondary to exogenous exposure to testosterone/early puberty, Tanner III pubic hair/slight hair on his upper lip/small amount of axillary hair, bone age at most 12-1/2, acne/a few blackheads on his face, some increased thirst and appetite, one cafe au lait spot on abdomen and two ear infections. The reporter, who is 46 years old, indicated he had initially used Androgel from 2005 to 11/04/2008 then was switched to Androderm 5 mg for low testosterone on 11/05/2008. He stated that 2-3 years ago his son had fine pubic hair growth when he was 6 or 7 years old and he took him to see his pediatrician. Initially he thought it was a "hormone thing" from the milk he was drinking so he was switched to organic milk as the reporter's niece was growing one breast at the age of 6 and once she was switched to organic milk, it resolved. He was referred to a pediatric endocrinologist as his testosterone levels were also elevated (values unspecified). The reporter's son is now 9 years old and an xray of his hand shows that his bone growth was comparable to a 12 & 1/2 year old. Initially he was thought to grow up to be 6'2" but now he is estimated to grow to only 5'6". Per the reporter, he will need a surgically implanted hormone if the growth spurt does not stop. The reporter indicated his son's endocrinologist advised him to switch from Androgel to Androderm because a transfer of testosterone from him was suspected. The reporter was concerned his son is still "getting testosterone somehow" and contemplated if it may be from his clothes, the sofa or carpet. He stated he applies a new patch in the morning after showering and his son does not have access to the patches. The reporter is divorced and moved out of the house that he shared with his son and ex-wife in June 2006; he only sees his son every other weekend. He confirmed his son's mother is not on any hormone replacement therapy and his son is not exposed to anyone at home or school who are on any kind of hormones. The mother has a recessive gene for CAH (exact name unknown to reporter) which may cause symptoms of precocious puberty such as pubic hair growth. The reporter and his son were tested for the CAH gene, and they both tested negative. The reporter indicated his daughter, is starting to have a "spike in her growth" since he has been using Androderm. Please refer to case 2009-07340 for this report. Additional information received 04-SEP-2009 via clinic notes from the pediatric endocrinologist (forwarded from the initial reporter, patient's father): "I was pleased to see --- in clinic for follow-up of his</p> |

| ISR # | Recv Date | Narratives |
|---------|-----------|--|
| 6454750 | 24-Nov-09 | <p>premature adrenarche secondary to exogenous exposure to testosterone. Since he was last seen in March, he has had a significant change in the amount of pubic hair present. His mom is quite concerned. However, in that interval dad reports that he has not used AndroGel and he has cleaned the house to remove traces of it. He is currently using a testosterone patch instead. Otherwise he has been healthy. REVIEW OF SYSTEMS: Significant for 2 ear infections in August. Acne and facial hair as before. Some increased thirst and appetite but otherwise negative for all other general, eye, ear, nose throat, heart, lung, digestive, skin, urinary, neurological, muscle, bone, blood, allergy, or other endocrine complaint not addressed above. PHYSICAL EXAMINATION: Weight is 52.2 kg (greater than 97th percentile), height is 146.7 cm (greater than 97th percentile). Growth velocity equals 2.4 cm in 5 months. Pulse 85, blood pressure 114/59. BMI 24.3. GEN: Alert, interactive HEENT: Normocephalic, atraumatic, slight hair on his upper lip NECK: Supple, no LAD, no thyromegaly LUNGS: Clear to auscultation CV: RRR, no audible murmur ABD: soft, ND, NABS BREAST: normal male G-U: Tanner III pubic hair with 2 mL testicles that are firm. There is some slight broadening of the phallus, but normal length for age. small amount of axillary hair. NEURO: Normal speech, gait, affect, language and strength DERM: No birthmarks, acanthosis nigricans, or lipohypertropy, one small cafe au lait spot on his abdomen, A few blackheads on his face MUSC: Normal hands and feet LABORATORY: Bone age read by me today at most 12-1/2 but ranges from 11 to 12/1/2 in features. ASSESSMENT: Premature adrenarche secondary to exogenous exposure to testosterone with further progression and advancement of bone age now up to 12-1/2 and predicted height 25th percentile. RECOMMENDATIONS: 1. Based on the above laboratory testing [refer to patient laboratory section of report], we will recommend further cleaning of the environment. 2. The bone age advancement that has continued may be related to catch up on the bone age from prior exposure and may not reflect ongoing exposure, however, the increase in pubic hair may be either due to continued exposure versus central precocious puberty. 3. LH and FSH are pending as well. 4. We will see him back in 3 months. ADDENDUM: All levels are normal and no evidence of central puberty at this time and no evidence of current exposure to testosterone. However, the half life of testosterone is at most 5 hour which means it could be completely cleared from the system in 12 hours. This is the limitation of testing." Additional information received 18-NOV-2009 from the patient's pediatric endocrinologist via health care professional form and medical records: The pediatric endocrinologist stated that the patient's father, who is not her patient, was using Androderm for hypogonadism. She indicated that "my patient's exposure was from Dad's use. My patient was not on anything else." She reported that the date of event onset was "unclear." She also stated that "the patient developed early pubertal signs including pubic hair, acne, body odor, rapid growth ad advanced bone age. This lead [sic] to a shortened predicted adult height. Symptoms continued despite switch from Androgel to Androderm but environmental contamination with gel [Androgel] can't be ruled out either." The pediatric endocrinologist also provided her clinic notes from the patient's previous visits on 03/03/2009 and from 10/31/2008 (when patient's father was using Androgel, prior to commencing Androderm). "AGE: 8-years-7 months. I was please to see --- in the clinic for followup and reevaluation of his early pubertal signs secondary to exogenous testosterone exposure. Since he was last seen he has not had any further progression in pubertal finds. His data [sic] has changed from the topical gel testosterone to a patch and that seems to be working well for him. Otherwise, --- is doing quite well without complaint, with the exception of the last 3 days in which he has had a fever, respiratory infection and vomiting illness. MEDICATIONS: Singulair SOCIAL HISTORY: He is in the third grade. REVIEW OF SYSTEMS: Otherwise negative for all other general, eye, ear, nose, throat, heart, lung, digestive, skin, urinary, neurological, muscle, bone, blood, allergy, or other endocrine complaint not addressed above. PHYSICAL EXAMINATION: Vital signs: Wight is 48.2 kg, to 0.7 kg (greater than 95th percentile), height is 144.3 cm (greater than 95th percentile), growth velocity 6 cm per year. Annualized BMI is 23.1. Pulse 93, blood pressure 112/74. GEN: Alert, interactive HEENT: Normocephalic, atraumatic, slight hair on his upper lip NECK: Supple, no LAD, no thyromegaly</p> |

