CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204399Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 204399	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Vogelxo Established/Proper Name: testosterone gel Dosage Form: gel Strengths: Tube (contains 50 mg testosterone per 5 g tube) Packet (contains 50 mg testosterone per 5 g tube) Pump (dispenses 75 g or 60 metered 1.25 g doses)		
Applicant: Upsher-Smith Laboratories, Inc		
Date of Receipt: October 18, 2013 Resubmitted December 4, 2013		
PDUFA Goal Date: June 4, 2014	Action Goal Date (if different):	
RPM: Jeannie Roule		
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 by reliance on published literature, or by reliance on a final OTC monograph. *(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 listed drug(s), OTC final drug monograph)	Information relied-upon (e.g., specific sections of the application or labeling)
Published Literature	Non-Clinical Labeling
NDA 021454	Testim (RLD)

*each source of information should be listed on separate rows, however individual literature articles should not be listed separately

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)

The applicant is relying on previous findings of the potential toxicities of testosterone in nonclinical species and provided references that support the current language in Sections 8.1 and 13.1 of their label. The testosterone in this drug product is equivalent to the testosterone in the submitted references, and was evaluated at or above the proposed human doses.

The sponsor conducted a single-dose, randomized, 2-treatment 4-way replicate crossover bioequivalence study comparing equal doses (100 mg testosterone) of the test (USL240) and reference (Testim) products.

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 cited reliance on 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 #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Listed Drug	NDA #	Did applicant specify reliance on the product? (Y/N)
Testim	021454	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 final OTC drug monograph?

YES ☐ NO ☒

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

Name of drug(s) described in a final OTC drug 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 penetration enhancers (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 different penetration enhancers.

Upsher-Smith's formulation and that of the RLD differ in the following inactive ingredients:

- The USL formulation contains 3 ingredients not found in the RLD: diisopropyl adipate, methyl laurate, and oleyl alcohol
- The RLD contains 1 ingredient not found in the USL formulation: oxacyclohexadecan-2-one
- The amount of alcohol differs between the 2 formulations: USL (b) (4) mg/g, RLD (b) (4) mg/g.

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 intended for the same route of administration 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), FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the Orange Book)).*

***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?

N/A ☐ YES ☒ NO ☐

*If this application relies only on non product-specific published literature, answer **"N/A"***
*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):
NDA 21015, Androgel 1%, Abbvie Pharmaceuticals
NDA 202763, testosterone gel, Teva Pharmaceuticals
NDA 203098, testosterone gel, Perrigo

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)?

N/A ☐ YES ☐ NO ☒

*If this application relies only on non product-specific published literature, answer **"N/A"***
*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):
There are multiple generic and Rx pharmaceutical alternatives listed in the Orange Book.

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):

7320968 Jan 18, 2025
7608605 Apr 21, 2023
7608606 Apr 21, 2023
7608607 Apr 21, 2023
7608608 Apr 21, 2023
7608609 Apr 21, 2023
7608610 Apr 21, 2023
7935690 Apr 21, 2023
8063029 Apr 21, 2023
8178518 Apr 21, 2023

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):
7320968 Jan 18, 2025
7608605 Apr 21, 2023
7608606 Apr 21, 2023
7608607 Apr 21, 2023
7608608 Apr 21, 2023
7608609 Apr 21, 2023
7608610 Apr 21, 2023
7935690 Apr 21, 2023
8063029 Apr 21, 2023
8178518 Apr 21, 2023

(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):

Date(s): *12/21/12*

***Note**, the date(s) entered should be the date the notification occurred (i.e., delivery date(s)), not the date of the submission in which proof of notification was provided*

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

Upsher –Smith was served a summons on February 1, 2013

***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 ☐

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
06/04/2014

Selected Requirements of Prescribing Information (SRPI)

NDA 204399

The Applicant was informed of all of the "NO" responses in their 74 day letter.

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:

NO 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 is 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:

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

Selected Requirements of Prescribing Information (SRPI)

• **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*
• **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:

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:

YES

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**").

Comment:

NO 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment: *Requested in 74 day letter. In the Highlights sectionApplicant will need to add the above statement*

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:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES 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 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:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

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 <u>one</u> of the following three **bolded** verbatim statements (without quotation marks):

<u>If a product **does not** have FDA-approved patient labeling</u>:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

<u>If a product **has** FDA-approved patient labeling</u>:

- **"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: *Requested in 74 day letter. Applicant will need to change to MM/YYYY*

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**.

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:

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
10 OVERDOSAGE

Selected Requirements of Prescribing Information (SRPI)

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:

YES 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:

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

YES 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:

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/s/

JEANNIE M ROULE
06/04/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: May 8, 2014

To: Jeannie Roule
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Trung-Hieu Brian Tran, PharmD, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 204399**
Vogelxo™ (testosterone) gel, for topical use, CIII

This consult is in response to DBRUP's December 30, 2013 request for OPDP's review on the proposed Package Insert (PI) and Medication Guide for Vogelxo™ (testosterone) gel, for topical use, CIII.

OPDP appreciates the opportunity to provide comments on the PI and Medication Guide. OPDP's comments on the Medication Guide for Vogelxo are based on the Medication Guide titled, "Medguide Vogelxo from Sponsor May 02 2014" which was received via email from DBRUP on April 28, 2014 and updated on May 06, 2014.

Please see the attached Medication Guide with our comments incorporated therein. Comments on the PI for Vogelxo were provided under separate cover on April 10, 2014.

If you have any questions, please contact Trung-Hieu Brian Tran, (240) 402-0281, or trung-hieu.tran@fda.hhs.gov.

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/s/

TRUNG-HIEU B TRAN
05/08/2014

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

Date: May 1, 2014

To: Hylton V. Joffe, M.D., Director
Division of Bone, Reproductive and Urologic Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff

From: Alicja Lerner, M.D., Ph.D., Medical Officer
Controlled Substance Staff

Subject: **NDA 204399**
Name: VOGELXO (Testosterone gel 1%)
Indication: 1) Primary hypogonadism (congenital or acquired).
2) Hypogonadotropic hypogonadism (congenital or acquired)
Dosage: 5 g gel daily which corresponds to 50 mg testosterone; it may be increased to 10 g gel daily (100 mg testosterone) after 14 days
Company: Upsher-Smith Laboratories, Inc.

Materials reviewed: NDA is in EDR (Dec 18 2013)
CSS review for Aveed NDA 22219 from Jan 24 2014 (in DARRTS)
Documentation for DBRUP for proposed label changes for section 9 (b) (4) related to all testosterone products

Table of Contents

I. BACKGROUND

This memorandum responds to a consult request from the Division of Bone, Reproductive and Urologic Products, regarding review of the label for Vogelxo (NDA 204399), testosterone gel 1%.

The Sponsor is re-submitting a 505(b)(2) New Drug Application (NDA) for Testosterone Gel 1% (50 mg), identified as USL240, for use in testosterone replacement therapy.
The Sponsor is relying on the Agency's findings of safety and efficacy for the reference listed drug, Testim® 1% (testosterone gel), currently marketed by Auxilium Pharmaceuticals, Inc. (NDA 021-454.

The Sponsor has conducted bioavailability and bioequivalence studies utilizing Testim® as a reference product and states that the results from these studies demonstrated that USL240 is bioequivalent to Testim®. The Sponsor is seeking approval to market Testosterone Gel, 1% in the US for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

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

The drug development program included 5 clinical studies to evaluate USL240 as a new drug for testosterone replacement therapy in the treatment of males with low or no testosterone:

- two studies P06-001 and P06-011 were bioequivalence/bioavailability studies that compared USL240 to the reference drug Testim® 1% (testosterone gel)
- one study P08-001was designed to evaluate irritation and sensitization of USL240 compared with Testim®
- two studies P10-002, and P10-003 assessed the potential for transferability of USL240:
    - one evaluating the ability of hand washing to remove testosterone
    - one to measure transfer through skin-to-skin contact of the application site dosed with USL240 to non-dosed female subjects in the presence of clothing, in the absence of clothing, and after the application site had been washed.