| ISR # | Recv Date | Narratives |
|-------|-----------|---|
| | | <p>LUNGS: Clear to auscultation CV: RRR, no audible murmur ABD: soft, ND, NABS BREAST: normal male G-U: Tanner III pubic hair with 2 mL testicles that are firm. There is some slight broadening of the phallus, but normal length for age. No axillary hair. NEURO: Normal speech, gait, affect, language and strength DERM: No birthmarks, acanthosis nigricans, or lipohypertropy, one small cafe au lait spot on his abdomen, A few blackheads on his face MUSC: Normal hands and feet LABORATORY: Bone age according to the Radiographic Atlas of Skeletal Development of the Hand and Wrist by Greulich and Pyle is approximately 10 years for a male standard. ASSESSMENT: Early pubertal development secondary to exogenous exposure to testosterone. Now without progression and with elimination of exposure.</p> <p>RECOMMENDATIONS: 1. Continue to maintain absence of exposure and careful use of testosterone. 2. Recheck the levels and a bone age to see if there is any progression. Currently his predicted height with his mildly advanced bone age is on track to be at his genetic target near 6 feet, likely a little less than that, but we will monitor for further changes. ADDENDUM: No change in bone age All labs have normalized" The pediatric endocrinologist also provide her clinic notes from the patient's visit on 10/31/2008, prior to the patient's father initiating Androderm, but while he was using AndroGel. "AGE: Eight years, 3 months CHIEF COMPLAINT: Early puberty HISTORY OF PRESENT ILLNESS: --- is a lovely 8-year-old here for evaluation of early pubertal development. His family had noted for just over a year some increasing pubic hair, primarily body hair in the beginning, but now coarsening and darkening. He has had no body odor, and and no acne, and there is an interesting strong family history of CAH. Mom is a carrier of nonclassical CAH. She had two siblings with it including ---, his aunt who is 5 feet, 5 inches, and --- his uncle, who is 5 feet, 8 inches. Two siblings did not carry the gene, but mom is a carrier. The genetic testing was done through --- Group. Mom's height is 5 feet, 3 inches. Dad is 6 feet, 2 inches and has taller family members in the males on his side. Of note, there is a potential exogenous exposure to testosterone as dad is on AndroGel. He reports being careful to wear a shirt after he puts the medication on, and he is keeping the area clean. However, there is some potential for cross contamination potentially in the sheets, and the medication is not at this point kept locked away. The patient denies any use of the medication. He is only with his father in that environment every other week for the potential exposure. No dietary exposure. No other potential exposures. No family history of precocious puberty other than the issues with the family members who had nonclassical CAH. MEDICATIONS: Singulair and Allegra. BIRTH HISTORY: He was a term pregnancy. Mom had gestational diabetes, diet controlled, 37 weeks, 8 pounds, 19.5 inches, C-section after 2 days of induced labor attempt. He had jaundice for a week. He was breast-fed until 7 months. HIs developmental milestones were on target. SOCIAL HISTORY: He is in the third grade, doing very well. He is shy and has low-self esteem, but is very smart. He has a potential allergy to red food dye. He has a history of asthma and gastroesophageal reflux. No hospitalizations. No surgeries. REVIEW OF SYSTEMS: His review of systems is also significant for low energy and activity, poor sleep through age of about five years. A little bit of acne in the past year. Occasional poor coordination, occasional headaches, increased thirst, rare diarrhea. Otherwise negative for all other general, eye, ear, nose, throat, heart, lung, digestive, skin, urinary, neurological, muscle, bone, blood, allergy, or other endocrine complaint not addressed above. FAMILY HISTORY: Dad is 6 feet, 2 inches. Mom is 5 feet, 3 inches. Both had pubertal onset at 14. One sister is age six and in good health. paternal grandparents are 5 feet, 6 inches and 6 feet, 1 inch. Maternal grandparents are 5 feet and grandfather is deceased. Type 2 diabetes, Waldenstrom's macroglobulinemia. A triple bypass in maternal grandmother. There is some depression and OCD in the family. No other endocrinopathy. PHYSICAL EXAMINATION: Vital signs: Weight is 47.5 kg. (This is the 95th percentile). Height is 142.6 cm, greater than the 95th percentile. Pulse is 88. Blood pressure is 136/65 with a repeat of 116/70. BMI is 23.4. GEN: Alert, interactive HEENT: Normocephalic, atraumatic, slight hair on his upper lip NECK: Supple, no LAD, no thyromegaly LUNGS: Clear to auscultation CV: RRR, no audible murmur ABD: soft, ND, NABS BREAST: normal male G-U: Tanner III pubic hair with 2 mL testicles that are firm. There is some slight broadening of the</p> |

| ISR # | Recv Date | Narratives |
|---------|-----------|--|
| | | <p>phallus, but normal length for age. No axillary hair. NEURO: Normal speech, gait, affect, language and strength DERM: No birthmarks, acanthosis nigricans, or lipohypertropy, one small cafe au lait spot on his abdomen, A few blackheads on his face MUSC: Normal hands and feet LABORATORY: Bone age according to the reference by Pyle: 10 years. ASSESSMENT: Precocious puberty. He appears to be non-testicular in source. Potentially, a CAH carrier versus hyperprolactinemia versus endogenous exposure to testosterone. RECOMMENDATIONS: 1. We used the above testing to evaluate for possible etiology of the adrenarche. 2. We will repeat the bone age, as this was reported to be advanced at age 12 years, 6 months, when he was 8 years, 2 months which is very concerning, as this would give him a height prediction at the 10th percentile. ADDENDUM: ---'s bloodwork reveals no sign of CAH or precocious puberty. His bone age is clearly advanced, but not as much as originally thought. The height prediction is closer to 5 ft 11 in. The conclusion I can draw from this information is that previous exogenous exposure to hormones have advanced his bone age."</p> |
| 6282475 | 21-Jul-09 | <p>My daughter was harmed by Androgel at the age of 3 and continues to suffer the side effects at the age of 9. I have read your warnings regarding the use of this product and to wash hands and cover the area in which the Androgel is applied. My daughter was absorbing the testosterone from my husband's sweating at night since she slept with us. It was not necessarily from the site the gel was applied that it was being transferred from. I saw NO warnings about contact in general with someone using the Androgel or similar product. At the age of 3, she had the testosterone level of a 13-15 year old boy- I believe her testosterone level was 413!-He was switched from the original testosterone mixture to the Androgel from a pediatric endocrinologist we went to see. Her levels began to go up again and he said he was calling the pharmaceutical company to let them know what was going on since there was no warning label regarding this transference. We are not sure of the long term effects from this exposure other than the physical defects that now exist because of this! It was a terrible experience emotionally and financially. What took so long to get his warning label first of all?? And, secondly, what about it being transferred from a user's perspiration??</p> |
| 6531930 | 07-Jan-10 | <p>My husband has been on Androgel for several months and was given basic instructions to wash his hands after using it. We were never given instructions that I should not come in contact with his skin even after the Androgel was dried, or that I should avoid linens used by my husband. Now, I have tested for high levels of DHEA after reporting symptoms of facial hair growth and swelling in the genital area. It is only today that we have made the connection of my being exposed to the Androgel and now I have to see an endocrinologist. My husband's doctor has never given him the information about the FDA's findings and the letter given to the pharm. companies, instructing the changes in the warnings to consumers.</p> |
| 6596945 | 22-Feb-10 | <p>Skin to skin exposure to Androgel soon after application resulted in a highly irregular period in a 52yr old menopausal woman, who had not had a regular period in over 2 years. The period grew quite heavy, day and night, causing fatigue and anemia, extending to 7 days with no signs of abating until -after internet research-exposure to the medication through dermal touch was halted. Swollen clitoris and increased sexual libido was experienced during this period. While skin to skin contact is no longer happening adjacent to application, due to the above events, male partner does wear a shirt over application area, but has not been washing it off after application and female partner is experiencing unusual level of hair on forearms, belly, upper thighs and face. Also concerned about air born effects from breathing what may be suspended in the alcohol gell base. No instruction is provided to male patient about how long to wait before washing off the gell. Pharmacy said contact after application, once dried, is safe. Which current online information warns against.</p> |
| | | <p>Total hysterectomy. ***Additional information received on 04 JAN 2010: Unknown dates: Endometriosis; 1971: 1st menstruation (menstruation always painful), saw MD multiple times; 1982: oral contraceptive trial- few as not able to tolerate. Then IUD used; 1994: Removal of first</p> |

| ISR # | Recv Date | Narratives |
|---------|-----------|--|
| 6538766 | 15-Jan-10 | <p>ovary, no treatment until abdominal infection - then surgery, treatment; 1998: Removal of second ovary, physiotherapy (physical therapy) for joint/muscle pain, 17 SEP 2007: First Estrogen therapy filled, 05 MAY 2009: First Progesterone and Testosterone (ANDROGEL) filled. 19 OCT 2009: First testosterone was filled (ANDROGEL). Allergies: Sulfa allergy-loss of consciousness and ferrous fumarate-rash (body).</p> |
| 6907674 | 05-Aug-10 | <p>A consumer report concerning a 67-year-old male who experienced 'mind got suicidal', 'weight loss' and 'used half of the prescribed dose' while being treated with ANDROGEL. ANDROGEL (5g/day) via pump was started in JUN 2009 for low testosterone. In JAN 2010, he decreased the dose without the doctor's advice to 2.5g daily to save money. The consumer reported weight loss which began in MAR 2010. In MAY 2010, his 'mind got suicidal'. The doctor told him to go back to the full dose of ANDROGEL. In MAY 2010, he began using the 5g dose again and one day later, the suicidal mind resolved, in MAY 2010. The doctor prescribed Bupropion 150mg twice a day as treatment, in MAY 2010. His weight went from 180 pounds to the current weight of 149 pounds. He had been eating right and working out at a gym. As of 04 JUN 2010, ANDROGEL was ongoing. The suicidal mind resolved and the weight loss continued. Outcome: Not yet recovered. The reporter assessed the causal relationship between ANDROGEL and the adverse events as 'possible'. Abbott Products (formerly Solvay Pharmaceuticals) judged the case as 'suspect'. The reporter assessed the case as 'serious' due to 'other reason for seriousness'. ***ADDITIONAL INFORMATION RECEIVED ON 26 JUL 2010: The adverse event of "mind got suicidal" was removed and the causality assessment for "weight loss" was updated to unrelated. The case was changed from "serious" to "nonserious." The consumer reported that the day he made the initial report he was concerned about his chest as he was using this as an application site for ANDROGEL. He was told by the pharmacist that using the chest as his application site would not cause him any harm. He was also assured that applying only half the dosage (2.5 g) was not harmful either. Then he was told that there was no data on a person using only half the amount that was prescribed for him (2.5 g). He states "I did not have any suicidal thoughts, the pharmacist did not understand what he was saying at the time." Also, he contributes his weight loss to the fact that he was "on a diet." He declined to provide his physician's contact information.</p> |