In the tentative approval package there is MedGuide as for other testosterone gel products.
The sponsor states that regarding abuse potential no information related overdose was gained from the USL240 clinical program as all doses were administered by, or under the close supervision of study personnel.

II. CONCLUSIONS

1. Section **9 Drug Abuse and Dependence** of the label for Vogelxo NDA 204399 does not provide the consumers (physicians and patients) current information related to abuse/misuse of this drug, or provide updated safety data related to abuse, misuse, overdose, dependency and withdrawal symptoms.

2. The proposed language in the label under Section 9 Drug Abuse and Dependence is provided in section III Recommendations.
3. All label issues which were discussed in CSS review for Aveed NDA 22219 (Dr. Alicja Lerner, Jan 24 2014, Aveed, NDA 22219 in DARRTS) apply to Vogelxo NDA 204399 label.

III. RECOMMENDATIONS

1. Introduce in Section **9 Drug Abuse and Dependence** of the label for Vogelxo (NDA 204399) a description of the abuse potential of the drug product (b) (4) with goal to review abuse and misuse information of all testosterone products..
2. CSS proposed changes for the Vogelxo label.

9.2 Abuse

Drug abuse is the intentional non-therapeutic use of a drug, even once, for its rewarding psychological and physiological effects. Testosterone, typically in combination with other anabolic steroids, is abused by male and female athletes (b) (4) with the intent of gaining a competitive advantage in sports and is abused by bodybuilders intending to increase muscle mass, decrease fat mass, and improve body appearance. Abuse has been seen in young adult men and women and male and female adolescents, though anabolic androgenic steroids (AAS) are abused and misused in adults, and also older men.

Behaviors Associated with Addiction

Continued abuse of testosterone and other anabolic steroids, leading to addiction is characterized by the following behaviors:

Taking greater dosages than prescribed
Continued drug use despite medical and social problems due to drug use
Spending significant time to obtain the drug when supplies of the drug are interrupted
Giving a higher priority to drug use than other obligations
Having difficulty in discontinuing the drug despite desires and attempts to do so
Experiencing a withdrawal syndrome upon abrupt discontinuation of use

Potential Abuse-Related Adverse Reactions (listed by the order of severity)

Potential adverse reactions of abuse of high dose testosterone in combination with other anabolic steroids include cardiovascular complications, such as cardiomyopathy with impaired systolic and diastolic function, left ventricular hypertrophy, myocardial infarctions, myocardial fibrosis; cerebrovascular complications including strokes, and transient ischemic attacks; convulsions; sleep apnea; dyslipidemias e.g. lowering of HDL cholesterol and psychiatric effects: mood disorders: major depression, mania and hypomania with irritability, psychotic symptoms, hostility, aggression, violence, suicides and homicides. In men, anabolic steroid abuse causes prolonged suppression of the hypothalamic-pituitary-testicular axis (e.g., testicular atrophy, subfertility, or infertility. Adverse reactions that occur in women include hirsutism, virilization, clitoral enlargement, breast atrophy, and menstrual irregularity.

9.3 Dependence

Physical dependence is characterized by withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Although drug dependence has not been documented in individuals using approved doses of testosterone for approved indications, dependence has been observed in some individuals who abused higher doses of testosterone in combination with other anabolic steroids. The withdrawal syndrome can last for weeks or months and is characterized by depressed mood, major depressions, and suicides, fatigue, craving, restlessness, anorexia, insomnia, and decreased libido and suppression of the hypothalamic-pituitary-testicular (HPT) axis and hypogonadotropic hypogonadism.

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/s/

ALICJA LERNER
05/01/2014

MICHAEL KLEIN
05/01/2014

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

PATIENT LABELING REVIEW

Date:	April 29, 2014
To:	Hylton Joffe, MD Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Focused Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	VOGELXO (testosterone)
Dosage Form and Route:	Gel for Topical Use
Application Type/Number:	NDA 204-399
[redacted] (b) (4)	
Applicant:	Upsher-Smith Laboratories Inc.

1 INTRODUCTION

On October 17, 2012, Upsher-Smith Laboratories Inc., submitted for the Agency's review a request for final approval of the New Drug Application (NDA 204399) for Vogelxo (testosterone) gel. Vogelxo (testosterone) gel, received tentative approval on August 16, 2013, and is indicated for indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

This focused review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on December 20, 2013, for DMPP to provide a focused review of the Applicant's proposed Medication Guide (MG) for Vogelxo (testosterone) gel.

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

2 MATERIAL REVIEWED

- Draft Vogelxo (testosterone) gel MG received on December 04, 2013 and received by DMPP on April 29, 2014.
- Draft Vogelxo (testosterone) gel Prescribing Information (PI) received on December 04, 2013, revised by the Review Division throughout the review cycle, and received by DMPP on April 29, 2014.
- VOGELXO (testosterone) gel comparator labeling tentatively approved August 16, 2013.

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.

In our focused 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 focused review of the MG is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
04/29/2014

MELISSA I HULETT
04/29/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 20, 2014
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 204399
Product Names and Strengths:	Vogelxo (testosterone) gel, 50 mg Testosterone gel, 50 mg
Product Type:	Single Ingredient
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Upsher-Smith Laboratories, Inc.
Submission Date:	December 5, 2013
OSE RCM #:	2014-779
DMEPA Primary Reviewer:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lisa V. Khosla, PharmD, MHA

1. REASON FOR REVIEW

The Division of Medication Error Prevention and Analysis (DMEPA) has been requested by the Division of Bone, Reproductive and Urologic Products (DBRUP) to evaluate the container label, carton and insert labeling for Vogelxo and for its proposed authorized generic, Testosterone Gel for vulnerabilities to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
ISMP Newsletters	C
Previous DMEPA Reviews	D
ISMP MERP Database	E
Regulatory History	F
Container Label, Carton, and Insert Labeling	G

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton and insert labeling to identify deficiencies that may lead to medication errors. We identified statements that could be revised to decrease clutter and to better communicate how to safely use the product on the container and carton labeling. Therefore, we made recommendations to improve clarity and increase prominence of important information in Section 4.

4. CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label and carton labeling can be improved to increase the prominence of important information on the label in order to promote the safe use of the product.

If you have further questions or need clarifications, please contact Jamila Mwidau, OSE Regulatory Project Manager, at (301) 796-4989.

4.1 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

DMEPA advises the recommendations below be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling for Vogelxo (testosterone gel)

1. Revise the usual dosage statement on the container label for the tube and packet, [redacted] (b) (4) to read "Usual dosage: See package insert" so that the user is directed to read all pertinent dosage and administration information to safely use this product. This recommendation is also meant to de-clutter the label.

2. Consider modifying the statement (located on the principal display panel [PDP] of the carton labeling for all package configurations) [redacted] (b) (4) to read "To be applied to the shoulders and upper arms" for clarity and to decrease clutter on the PDP.

3. Increase the prominence of the NDC number to assist the pharmacy in dispensing the correct product. Improving the prominence may be done by improving the color contrast or by removing this information from the color block.

4. Revise the statement "Alcohol based gels are flammable. Avoid fire, flame . . ." from all upper case letters to mixed case letters.

B. Container Labels and Carton Labeling for Authorized Generic for Testosterone Gel

1. See recommendations A1 through A4**.**

4.2 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

1. Add the NDC number for the individual tube to Section 16 (How Supplied/Storage and Handling) to complete this section of the insert labeling**.**

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vogelxo that Upsher-Smith Laboratories, Inc. (USL) submitted on December 4, 2013, and the reference listed drug (RLD).