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/s/

TERRI WOOD-CUMMINGS
05/11/2012

ZACHARY A OLESZCZUK
05/11/2012

CAROL A HOLQUIST
05/11/2012

MEMORANDUM

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

DATE: May 2, 2012

TO: Audrey L. Gassman, M.D.
Deputy Director, Division of Reproductive and Urologic
Products

Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology 3 (DCP3)
Office of Clinical Pharmacology

FROM: Gopa Biswas, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., RPh
Chief, Bioequivalence Investigations Branch,
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

William H. Taylor, Ph.D., DABT
Director (Acting)
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

SUBJECT: Addendum to Review of EIRs Covering NDA 203-098,
Testosterone Gel (b) (4) sponsored by Perrigo Israel
Pharmaceuticals

At the request of DRUP and DCP3, FDA staff, including Gopa Biswas, Ph.D. (DBGC) and Tonia L. Sawyer (ORA) conducted inspection of the analytical portion and Gene R. Gunn and Brian Keefer(ORA) conducted inspection of the clinical portion of the following bioequivalence study:

Study Number: 03-0415-001

Study Title: "A Randomized, Single-Dose, Three-Way Crossover
Relative Bioavailability Study of Testosterone Gel
Formulations in Hypogonadal Men"

DBGC's evaluation of inspectional findings at the clinical and analytical sites for this study was provided to DRUP and DCP3 in

a memorandum dated April 4, 2012, followed by an addendum to provide evaluation of responses to Form FDA 483 observations for the clinical portion, received from (b) (4) (CRO, clinical site) and Perrigo Israel Pharmaceuticals (sponsor) on April 20, 2012. DBGC received a response to inspectional findings for the analytical portion of the study from (b) (4) (CRO) on April 27, 2012 (**Attachment 1**). This second addendum provides our evaluation of the responses for the analytical portion:

Analytical site: (b) (4)

1. Failure to adjust calibrator and QC samples concentrations for endogenous testosterone in blank plasma matrix used for preparing them.

In response to this observation, and employing a suggestion from OSI on how the endogenous testosterone concentration might be estimated from available records, (b) (4) calculated the endogenous concentration of testosterone by extrapolation of calibration lines from 25 analytical runs. (b) (4) claimed that a single source of blank plasma was used for both calibrator and QC samples for all of the analytical runs. The firm used the estimate of endogenous testosterone concentration (0.128 ng/mL) from the extrapolated data to adjust the concentrations of calibration standards and QCs for all analytical runs. (b) (4) response did not include data for adjusted testosterone concentrations in study samples.

2. Failure to document the following aspects of method validation and study conduct:

- a) For freeze-thaw stability demonstration (b) (4) movements of QC samples during freeze-thaw cycles were not documented in sample processing sheet or freezer log book.
- b) A freezer log for (b) (4) freezer was not maintained to record sample movement from and to the freezer during validation and study sample analysis.

In response to this observation, (b) (4) stated that their current procedures and method SOPs better document the activities mentioned in the observations. They are also planning to replace the paper based documentation with a software-based laboratory information management system (LIMS). In this reviewer's opinion, the incomplete tracking of freezer conditions does not detract significantly from data integrity.

- c) Failure to document anticoagulant used for all the plasma lots used as blanks or for preparing

calibrators and, QC samples, during method validation and study sample analysis.

- d) Documents were not available to ensure that all plasma lots used during method validation and study were stripped with charcoal in order to eliminate endogenous testosterone.

In their response, (b) (4) provided additional documentation that Li-heparin was used as anticoagulant for blank plasma. The firm stated that in laboratory records, plasma lots were documented as "cleaned once," which referred to one stripping with charcoal. The firm has revised method SOPs to document details of blank plasma treatments.

3. Failure to reject analytical runs with blank samples showing 20% or more of LLOQ response. Blank samples in the majority of analytical runs showed 20% to 30% of LLOQ response but all the runs were accepted based on SOP BAS-RMT-02.

The signal in blank samples was probably due to endogenous testosterone. The firm's revised SOP includes Agency-recommended criteria for evaluating blank chromatograms. The firm will further revise their SOP for determination of endogenous analytes and reporting baseline concentrations in blank matrices. The revised SOP will be provided to the Agency by mid-June 2012.

- 4a) Failure to demonstrate selectivity in charcoal stripped plasma.
- 4b) Failure to reject selectivity experiment in non-stripped plasma although the selectivity samples failed acceptance criteria (b) (4)

In their response, (b) (4) provided additional documentation to show that the plasma lots used for the selectivity experiment were stripped with charcoal. The firm provided additional data to demonstrate selectivity in blank plasma. The reviewer finds the results acceptable.

Conclusions:

Following evaluation of the responses to Form FDA 483 observations for the analytical portion of study 03-0415-001, this DBGC reviewer's recommendations remain the same as provided earlier:

1. The proper dosing of subjects at (b) (4) during Period 3 cannot be assured. Data from Period 3 should be excluded from statistical evaluation.
2. The measured concentrations of plasma testosterone in study samples have not yet been adjusted for endogenous testosterone levels from blank plasma samples used to prepare calibrators and QCs. The concentrations of calibration standards and QCs were adjusted with an extrapolated value (0.128 ng/mL) for endogenous testosterone derived from calibration lines in 25 analytical runs. This reviewer recommends adding the same 0.128 ng/mL concentration to study sample measurements.

Gopa Biswas, Ph.D.

Bioequivalence Branch, DBGC, OSI

Final Classifications:

VAI-

VAI:

cc:

OSI/Ball/Moreno

OSI/DBGC/Taylor/Dejernett

OSI/DBGC/BB/Haidar/Skelly/Biswas

OTS/OCP/DCPIII/Bashaw/Kim/Li

OND/ODE3/DRUP/Kaul/Roule/Gassman

SE-FO/FLA-DO/FIB/Torres/Sinninger

HFR-CE1520/Keefer

HFR-SE2585/Gunn

HFR-PA2530/Sawyer

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SAM H HAIDAR
05/02/2012

WILLIAM H TAYLOR
05/02/2012

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****PRE-DECISIONAL AGENCY MEMO****

Date: April 23, 2012

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

From: Jessica Cleck Derenick, PhD
Regulatory Review Officer
Division of Professional Promotion (DPP)
Office of Prescription Drug Promotion (OPDP)

Jina Kwak, PharmD
Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
OPDP

Subject: NDA 203098
OPDP labeling comments for Testosterone Gel, (b) (4)

We acknowledge receipt of DRUP's July 13, 2011, consult request for the proposed product labeling for Testosterone Gel, (b) (4). OPDP was notified by DRUP on April 23, 2012, that final labeling negotiations would not be initiated during the current review cycle and that a Complete Response letter would be issued. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP kindly requests that DRUP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions, please contact:

Jessica Cleck Derenick: 301-796-0390; Jessica.Cleck-Derenick@fda.hhs.gov

Jina Kwak: 301-796-4809; Jina.Kwak@fda.hhs.gov

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/s/

JESSICA N CLECK DERENICK
04/23/2012

JINA KWAK
04/23/2012



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: April 9, 2012

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

From: James M. Tolliver, Ph.D., Pharmacologist
 Controlled Substance Staff

Subject: NDA 203098 Testosterone Gel, (b) (4)
Indication: Testosterone 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).
Dosages: Transdermal Gel, 5 mg, 7.5 mg, and 10 mg strengths
Sponsor: Perrigo Israel Pharmaceuticals Ltd.

Materials reviewed: Proposed Labeling for Testosterone Gel (b) (4) submitted under NDA 203,098

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I. Summary

A. Background

This memorandum is in response to a consult request dated July 13, 2011, from the Division of Reproductive and Urologic Products (DRUP) for CSS to review the "9. DRUG ABUSE AND DEPENDENCE" section of the proposed label for Testosterone Gel (b) (4) under NDA 203,098,

submitted by Perrigo Israel Pharmaceuticals. CSS has reviewed the labeling and provides the comments and recommendations listed below.

B. Conclusions:

1. The language under Section 9 DRUG ABUSE AND DEPENDENCE " should be modified to read [REDACTED] (b) (4) as previously proposed by CSS. This would include modifying section "9.1 Controlled Substance" and adding sections "9.2 Abuse" and "9.3 Dependence."

C. Recommendations:

1. The proposed language under section "9 DRUG ABUSE AND DEPENDENCE" should be modified (deletions in strikeout and additions in italic) as follows:

9.1 Controlled Substance

Testosterone Gel (b) (4) contains testosterone, a Schedule III controlled substance [REDACTED] (b) (4) -in the Controlled Substances Act.

[REDACTED] (b) (4)

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 drug are interrupted*
- *Difficulty in discontinuing use of the drug despite desires and attempts to do so*
- *Experience of withdrawal syndrome upon discontinuation of anabolic steroid use*

II. Discussion

A. Chemistry

1. Product information

Testosterone Gel (b) (4) is a transdermal testosterone formulation indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. It is a clear, colorless hydroalcoholic gel containing (b) (4) testosterone. Inactive ingredients include carbomer 980, ethanol 67.0%, isostearic acid, purified water, and sodium hydroxide. Topical administration of Testosterone Gel (b) (4) 5 g, 7.5 g or 10 g contains 50 mg, 75 mg, or 100 mg testosterone, respectively. The product would be available as: 1) 2 x 75 g pumps with each pump dispensing 60 metered 1.25 g testosterone doses; and 2) individual 2.5 g testosterone packets or 5 g testosterone packets. The recommended starting dose is 5 grams for adult males, applied topically once daily to the shoulders, upper arms or abdomen. If with the starting dose, the serum testosterone level is below the normal range, the dose may be adjusted from 5 grams to 7.5 grams and from 7.5 grams to 10 grams.