Table 2. Relevant Product Information for Vogelxo and the Reference Listed Drug [RLD], Testim

Product Name	**Vogelxo** (Testosterone) Gel	**Testim** (Testosterone) Gel (RLD)
Active Ingredient	Testosterone	Testosterone
Indication	Testosterone replacement therapy in adult males for the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)	Testosterone replacement therapy in adult males for the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)
Route of Administration	Topical	Topical
Dosage Form	Gel	Gel
Strength	50 mg of testosterone per tube/packet or 12.5 mg of testosterone per pump actuation	50 mg of testosterone per tube/packet or 12.5 mg of testosterone per pump actuation
Dose and Frequency	The starting dose is 50 mg of testosterone (one tube or packet or 4 pump actuations) applied topically once daily preferably in the morning to clean, dry, intact skin of the shoulders and/or upper arms. Dose may be increased to 100 mg of testosterone (two tubes/packets or 8 pump actuations)	The starting dose is 50 mg of testosterone (one tube or packet or 4 pump actuations) applied topically once daily preferably in the morning to clean, dry, intact skin of the shoulders and/or upper arms. Dose may be increased to 100 mg of testosterone (two tubes/packets or 8 pump actuations)
How Supplied	Unit-dose tubes in cartons of 30 and unit-dose packets in cartons of 30. Each tube or packet contains 50 mg of testosterone Metered-dose pump is supplied in cartons of 2. Each pump delivers 12.5 mg of testosterone per complete pump actuation. Each pump actuation delivers 1.25 gram of gel. Each metered-dose pump contains 75 gram of gel and can dispense 60 doses.	Unit dose tubes in cartons of 30; each tube delivers 50 mg of testosterone
Storage	Controlled Room Temperature	Controlled Room Temperature

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 15, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the Androgel (NDA 021015) label and labeling because this testosterone product is supplied as a pump packaging configuration as is Vogelxo. The RLD, Testim, is available in a tube.

Table 3: FAERS Search Strategy	
Date Range	**From December 17, 2013 (date of last search in OSE Review # 2013-2654/S-020 dated January XX, 2014) though January 16, 2014**
Drug Names	**Product Name: "Testim"** **Verbatim Name: "Testim"***
MedDRA Search Strategy	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

No cases were retrieved from this search.

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. ISMP NEWSLETTERS

C.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on January 16, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Range	No date limitation used
ISMP Newsletter Search Strategy	ISMP Community Newsletter ISMP Acute Care Newsletter
Search Terms	"Testim"

C.2 Results

Although there were reports of secondary exposure involving children and adult women, no cases have been reported since 2010. Testim (NDA 021454) was approved October 31, 2002.

APPENDIX D. PREVIOUS DMEPA REVIEWS

D.1 Methods

We searched the "L: Drive" (also known as the shared drive) using the term, "Vogelxo" to identify reviews previously performed by DMEPA.

D.2 Results

One review was retrieved. This review (OSE Review # 2013-1080 dated July 11, 2013 under NDA 204399) found the proposed proprietary name, Vogelxo, to be acceptable.

APPENDIX E. MERP Reports (ISMP Data Request)

E.1 Methods

We searched the ISMP MERP database on December 13, 2013 using the criteria in Table 4, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the current container label, carton and insert labeling.

Table 4: ISMP MERP Search Strategy

Date	December 13, 2013 (from the date of the last search in OSE Review # 2013-2654/S-020 dated January XX, 2014) to January 23, 2014
Drug Names	"Testim 1 % (Testosterone)"
MedDRA Search Strategy	General medication errors (including secondary exposures and cases of labeling confusion)

E.2 Results

No cases were retrieved from this search.

APPENDIX F. Regulatory History

NDA 204399 received tentative approval on August 16, 2013 because the listed drug upon which the application relied (Testim) was subject to a period of patent protection and could, therefore, not be approved until the period had expired. In addition Upsher-Smith Pharmaceuticals (USL), Inc informed the Agency that the patent owner (Auxilium Pharmceuticals) had initiated a patent infringement suit against USL. On December 4, 2013, this infringement was decided in USL's favor and therefore, USL submitted a Request for Final Approval. Simultaneous to this request, the Applicant submitted a proposed REMS and draft labeling for an authorized generic product.

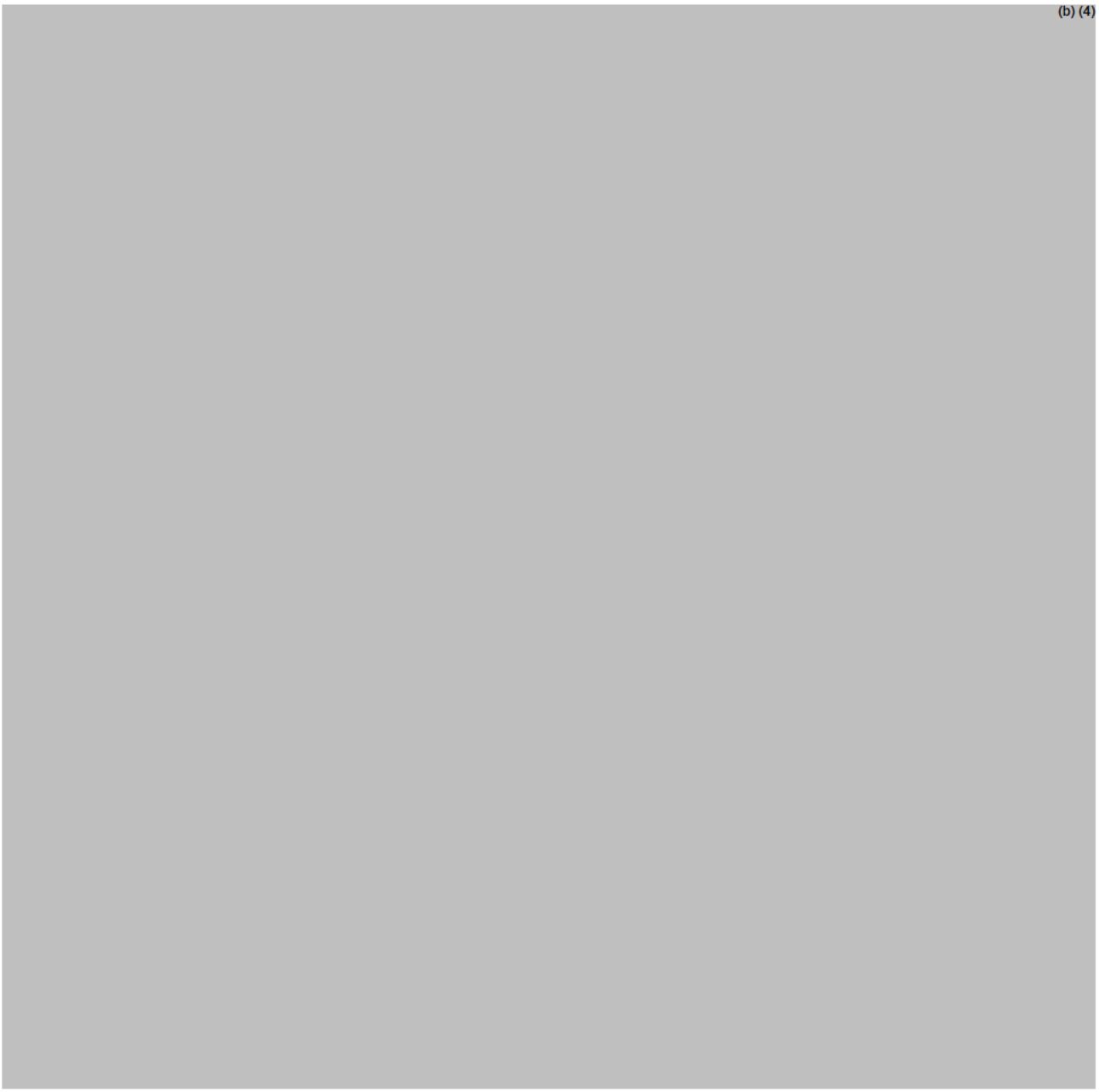
APPENDIX G. CONTAINER LABEL and CARTON LABELING

G.1 List of Label and Labeling Reviewed

We reviewed the following Vogelxo container labels and carton labeling submitted by Upsher-Smith Laboratories, Inc. on July 29, 2013 and the container labels and carton labeling for the authorized generic product, testosterone gel, submitted December 4, 2013.