B. Integrated assessment

CSS reviewed the proposed language under Section 9 DRUG ABUSE AND DEPENDENCE of the label for Testosterone Gel (b) (4). The language proposed by the Sponsor is as follows:

9.1 Controlled Substance

(b) (4)

The Anabolic Steroid Control Act of 1990 amended the Controlled Substances Act (CSA) to place testosterone in Schedule III (21 U.S.C. 802(41)(A)(xlvii)). As such, Testosterone Gel (b) (4) which contains testosterone, is a product in Schedule III of the CSA. The language of section "9.1 Controlled Substance" should be changed to reflect this. The revised language would also be similar to the language proposed by CSS (b) (4)

(b) (4)

Sections "9.2 Abuse" and "9.3 Dependence" are currently missing from the labeling proposed by the Sponsor. Both sections should be added with language identical to the language proposed by CSS (b) (4)

(b) (4)

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

/s/

JAMES M TOLLIVER
04/09/2012

SILVIA N CALDERON
04/09/2012

MICHAEL KLEIN
04/09/2012

MEMORANDUM

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

DATE: March 22, 2012

TO: NDA 203098

THROUGH: Jeannie Roule

SUBJECT: Carton and Container edits

APPLICATION NUMBER: NDA 203098 (testosterone gel)

Comments from DMEPA and CMC reviewers concerning the cartons and containers were emailed to the Sponsor.

Please see attached email correspondences for all of the details.

From: Roule, Jeannie
Sent: Thursday, March 22, 2012 3:33 PM
To: 'Dalit Fuchs'
Subject: NDA 203098 carton and container

Dalit,

The DMEPA and CMC reviewers have the following comments concerning your carton and container:

We have been evaluating possible revisions to the packet labels and container labeling as well as to the pump label and carton labeling to enable incorporation of the statement on interchangeability. Please note that the statement has been revised.

1. 25 mg and 50 mg Packet Labels

1.1 For the 25 mg packet principal display panel, please clarify what the "CODE AREA" within the color bar is for. For both the 25 mg and 50 mg packet principal display panels, the size of the color bar may be reduced to create more text space.

1.2. The statements (b) (4) on the right lower corner of both principal display panels is redundant and may be deleted.

1.3. The US distributor address on the back panels of both packets is sufficient for regulation 21 CFR 201.1(h)(5) (b) (4)

1.4. To further increase space on both principal display panels move the statements "Use complete contents of foil packet. Used packets should be discarded safely. Patient: please read patient leaflet." from the principal display panels to the back panels of both packets and place them underneath the warning statements regarding keeping out of the reach of children and the non-child resistant container.

1.5. These changes should allow enough space on both principal display panels to include the abbreviated statement "*Topical testosterone products may have different doses strengths, or application instructions that may result in different systemic exposure. See prescribing information*".

1.6. Please revise the packet labels to include a lot number and expiration date per 21 CFR 201.17 and 21 CFR 201.18.

Thus, the following text would appear on the front display panel:

Testosterone Gel
25 mg of testosterone per packet or 50 mg of testosterone per packet
Topical testosterone products may have different doses strengths, or application instructions that may result in different systemic exposure. See prescribing information.
Dispense the enclosed Medication Guide to each patient.

The following text would appear on the back display panel:

Warnings
Keep out of reach of children;
this packet is not child-resistant.
ALCOHOL BASED GELS ARE FLAMMABLE. AVOID FIRE, FLAME, OR SMOKING UNTIL THE GEL HAS DRIED.

*Use complete contents of foil packet.
Used packets should be discarded safely.
Patient: please read patient leaflet.*

*Distributed By Perrigo
Allegan, MI 49010 . www.perrigo.com
Rev. 03/12*

2. 25 mg and 50 mg Carton Labels

2.1 Please add to the principal display panels of both cartons the statement "*Topical testosterone products may have different doses strengths, or application instructions that may result in different systemic exposure. See prescribing information.*"

3. Pump Labels and Carton Labeling for the Metered Dose Pump

3.1. Please revise the pump labels to include a lot number and expiration date per 21 CFR 201.17 and 21 CFR 201.18.

3.2. Please add to the principal display panels of the pump label and carton labeling the abbreviated statement "*Topical testosterone products may have different doses strengths, or application instructions that may result in different systemic exposure. See prescribing information.*"

The size of the text should remain similar to the current proposal.

Additionally, for the pump label we have the following comment to be consistent with language used in the prescribing information:

The language used within the dosing table (b) (4) on the principal display panel of the pump label and the side panel of the carton labeling is not consistent with the language within the equivalent table in Section 2.2 Administration Instructions of the Full Prescribing Information which refers to "Number of 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 on the pump label and carton labeling to read "Number of Pump Actuations" to maintain consistency.

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

/s/

JEANNIE M ROULE
03/23/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

| Application Information | | |
|--|---|--|
| NDA # 203098 BLA# | NDA Supplement #:S- BLA STN # | Efficacy Supplement Type SE- |
| Proprietary Name: N/A Established/Proper Name: testosterone gel (b) (4) Dosage Form: topical gel Strengths: (b) (4) | | |
| Applicant: Perrigo Israel Pharmaceuticals, Ltd. Agent for Applicant (if applicable): Valerie Gallagher | | |
| Date of Application: July 4, 2011 Date of Receipt: July 5, 2011 Date clock started after UN: | | |
| PDUFA Goal Date: May 5, 2012 | | Action Goal Date (if different): |
| Filing Date: September 3, 2011 | | Date of Filing Meeting: August 31, 2011 |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) 3 | | |
| Proposed indication(s)/Proposed change(s): Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone | | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: | | <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i> | | |
| Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i> | | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted |
| Resubmission after withdrawal? <input type="checkbox"/> | | Resubmission after refuse to file? <input type="checkbox"/> |
| Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i> | <input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product) | |

| | | | | |
|---|--|-----------|-----------|----------------|
| <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) | | | |
| Collaborative Review Division (<i>if OTC product</i>): | | | | |
| List referenced IND Number(s): | | | | |
| Goal Dates/Product Names/Classification Properties | YES | NO | NA | Comment |
| PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | X | | | |
| Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i> | X | | | |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i> | X | | | |
| Application Integrity Policy | YES | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> | | X | | |
| <i>If yes, explain in comment column.</i> | | | | |
| <i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i> | | | | |
| User Fees | YES | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature? | X | | | |

| <p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p> | <p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p> | | | | | | | | | | | | | | | | | | | |
|--|--|------------------|------------------------|------------------------|-----------|----------|----|--------------|-----------|--------|----|--------------|-----------|----------------|----------------|--------------|----------|--|--|--|
| <p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p> | <p>Payment of other user fees:</p> <p><input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p> | | | | | | | | | | | | | | | | | | | |
| <p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p> | <p>YES</p> | <p>NO</p> | <p>NA</p> | <p>Comment</p> | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> | | <p>X</p> | | | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p> | | <p>X</p> | | | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p> | | <p>X</p> | | | | | | | | | | | | | | | | | | |
| <p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>NDA 21463</td> <td>Fortesta</td> <td>NP</td> <td>Dec 29, 2013</td> </tr> <tr> <td>NDA 22504</td> <td>Axiron</td> <td>NP</td> <td>Nov 23, 2013</td> </tr> <tr> <td>NDA 22309</td> <td>Androgel 1.62%</td> <td>April 29, 2014</td> <td>Aug 30, 2020</td> </tr> </tbody> </table> | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | NDA 21463 | Fortesta | NP | Dec 29, 2013 | NDA 22504 | Axiron | NP | Nov 23, 2013 | NDA 22309 | Androgel 1.62% | April 29, 2014 | Aug 30, 2020 | <p>X</p> | | | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | | | |
| NDA 21463 | Fortesta | NP | Dec 29, 2013 | | | | | | | | | | | | | | | | | |
| NDA 22504 | Axiron | NP | Nov 23, 2013 | | | | | | | | | | | | | | | | | |
| NDA 22309 | Androgel 1.62% | April 29, 2014 | Aug 30, 2020 | | | | | | | | | | | | | | | | | |
| <p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p> | | | | | | | | | | | | | | | | | | | | |
| <p>Exclusivity</p> | <p>YES</p> | <p>NO</p> | <p>NA</p> | <p>Comment</p> | | | | | | | | | | | | | | | | |
| <p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the <i>Orphan Drug Designations and Approvals</i> list at: http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p> | | <p>X</p> | | | | | | | | | | | | | | | | | | |

| | | | | |
|--|---|-------|--|--|
| <p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p> | | | | |
| <p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: number of years mentioned</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> | X | 3year | | |
| <p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p> | | X | | |
| <p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p> | | | | |

| Format and Content | | | | |
|--|--|-----------|-----------|----------------|
| <p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | |
| <p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p> | | | | |
| Overall Format/Content | YES | NO | NA | Comment |
| <p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p> | X | | | |
| <p>Index: Does the submission contain an accurate comprehensive index?</p> | X | | | |
| <p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> | X | | | |

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

| | | | | |
|--|------------|-----------|-----------|----------------|
| <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only) | | | | |
| If no, explain. | | | | |
| BLAs only: Companion application received if a shared or divided manufacturing arrangement? | | | | |
| If yes, BLA # | | | | |
| Forms and Certifications | | | | |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> | | | | |
| Application Form | YES | NO | NA | Comment |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? | X | | | |
| <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i> | | | | |
| Are all establishments and their registration numbers listed on the form/attached to the form? | X | | | |
| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)? | X | | | |
| Financial Disclosure | YES | NO | NA | Comment |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? | X | | | |
| <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> | | | | |
| <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> | | | | |
| Clinical Trials Database | YES | NO | NA | Comment |
| Is form FDA 3674 included with authorized signature? | X | | | |
| <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> | | | | |
| <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i> | | | | |
| Debarment Certification | YES | NO | NA | Comment |
| Is a correctly worded Debarment Certification included with authorized signature? | X | | | |

| | | | | |
|--|------------|-----------|-----------|-----------------------|
| <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> | | | | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| <p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p> | | | | Electronic submission |

| Controlled Substance/Product with Abuse Potential | YES | NO | NA | Comment |
|---|------------|-----------|-----------|----------------|
| <p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i> July 13, 2011</p> | X | | | |

| Pediatrics | YES | NO | NA | Comment |
|---|------------|-----------|-----------|----------------|
| <p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> | | X | | |

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

| | | | | |
|---|---|-----------|-----------|--|
| If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included? | | | | N/A |
| If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i> | | | | N/A |
| If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i> | | | | N/A |
| <u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i> | | | | N/A |
| Proprietary Name | YES | NO | NA | Comment |
| Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i> | | X | | |
| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/DCRMS via the DCRMSRMP mailbox</i> | X | | | Only the Medguide was submitted. The REMS template and supporting doc will be sent soon. |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i> | X | | | |
| Is the PI submitted in PLR format? ⁴ | X | | | |

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

| | | | | |
|--|--|-----------|-----------|----------------|
| If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i> | | | | N/A |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC? | X | | | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available) | X | | | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)? | X | | | |
| OTC Labeling | <input checked="" type="checkbox"/> Not Applicable | | | |
| Check all types of labeling submitted. | <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i> | | | | |
| Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> | | | | |
| If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> | | | | |
| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA? | | | | |
| Other Consults | YES | NO | NA | Comment |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> | | | | N/A |
| Meeting Minutes/SPAs | YES | NO | NA | Comment |
| End-of Phase 2 meeting(s)? Date(s): | | | X | |

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

| | | | | |
|---|---|--|--|-----|
| <i>If yes, distribute minutes before filing meeting</i> | | | | |
| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): May 19, 2011 <i>If yes, distribute minutes before filing meeting</i> | X | | | |
| Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | | | | N/A |

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 31, 2012

BLA/NDA/Supp #: NDA 203098

PROPRIETARY NAME: N/A

ESTABLISHED/PROPER NAME: testosterone gel (b)(4)

DOSAGE FORM/STRENGTH: (b)(4) topical gel

APPLICANT: Perrigo Israel Pharmaceuticals Ltd.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone

BACKGROUND: The Sponsor has developed a testosterone gel (b)(4) formulation that contains different inactive ingredients from that specified in the reference listed drug (RLD), Androgel® (testosterone gel) 1%.