G.2 Label and Labeling Images

Container Labels (TUBE) for Vogelxo and for the authorized generic, Testosterone Gel



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/s/

DENISE V BAUGH
04/21/2014

LISA V KHOSLA
04/22/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: April 21, 2014

To: Jeannie Roule
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Trung-Hieu Brian Tran, PharmD/ MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Twyla Thompson, PharmD
Group Leader
Office of Prescription Drug Promotion

Subject: **NDA: 204399**
Vogelxo™ (testosterone) gel, for topical use, CIII

This consult is in response to DBRUP's December 30, 2013 request for OPDP's review on the proposed PI and Medication Guide for Vogelxo™ (testosterone undecanoate) injection, for intramuscular use CIII.

OPDP appreciates the opportunity to provide comments on the PI and Medication Guide. OPDP's comments on the PI for Vogelxo are based on the substantially complete version of the PI titled, "Proposed PI Vogelxo Dec 2013" which was received via email from DBRUP on March 27, 2014 and updated on April 17, 2014.

Please see the attached PI with our comments incorporated therein. Comments on the Medication Guide for Vogelxo will be provided under separate cover.

If you have any questions, please contact Trung-Hieu Brian Tran, (240) 402-0281, or trung-hieu.tran@fda.hhs.gov.

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TRUNG-HIEU B TRAN
04/21/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 1, 2014
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 204399
Product Names and Strengths:	Vogelxo (testosterone) gel, 50 mg Testosterone gel, 50 mg
Product Type:	Single Ingredient
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Upsher-Smith Laboratories, Inc.
Submission Date:	December 5, 2013
OSE RCM #:	2013-2867
DMEPA Primary Reviewer:	Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader:	Lisa V. Khosla, PharmD, MHA

1. REASON FOR REVIEW

The Division of Medication Error Prevention and Analysis (DMEPA) has been requested by the Division of Bone, Reproductive and Urologic Products (DBRUP) to evaluate the container label, carton and insert labeling for Vogelxo and for its proposed authorized generic, Testosterone Gel for vulnerabilities to medication errors.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B
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Previous DMEPA Reviews	D
ISMP MERP Database	E
Regulatory History	F
Container Label, Carton, and Insert Labeling	G

3. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton and insert labeling to identify deficiencies that may lead to medication errors. We identified statements that could be revised to decrease clutter and to better communicate how to safely use the product on the container and carton labeling. Therefore, we made recommendations to improve clarity and increase prominence of important information in Section 4.

4. CONCLUSION & RECOMMENDATIONS

We conclude that the proposed container label and carton labeling can be improved to increase the prominence of important information on the label in order to promote the safe use of the product.

If you have further questions or need clarifications, please contact Jamila Mwidau, OSE Regulatory Project Manager, at (301) 796-4989.

4.1 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

DMEPA advises the recommendations below be implemented prior to approval of this NDA:

A. Container Labels and Carton Labeling for Vogelxo (testosterone gel)

1. Revise the usual dosage statement on the container label for the tube and packet, (b) (4) to read "Usual dosage: See package insert" so that the user is directed to read all pertinent dosage and administration information to safely use this product. This recommendation is also meant to de-clutter the label.

2. Consider modifying the statement (located on the principal display panel [PDP] of the carton labeling for all package configurations) (b) (4) to read "To be applied to the shoulders and upper arms" for clarity and to decrease clutter on the PDP.

3. Increase the prominence of the NDC number to assist the pharmacy in dispensing the correct product. Improving the prominence may be done by improving the color contrast or by removing this information from the color block.

4. Revise the statement "Alcohol based gels are flammable. Avoid fire, flame . . ." from all upper case letters to mixed case letters.

B. Container Labels and Carton Labeling for Authorized Generic for Testosterone Gel

1. See recommendations A1 through A4**.**

4.2 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review division prior to the approval of this NDA:

1. Add the NDC number for the individual tube to Section 16 (How Supplied/Storage and Handling) to complete this section of the insert labeling**.**

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vogelxo that Upsher-Smith Laboratories, Inc. (USL) submitted on December 4, 2013, and the reference listed drug (RLD).

Table 2. Relevant Product Information for Vogelxo and the Reference Listed Drug [RLD], Testim

Product Name	**Vogelxo** (Testosterone) Gel	**Testim** (Testosterone) Gel (RLD)
Active Ingredient	Testosterone	Testosterone
Indication	Testosterone replacement therapy in adult males for the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)	Testosterone replacement therapy in adult males for the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)
Route of Administration	Topical	Topical
Dosage Form	Gel	Gel
Strength	50 mg of testosterone per tube/packet or 12.5 mg of testosterone per pump actuation	50 mg of testosterone per tube/packet or 12.5 mg of testosterone per pump actuation
Dose and Frequency	The starting dose is 50 mg of testosterone (one tube or packet or 4 pump actuations) applied topically once daily preferably in the morning to clean, dry, intact skin of the shoulders and/or upper arms. Dose may be increased to 100 mg of testosterone (two tubes/packets or 8 pump actuations)	The starting dose is 50 mg of testosterone (one tube or packet or 4 pump actuations) applied topically once daily preferably in the morning to clean, dry, intact skin of the shoulders and/or upper arms. Dose may be increased to 100 mg of testosterone (two tubes/packets or 8 pump actuations)
How Supplied	Unit-dose tubes in cartons of 30 and unit-dose packets in cartons of 30. Each tube or packet contains 50 mg of testosterone Metered-dose pump is supplied in cartons of 2. Each pump delivers 12.5 mg of testosterone per complete pump actuation. Each pump actuation delivers 1.25 gram of gel. Each metered-dose pump contains 75 gram of gel and can dispense 60 doses.	Unit dose tubes in cartons of 30; each tube delivers 50 mg of testosterone
Storage	Controlled Room Temperature	Controlled Room Temperature

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on January 15, 2014 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the Androgel (NDA 021015) label and labeling because this testosterone product is supplied as a pump packaging configuration as is Vogelxo. The RLD, Testim, is available in a tube.

Table 3: FAERS Search Strategy	
Date Range	**From December 17, 2013 (date of last search in OSE Review # 2013-2654/S-020 dated January XX, 2014) though January 16, 2014**
Drug Names	**Product Name: "Testim"** **Verbatim Name: "Testim"***
MedDRA Search Strategy	**Medication Errors** [HLGT] **Product Packaging Issues** [HLT] **Product Label Issues** [HLT] **Product Quality Issues** (NEC)[HLT]

B.2 Results

No cases were retrieved from this search.

B.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

APPENDIX C. ISMP NEWSLETTERS

C.1 Methods

We searched the Institute for Safe Medication Practices (ISMP) newsletters on January 16, 2014 using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
Date Range	No date limitation used
ISMP Newsletter Search Strategy	ISMP Community Newsletter ISMP Acute Care Newsletter
Search Terms	"Testim"

C.2 Results

Although there were reports of secondary exposure involving children and adult women, no cases have been reported since 2010. Testim (NDA 021454) was approved October 31, 2002.

APPENDIX D. PREVIOUS DMEPA REVIEWS

D.1 Methods

We searched the "L: Drive" (also known as the shared drive) using the term, "Vogelxo" to identify reviews previously performed by DMEPA.

D.2 Results

One review was retrieved. This review (OSE Review # 2013-1080 dated July 11, 2013 under NDA 204399) found the proposed proprietary name, Vogelxo, to be acceptable.

APPENDIX E. MERP Reports (ISMP Data Request)

E.1 Methods

We searched the ISMP MERP database on December 13, 2013 using the criteria in Table 4, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the current container label, carton and insert labeling.

Table 4: ISMP MERP Search Strategy

Date	December 13, 2013 (from the date of the last search in OSE Review # 2013-2654/S-020 dated January XX, 2014) to January 23, 2014
Drug Names	"Testim 1 % (Testosterone)"
MedDRA Search Strategy	General medication errors (including secondary exposures and cases of labeling confusion)

E.2 Results

No cases were retrieved from this search.

APPENDIX F. Regulatory History

NDA 204399 received tentative approval on August 16, 2013 because the listed drug upon which the application relied (Testim) was subject to a period of patent protection and could, therefore, not be approved until the period had expired. In addition Upsher-Smith Pharmaceuticals (USL), Inc informed the Agency that the patent owner (Auxilium Pharmceuticals) had initiated a patent infringement suit against USL. On December 4, 2013, this infringement was decided in USL's favor and therefore, USL submitted a Request for Final Approval. Simultaneous to this request, the Applicant submitted a proposed REMS and draft labeling for an authorized generic product.

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

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

/s/

DENISE V BAUGH
04/01/2014

LISA V KHOSLA
04/03/2014

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

Product Title	**VOGELXO ™ (testosterone) gel for topical use CIII**
Applicant	Upsher-Smith Laboratories, Inc.
Application/Supplement Number	NDA 204399
Type of Application	Original
Indication(s)	For replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired) • Hypogonadotropic hypogonadism (congenital or acquired)
Established Pharmacologic Class[1]	Androgen
Office/Division	ODE III/DBRUP
Division Project Manager	Jeannie Roule
Date FDA Received Application	October 18, 2012
Goal Date	August 18, 2013
Date PI Received by SEALD	August 12, 2013
SEALD Review Date	August 13, 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.

Highlights (HL)

GENERAL FORMAT

NO 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: *Top, left and right margins are > ½ inch. Decrease to ½ inch.*

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 is 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: *The length of HL is greater than one-half page. DBRUP will grant a waiver in the approval letter.*

NO 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *The Indications and Usage heading in HL is not in the center of the horizontal line. Center it.*

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

Comment:

NO 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: *The numerical identifier in parenthesis [(e.g., (5.4)] is not included at the end of the third bullet under the Warnings and Precautions heading in the HL.*

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

Selected Requirements of Prescribing Information

• **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*
• **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: *We recommend that commas be inserted after the dosage form and route of administration in the product title as follows: VOGELXO ™ (testosterone) gel, for topical use, CIII*

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:

Selected Requirements of Prescribing Information

YES 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**").

Comment:

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: *The bolded italicized verbatim statement "See full prescribing information for complete boxed warning" is not centered immediately beneath the heading in the Boxed Warning. There is a white space between the two. Delete the white space.*

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

N/A 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

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

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.
Comment:

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:

NO 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: *Subsection heading 7.2 reads correctly as "Oral Anticoagulants" in the TOC but reads as* (b) (4) *in the FPI. Correct the subsection heading in the FPI so that it matches the TOC.*

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**.

Comment:

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

Comment:

NO 33. All subsection headings must be indented, not bolded, and in title case.

Comment: *The second sentence of the heading for subsection 17.4 in the TOC is not indented. Indent it.*

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:

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

Selected Requirements of Prescribing Information

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
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: *Under subsection 5.4, the cross-reference should read as "[see Adverse Reactions (6.2)]" and not* (b) (4)

The following cross-references are not in italics:

- *In the Boxed Warning, all the cross-references are not italicized. Italicize all of them.*
- *Under the second bullet in Section 4, the cross-reference* (b) (4) should read as "*[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)]."*
- *Under the second bullet in subsection 5.1 the cross-reference* (b) (4) should read as "*[see Contraindications (4)]*."

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

Selected Requirements of Prescribing Information

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

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 at the beginning of Section 17 is italicized. It does not need to be italicized as shown above.*

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

/s/

ABIMBOLA O ADEBOWALE
08/13/2013

LAURIE B BURKE
08/13/2013

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: August 6, 2013

To: Jeannie Roule, RPM
Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA 204399**
OPDP labeling comments for VOGELXO™ (testosterone) gel for topical use CIII

OPDP has reviewed the draft product labeling (PI) for VOGELXO™ (testosterone) gel for topical use CIII as requested in the consult from DBRUP dated December 14, 2012.

OPDP's comments on the labeling, which are based on the draft version of the PI emailed by Jeannie Roule on July 24, 2013, are provided below.

If you have any questions, please feel free to contact me:

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

Thank you! OPDP appreciates the opportunity to provide comments on this material.

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

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

/s/

JINA KWAK
08/06/2013

Selected Requirements of Prescribing Information (SRPI)

NDA 204399

The Applicant was informed of all of the "NO" responses in their 74 day letter.

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:

NO 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 is 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:

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

Selected Requirements of Prescribing Information (SRPI)

• **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*****
• **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:

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:

YES

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**").

Comment:

NO 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment: *Requested in 74 day letter. In the Highlights sectionApplicant will need to add the above statement*

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:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES 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 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:

Selected Requirements of Prescribing Information (SRPI)

Contraindications

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: *Requested in 74 day letter. Applicant will need to change to MM/YYYY*

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**.

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:

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
10 OVERDOSAGE

Selected Requirements of Prescribing Information (SRPI)

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:

YES 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:

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

YES 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:

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/s/

JEANNIE M ROULE
08/05/2013

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

Date: July 31, 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 204-399 Sequence 0004 - Vogelxo (Testosterone Gel)
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: 5 g unit dose tube or packet providing 50 mg of testosterone per tube/packet.
Sponsor: Usher Smith Laboratories Inc.

Materials reviewed: Proposed Labeling for Vogelxo (Testosterone Gel) submitted on January 22, 2013 under NDA

Table of Contents

I. Summary

A. Background

This memorandum is in response to a consult request dated December 13, 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 1% under the NDA 204-399 .

B. Conclusions:

1. This proposed language is identical to that recommended by CSS to the Division in April 2012, for Testosterone Gel 1% 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 Vogelxo (Testosterone Gel) 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

Vogelxo (Testosterone Gel) 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 translucent, alcohol-based gel containing 1% testosterone in dissolved form. The product is topically applied and provides transdermal absorption of testosterone following application to the skin.

Vogelxo (Testosterone Gel) is packaged in 5 g quantity containing 50 mg testosterone, into a unit dose tube and a unit dose packet. The product is also packaged as a multiple dose metered pump each capable of dispensing 15 x 50 mg doses (4 x 1.25 g actuations per 50 mg dose).

Components include testosterone, alcohol (Ethyl Alcohol, (b) (4)), glycerin ((b) (4)), diisopropyl adipate ((b) (4)), methyl laurate ((b) (4)), oleyl alcohol ((b) (4)), carbomer homopolymer type C ((b) (4)), propylene glycol, polyethylene glycol (b) (4) ((b) (4)), pruified water, and tromethamine ((b) (4)).

B. Integrated assessment

1. Labeling issues

The specific language of Section 9 of the proposed labeling for Vogelxo, is provided below in italics.

DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Vogelxo 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 1% 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 of NDA 22-219 for AVEED (DAARTS, NDA 22-219, August 19, 2009, Author: James M. Tolliver, Ph.D.). 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 Vogelxo (Testosterone Gel) 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
07/31/2013

MICHAEL KLEIN
07/31/2013

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

PATIENT LABELING REVIEW

Date:	July 30, 2013
To:	Hylton Joffe, MD Director **Division of Bone, Reproductive and Urologic Products (DBRUP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Melissa Hulett, MSBA, BSN, RN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Jina Kwak, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	VOGELXO (testosterone)
Dosage Form and Route:	Gel for Topical Use
Application Type/Number:	NDA 204-399 (b) (4)
Applicant:	Upsher-Smith Laboratories Inc.

1 INTRODUCTION

On October 17, 2012, Upsher-Smith Laboratories Inc., submitted for the Agency's review a New Drug Application (NDA 204399) for Vogelxo (testosterone) gel, indicated for indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on December 14, 2012, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for Vogelxo (testosterone) gel.

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

2 MATERIAL REVIEWED

- Draft Vogelxo (testosterone) gel MG received on October 18, 2012 and received by DMPP on July 24, 2013.
- Draft Vogelxo (testosterone) gel MG received on October 18, 2012 and received by OPDP on July 24, 2013.
- Draft Vogelxo (testosterone) gel Prescribing Information (PI) received on October 18, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on July 24, 2013.
- Draft Vogelxo (testosterone) gel Prescribing Information (PI) received on October 18, 2012, revised by the Review Division throughout the review cycle, and received by OPDP on July 24, 2013.
- Approved testosterone gel 1% (NDA 203098) comparator labeling dated January 31, 2013.