On June 15, 2007, and December 16, 2008, the Sponsor submitted (b)(4) for the multi-dose pump and unit dose packets (2.5 and 5 gram) to the Office of Generic Drugs (OGD).

On August 28, 2009, the Sponsor received written communication from OGD that, due to the differences in the Sponsor's formulation, clinical safety studies would be required to support the regulatory approval of the product and that the NDA should be filed as a 505(b)(2) with the Office of New Drugs.

On December 17, 2009, The Sponsor submitted IND 107130 to DRUP. On May 19, 2010, a meeting was held between representatives of Perrigo and the FDA. The purpose of the meeting was to discuss their clinical study plan and approval requirements for a 505(b)(2) NDA for testosterone gel (b)(4) Multi-dose Pump and Unit dose Packet.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|-------------------------------|---------------|------------------|-------------------------------------|
| Regulatory Project Management | RPM: | Jeannie Roule | Y |
| | CPMS/TL: | Jennifer Mercier | N |
| Deputy Director | George Benson | | Y |

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|---|-----------|-----------------|---|
| Clinical | Reviewer: | Donald McNellis | Y |
| Cross-Discipline Team Leader (CDTL) | TL: | Suresh Kaul | Y |
| Social Scientist Review (<i>for OTC products</i>) | Reviewer: | N/A | |
| | TL: | | |
| OTC Labeling Review (<i>for OTC products</i>) | Reviewer: | N/A | |
| | TL: | | |
| Clinical Microbiology (<i>for antimicrobial products</i>) | Reviewer: | N/A | |
| | TL: | | |

| | | | |
|---|-----------|-------------------------------------|--------|
| Clinical Pharmacology | Reviewer: | Li Li | Y |
| | TL: | Myong-Jin Kim | Y |
| Biostatistics | Reviewer: | Kate Dwyer | Y |
| | TL: | Mahboob Sobhan | N |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Jeffrey Bray | Y |
| | TL: | Lynnda Reid | Y |
| Statistics (carcinogenicity) | Reviewer: | N/A | |
| | TL: | | |
| Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>) | Reviewer: | N/A | |
| | TL: | | |
| Product Quality (CMC) | Reviewer: | Rajiv Agarwal | Y |
| | TL: | Donna Christner | Y |
| Quality Microbiology (<i>for sterile products</i>) | Reviewer: | | |
| | TL: | | |
| CMC Labeling Review | Reviewer: | Rajiv Agarwal | |
| | TL: | Donna Christner | |
| Facility Review/Inspection | Reviewer: | | |
| | TL: | | |
| OSE/DMEPA (proprietary name) | Reviewer: | Lena Maslov | N |
| | TL: | Zach Oleszczuk | N |
| OSE/DRISK (REMS) | Reviewer: | Shawna Hutchins Cynthia LaCavita | Y N |
| | TL: | Melissa Huelett/ Mary Dempsey | N N |
| OC/DCRMS (REMS) | Reviewer: | | |
| | TL: | | |

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|----------------------------------|---|----------------|---|
| Bioresearch Monitoring (DSI) | Reviewer: | | |
| | TL: | | |
| Controlled Substance Staff (CSS) | Reviewer: | James Tolliver | N |
| | TL: | Michael Klein | N |
| Other reviewers: DDMAC | Janice Maniwang | | N |
| Other attendees | Tapash Ghosh, Biopharmaceutics Reviewer, ONDQA | | Y |

FILING MEETING DISCUSSION:

| | |
|--|--|
| <p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p> | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p> | <input type="checkbox"/> Not Applicable |
| <p>CLINICAL</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: |

| | |
|---|---|
| <ul style="list-style-type: none"> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | |
| <ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>BIOSTATISTICS</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |

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| <p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |

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|---|--|
| <u>CMC Labeling Review</u> | |
| Comments: | <input type="checkbox"/> Review issues for 74-day letter |
| REGULATORY PROJECT MANAGEMENT | |
| Signatory Authority: Audrey Gassman, M.D. | |
| 21st Century Review Milestones (see attached) (listing review milestones in this document is optional): | |
| Comments: | |
| REGULATORY CONCLUSIONS/DEFICIENCIES | |
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input type="checkbox"/> | The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review |
| ACTIONS ITEMS | |
| <input type="checkbox"/> | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). |
| <input type="checkbox"/> | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). |
| <input type="checkbox"/> | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | BLA/BLA supplements: If filed, send 60-day filing letter |
| <input type="checkbox"/> | If priority review: <ul style="list-style-type: none"> notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) |

| | |
|--------------------------|--|
| | <ul style="list-style-type: none"> • notify DMPQ (so facility inspections can be scheduled earlier) |
| <input type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |
| <input type="checkbox"/> | BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822] |
| <input type="checkbox"/> | Other |

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

JEANNIE M ROULE
11/01/2011

JENNIFER L MERCIER
11/01/2011