3 REVIEW METHODS

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

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

In our collaborative 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 and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
07/30/2013

JINA KWAK
07/30/2013

MELISSA I HULETT
07/30/2013

LASHAWN M GRIFFITHS
07/30/2013

M E M O R A N D U M

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

DATE: May 20, 2013

TO: Hylton V. Joffe, M.D.
Director, Division of Reproductive and Urologic Products
Office of Drug Evaluation III

FROM: Seongeun Julia Cho, Ph.D.
Bioequivalence Branch
Division of Bioequivalence and GLP Compliance
Office of Scientific Investigations

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
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 (DBGLPC)
Office of Scientific Investigations (OSI)

SUBJECT: Review of EIR covering NDA 204-399, Testosterone Gel 1%, from Upsher-Smith Laboratories, Inc.

At the request of the Division of Division of Reproductive and Urologic Products (DRUP), DBGLPC conducted an inspection of the analytical portion of the following study.

P06-011: Randomized, Open-label, 2-Treatment, 4-Way Replicate Crossover, Bioequivalence Study of Testosterone 1% Topical Gel Formulation by Upsher-Smith Laboratories versus Testim (1% Testosterone, Reference) in Hypogonadal Male Volunteers

The ysis of testost ed at (b) (4) (now known as (b) (4) (b) (4) The audit was conducted by ORA investigato and OSI/DBGLPC scientist Seongeun Cho from (b) (4) . The audit included a thorough review of st

records and documentation, examination of facilities and equipment, and interviews and discussions with the firm’s management and staff.

Following the inspection, one-item Form FDA 483 was issued (Attachment 1). The observation and our evaluation of the site’s response follow.

1) **Failure to apply consistent integration parameters to all chromatograms in a run. Calibrators, quality control samples, and subject samples were individually re-integrated without proper documentations.**

In a number of runs for the study P06-011, integration parameters used for peak identification and quantification were not consistent for all samples in a run. The firm's standard operating procedure (SOP) at the time allowed modifying integration parameters in Analyst software to adjust baselines or peak shapes for chromatograms. It was verified during the inspection that the Analyst audit trail captured all activities during peak integration and data processing. The inspection evaluated a number of chromatograms to verify the reasons and processes for adjustments. In all cases examined, either modifications resulted in minimal change to peak areas, or the changes were justified to integrate the peaks correctly.

The firm stated that in 2009 they implemented a procedure to improve the integration process. During the inspection, the firm re-processed all runs according to the new integration procedure, which requires application of consistent integration parameters to all samples in a run. Re-processed data are attached in this memo (Attachment 2). Following re-integration, the acceptance of all runs in the study remained unchanged except for one (Run 96). For Run 96, the acceptance status changed from fail to pass, which was attributed to a minute change in the peak area value for a matrix blank sample. This discrepancy was verified by examining the chromatograms and determined not to be deliberate. The results of Run 96 from the original analysis, repeated analysis, and re-integration were compared and differences were found not to be significant (<5%) in the majority of the samples. Comparative results for Run 96 as well as for all other runs are included in the attachment (Attachment 2).

Conclusion and recommendation:

Although inconsistent integration in chromatogram processing is objectionable, the inspection did not identify any incidents in which integrity or accuracy of data was compromised. In addition, the firm provided results of chromatograms re-processed with an improved procedure (Attachment 2). It is recommended the team review the new results and take them into consideration in bioequivalence evaluation.

Seongeun (Julia) Cho, Ph.D.
Bioequivalence Branch, DBGLPC, OSI

Final Classifications:

VAI: (b) (4)

Attachments:

Attachment 1: Form FDA 483
Attachment 2: Results table comparing original and re-processed data

CC:
CDER OSI PM TRACK
OSI/DBGLPC/Taylor/Haidar/Skelly/Dejernett/CF
OCP/DCP3/Edward Bashaw/Lanyan Fang/Yow-Ming Wang
OND/ODEIII/DRUP/Hylton Joffe/Jeannie Roule
ORA/Lawrence Lee/Yvette Arline/Ann Montemurro
Draft: SC 5/17/2013
Edit: MFS 5/20/13
OSI: BE6409; O:\Bioequiv\EIRCover\204399.ups.tes.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laborat ctice Compliance/Electronic Archive/BEB
FACTS: (b) (4)

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/s/

SEONGEUN CHO
05/21/2013

SAM H HAIDAR
05/21/2013

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

Label, Labeling and Packaging Review

Date:	May 1, 2013
Reviewer:	Manizheh Siahpoushan, PharmD Division of Medication Error Prevention and Analysis
Team Leader:	Zachary Oleszczuk, PharmD Division of Medication Error Prevention and Analysis
Division Director:	Carol Holquist, RPh Division of Medication Error Prevention and Analysis
Drug Name and Strength:	Testosterone Gel 50 mg of testosterone per 5 grams of gel
Application Type/Number:	NDA 204399
Applicant/sponsor:	Upsher-Smith Laboratories Inc.
OSE RCM #:	2013-395 and 2013-713

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

Contents

1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling as well as the Medication Guide for Tradename NDA 204399 for areas of vulnerability that could lead to medication errors.

1.1 BACKGROUND AND REGULATORY HISTORY

The Applicant submitted a 505 (b)(2) application for NDA 204399 on October 18, 2012. Additionally, on January 30, 2013, the Applicant submitted a request for proprietary name review for (b) (4), which was found unacceptable by DMEPA. This decision was communicated to the Applicant in a teleconference dated March 11, 2013. Subsequently, the Applicant submitted the proposed proprietary name, (b) (4) to the Agency on March 19, 2013. DMEPA's preliminary assessment of the proposed name, (b) (4) has found this name unacceptable. This decision will be communicated to the Applicant in a teleconference scheduled on May 2, 2013.

The Reference Listed Drug (RLD) is Testim 1%, NDA 021454 held by Auxilium Pharmaceutical, Inc., approved on October 31, 2002. Although the labeling for the proposed product and Testim will be similar, due to differences of the inactive ingredients, the Applicant conducted a hand washing study to assess the removal of the drug product from the hands after being washed with soap and water as well as a transferability study to assess the extent of testosterone transfer following application of the proposed product.

1.2 PRODUCT INFORMATION

The following product information is provided in the March 19, 2012 proprietary name submission.

- Active Ingredient: Testosterone
- Indication of Use: Testosterone replacement therapy in adult males for the treatment of primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)
- Route of Administration: Topical
- Dosage Form: Gel
- Strength: 1% (50 mg of testosterone per tube/packet or 12.5 mg of testosterone per pump actuation)
- Dose and Frequency: The starting dose is 50 mg of testosterone (one tube or packet or 4 pump actuations) applied topically once daily preferably in the morning to clean, dry, intact skin of the shoulders and/or upper arms. Dose may be increased to 100 mg of testosterone (two tubes/packets or 8 pump actuations)
- How Supplied:
    - Unit-dose tubes in cartons of 30 and unit-dose packets in cartons of 30. Each tube or packet contains 50 mg of testosterone in 5 gram of gel

- Metered-dose pump is supplied in cartons of two. Each pump delivers 12.5 mg of testosterone per complete pump actuation. Each pump actuation delivers 1.25 gram of gel. Each metered-dose pump contains 75 gram of gel and can dispense 60 doses.

- Storage: Controlled Room Temperature
- Container and Closure System:
  - Tube: The package presentation is a printed 3" x 5" (b) (4) blind-end tube with a removable orifice seal and white ribbed screw cap and filled with 5 gram of drug product, and then the open end is crimped and sealed under (b) (4).
  - Packet: Consists of printed (b) (4) foil. The product contact layer of the foil is composed of (b) (4). The packet contains 5 grams of drug product and (b) (4) sealed.
  - Pump: Consists of a multiple dose 100 mL pouch contained within a bottle sealed with a metering pump. Each pump dispenses 1.25 gram of product when the pump mechanism is fully depressed once. The pump contains 60 metered actuations. Pouches are (b) (4) filled with 88 grams of drug product (b) (4).

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS and ISMP*** databases for Testim medication error reports on July 12, 2012 and August 12, 2012 in OSE Review #'s 2011-2653 and 2012-1975, dated February 12, 2013. Therefore, an updated FAERS search was not conducted in this review.

The July 12, 2012 and August 12, 2012 FDA AERS and ISMP databases retrieved a total of 430 relevant types of Testim medication error cases that were analyzed in OSE Review #'s 2011-2653 and 2012-1975. The type of errors included:

- Wrong technique of administration (n=145)
- Secondary exposure and transference (n=96)
- Dose omission (n=64)
- Wrong drug (n=49)
- Wrong dose (n=58)
- Wrong route of administration (n=10)
- Wrong time of administration (n=7)

*** This document contains proprietary data from the Institute for Safe Medication Practices (ISMP) and (b) (4) which cannot be shared outside of the FDA. Government users wanting this information must contact Matthew Grissinger, RPh, FISMP, FASCP, Director, Error Reporting Programs at (215) 947-7797.

- Wrong duration of administration (n=1)

DMEPA addressed these medication error cases and made recommendations to the Applicant for the Testim container labels, carton, and insert labeling as well as the Medication Guide in the February 12, 2013 review. We reviewed those comments to ensure the same or similar recommendations are made for the proposed product in this review, where appropriate.

Additionally, we reviewed the proposed product's container labels, carton, and package insert labeling as well as the Medication Guide submitted by the Applicant.

2.1 LABELS AND LABELING

Using the principles of Human Factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels (tube, packet, and pump) submitted March 19, 2013 (Appendix B)
- Carton Labeling (tube, packet, and pump) submitted March 19, 2013 (Appendix C)
- Insert Labeling submitted March 19, 2013 (no image)
- Medication Guide submitted March 19, 2013 (no image)

3 MEDICATION ERROR RISK ASSESSMENT

The following sections describe the results of our July 12, 2012 and August 12, 2012 FDA AERS and ISMP searches as they relate to this review, as well as the risk assessment of the proposed product design, labels, and labeling.

3.1 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

DMEPA identified eight types of errors in OSE Review #'s 2011-2653 and 2012-1975, dated February 12, 2013. The eight types of errors were wrong technique (including wrong application site), secondary exposure and transference, dose omission, wrong drug, wrong dose, wrong route of administration, wrong time of administration, and wrong duration of administration. However, of those, only the wrong technique (including wrong application site), secondary exposure and transference, and wrong drug medication errors were attributed to labels and labeling.

Regarding Wrong Technique errors, including wrong site of administration errors, we note that, unlike some other products within the class of topical testosterone products, the insert labeling for the proposed product does not contain a graphic diagram depicting approved product application sites (i.e., upper arms and/or shoulders). Although Testim 1% was only implicated in five out of 111 medication error cases involving wrong site of product application, the remaining 106 cases involved similar errors with other topical

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

testosterone products. The insert labeling of most topical testosterone products contains a diagram. A diagram may be especially helpful for patients who may be switched from one topical testosterone product to another if the products have different sites of application. Thus, the addition of a diagram to demonstrate proper application sites in the Dosing and Administration section as well as the Medication Guide may help minimize the risk of medication errors.

Additionally, although only a few cases of secondary exposure and transference involved Testim 1%, we did note cases of secondary exposure and transference both before and after the introduction of the REMS for Testim 1% and other similar products. Because modifications were approved for the REMS on November 22, 2011, which provided for modification of the language in the medication guide labeling to improve patient understanding and recognition of the signs of chronic testosterone exposure in children and adult women, DMEPA did not recommend any further action at that time. Our review of the proposed Medication Guide for this product indicates that the risk of secondary exposure to children and adult women is adequately addressed.

Our February 12, 2013 review of Testim also identified wrong drug errors across topical testosterone products in general. To help reduce the risk of wrong drug errors for topical testosterone products, the labels and labeling of all topical testosterone products will carry a statement warning practitioners of the different exposure levels of different topical testosterone products. Review of the container labels and carton labeling of the proposed product found that such statement does not appear on the labels and labeling of this product.

Additionally, our review of the proposed labels and labeling found that the Dosage and Administration Section of the insert labeling should be modified to include revisions to the dosing table provided for the pump packaging configuration to improve clarity and reduce the risk of confusion, as well as addition of a statement to warn patients to wait for at least two hours to wash the application site. The 'To Apply Tradename' section of the Medication Guide can be improved to include a statement indicating the application sites as well as inclusion of a dosing table in this section to provide more clarity on the number of pump actuations and where the product should be applied to. Furthermore, the presentation of the proprietary name and the strength statements are not consistent with our current recommendations for all the other testosterone products in the market, the 'For Topical Use Only' statement does not appear on the principal display panel of the container labels and carton labeling, a dosing chart does not appear on the pump container and carton labeling, and the container labels do not contain a statement warning patients that the packaging is not child-resistant.

4 RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information on the labels to promote the safe use of the product, to mitigate any confusion, and to clarify information. Based on this review, DMEPA recommends the comments in section 4.1 and 4.2 be implemented prior to approval of this NDA.

If you have further questions or need clarifications, please contact Shawnetta Jackson, OSE project manager, at 301-796-4952.

4.1 General Comment

Remove the proprietary name, [redacted] from all labels and labeling because the name was found unacceptable by DMEPA.

4.2 Comments to the Division

4.2.1 Insert Labeling

1. DMEPA recommends deleting the [redacted] descriptor that appears in conjunction with the root name, Tradename. This will provide consistency with other testosterone products [redacted]
2. **Highlights/Indications and Usage** and **Full Prescribing Information/Section 1 Indications and Usage**: we recommend including a Limitations of Use section that includes the statement "Tradename has not been clinically evaluated in males under 18 years of age." as well as the addition of 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.*"

3. **Full Prescribing Information**/Section **2.2 Administration Instructions/Multi-Dose Metered Pump**: if significant in the priming step and if the Division sees appropriate, we recommend revising the first sentence under this section to include the following statement in *italic:*

   "Patients should be instructed to prime the pump before using it for the first time by fully depressing the pump mechanism (actuation) 3 times [redacted] and discard this portion of the product to assure precise dose delivery."

4. **Full Prescribing Information**/Section **2.2 Administration Instructions/Multi-Dose Metered Pump/Table 1**: we recommend revising the 'Prescribed Daily Dose' column to reflect the prescribed dose in milligrams of testosterone instead of the grams of gel. The milligrams of testosterone, not the grams of gel, along with the number of pump actuations are key pieces of information that healthcare providers need to communicate to the patients. Additionally, this table should also reflect the number of application sites required for each dose of this product. The revised dosing table may appear similar to the following:

Prescribed Daily Dose	Number of Pump Actuations	Application Method
50 mg testosterone	4 (once daily)	Apply 2 pump actuations to one upper arm and shoulder and then apply 2 pump actuations to the opposite upper arm and shoulder
100 mg testosterone	8 (once daily)	Apply 4 pump actuations to one upper arm and shoulder and then apply 4 pump actuations to the opposite upper arm and shoulder

Additionally, if the Division concurs with the recommendation below, the above table should be re-assigned "Table 2".

5. **Full Prescribing Information**/Section **2.2 Administration Instructions/Unit-Dose Tube or Packet:** We recommend including a dosing table similar to table 1 above, in this section, to provide more clarity. The table can be titled as "**table 1: Specific Dosing Guidelines for Using the Unit-Dose Tube or Packets**" and may appear similar to the following:

Prescribed Daily Dose	Number of Pump Actuations	Application Method
50 mg testosterone	one packet or tube (once daily)	Apply one packet or tube to one upper arm and shoulder.
100 mg testosterone	two packets or tubes (once daily)	Apply one packet or tube to one upper arm and shoulder and then apply one packet or tube to the opposite upper arm and shoulder

6. **Full Prescribing Information**/Section **2.2 Administration Instructions:** We recommend adding a pictorial diagram which illustrates, using appropriately shaded areas on a human torso, approved sites for product application.

7. **Full Prescribing Information**/Section **2.2 Administration Instructions:** the use of the phrase [redacted] in the sentence "Application sites should be allowed to dry [redacted] prior to dressing." is ambiguous and may be confusing to the patients. [redacted] herefore, we recommend replacing [redacted] by the word "completely", or a specific number of minutes.

8. **Full Prescribing Information**/Section **2.2 Administration Instructions:** We recommend adding the following statement to this section: "*The patient should avoid swimming, showering, or washing the administration site for at*

least 2 hours after application." This statement may follow the sentence "If direct skin-to-skin contact with another….".

9. **Full Prescribing Information**/Section **16.1 How Supplied:** revise this section to incorporate the unique NDC numbers for both the tube label and the tube carton labeling as well as both the packet label and the packet carton labeling. As currently presented, only the NDC numbers for the carton labeling of the tube and the packet label packaging configurations appear in this section (i.e., 0245-0871-05 and 0245-0871-35).
10. **Full Prescribing Information**/Section **16.3 Handling and Disposal**: We recommend including the statement "*This package is not child resistant.*" following the (b) (4) statement to help minimize the risk of accidental exposure to children.
11. **Full Prescribing Information**/Section **17 Patient Counseling Information/"** (b) (4) **:":** to improve clarity, we recommend revising the third bullet point under this section to the following: "*Wait at least 2 hours before swimming, showering, or washing the application site. This will ensure that the greatest amount of Tradename is absorbed into the system."*

4.1.2 Medication Guide

1. **"**(b) (4)**Apply Tradename:"** section**:** we recommend including the following bullet points immediately under this section:

    - *Tradename comes in packets, tubes, or in a pump*
    - *Before applying Tradename make sure that your shoulders and upper arms are clean, dry, and that there is not broken skin.*
    - *The application sites for Tradename are the upper arms and shoulders that will be covered by a short sleeve t-shirt*

    Additionally, we recommend including a pictorial diagram which illustrates, using appropriately shaded areas on human torso, approved sites for product application.
2. **"**(b) (4)**Apply Tradename:"** section**:** We recommend including dosing tables similar to that recommended in section 4.1.1 (#4 and #5) above to provide more clarity for patients when administering this product.
3. (b) (4) **Apply Tradename:"** section**:** We recommend deleting (b) (4) from the bullet point (b) (4) because it may lead patients to think that they (b) (4) The statement (b) (4) may be replaced by the word (b) (4), or a specific number of minutes.

4.3 COMMENTS TO THE APPLICANT

4.3.1 General Comments for all Container Labels and Carton Labeling

1. The container labels and carton labeling do not clearly state that the exposure level for testosterone may differ for Tradename compared to other topical testosterone products. Please add the following statement to the principal display panels of all carton labeling and, if space permits, all container labels:

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

2. Remove the (b) (4) descriptor that appears in conjunction with the root name, Tradename. This revision will be consistent with other testosterone products that are marketed with (b) (4) (i.e., Axiron and Fortesta).

3. Revise the presentation of the proprietary name from all capital letters (i.e. TRADENAME) to title case (i.e., Tradename) to increase readability.

4. Replace the hyphen with the word "to" in the storage information to provide more clarity. Additionally add "°C" and "°F" to the numbers 20, 68, 15, and 30. The revised storage statement should appear as: "20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)."

5. Add the statement "This package is not child resistant." to follow the statement "Keep out of reach of children" on all container labels and carton labeling.

6. Please ensure the lot number and expiration date are stamped on all the container labels and carton labeling If not, revise the container labels and carton labeling to include a lot number and expiration date per 21 CFR 201.17 and 21 CFR 201.18.

4.3.2 Tube Label

1. Revise the statement (b) (4) to read: "50 mg testosterone per tube". Additionally, ensure this statement appears immediately below the established name and dosage form statement "testosterone gel", in the highlighted area with the same prominence as the established name and the dosage form statement. The presentation would appear as:

   "**Tradename**
   (testosterone gel)
   50 mg testosterone per tube"

2. Relocate (b) (4) to the bottom portion of the label.

3. Relocate the route of administration statement "For topical use only" to appear under the statement of strength after revisions (i.e., 50 mg testosterone per tube).

4. Relocate the bar code to the side panel where the manufacturer's information appears. As currently presented, the bar code crowds the principal display panel.
5. Relocate the manufacturer's logo to the bottom of the principal display panel in the space provided after relocating the barcode. Additionally, reduce the prominence of the logo. As currently presented, this information competes in prominence with that of the proprietary name and established name due to its coloring and size.
6. Revise the statement [redacted] (b) (4) to read "Usual Dosage: Apply complete contents of tube once daily."
7. Delete the statement [redacted] (b) (4) on the side panel. This information is presented on the carton labeling and its presence on the side panel of the container label is not necessary. Additionally, the space provided by removing this statement can be utilized for the placement of the bar code after being relocated from the principal display panel.

4.2.3 Packet Label

1. Revise the statement [redacted] (b) (4) to read: "50 mg testosterone per packet". Additionally, ensure this statement appears immediately below the established name and dosage form statement "testosterone gel", in the highlighted area with the same prominence as the established name and the dosage form statement. The presentation would appear as:

   "**Tradename**
   (testosterone gel)
   50 mg testosterone per packet"

2. Relocate the route of administration statement from the back panel to appear below the statement of strength after revisions (i.e., 50 mg testosterone per packet) on the principal display panel.
3. Revise the statement [redacted] (b) (4) to read "Usual Dosage: Apply complete contents of packet once daily."

4.2.4 Pump Label

1. Delete the word [redacted] (b) (4) that currently appears under the dosage form "testosterone gel".
2. Revise the statement [redacted] (b) (4) to read:

"12.5 mg of testosterone per pump actuation*"

*Each actuation delivers 1.25 grams of gel

Multi-dose pump capable of dispensing 60 metered pump actuations."

Additionally, the correct placement of these statements will be discussed below.

3. Place the statement "12.5 mg of testosterone per pump actuation*" immediately below the dosage form (testosterone gel) in the highlighted area, as this statement is considered the statement of strength and should appear below the dosage form. The statements "*12.5 mg of testosterone per pump actuation*" and "Multi-dose pump capable of dispensing 60 metered pump actuations" may appear further down in the white space of the principal display panel.
4. You may place a net quantity statement of "88 g" at the bottom of the principal display panel.
5. Relocate the route of administration statement 'For topical use only" to the principal display panel. Following the revisions, the order of information on the principal display panel would appear as:

"**Tradename**
(testosterone gel)
12.5 mg of testosterone
Per pump actuation*

*Each actuation delivers 1.25 grams of gel.
Multi-dose pump capable of dispensing
60 metered pump actuations

For topical use only.

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

Dispense the accompanying
Medication Guide to each patient.

88 g"

6. Include a dosing table on the side panel of the pump label. This recommendation is consistent with our current recommendations for testosterone pump labels (e.g., Androgel products). The dosing table may appear similar to:

Prescribed Daily Dose	Number of Pump Actuations
50 mg	4
100 mg	8

4.2.5 Tube Carton Labeling

1. Revise the statement "[redacted]" to read: "50 mg testosterone per tube". Additionally, ensure this statement appears immediately below the established name and dosage form statement "testosterone gel", in the highlighted area and with the same prominence as the established name and the dosage form statement. The presentation would appear as:

   "**Tradename**
   (testosterone gel)
   50 mg testosterone per tube"

2. Relocate the route of administration statement "For topical use only" to appear under the statement of strength after revisions (i.e., 50 mg testosterone per tube).

4.2.6 Packet Carton Labeling

1. Revise the statement [redacted] to read: "50 mg testosterone per packet". Additionally, ensure this statement appears immediately below the established name and dosage form statement "testosterone gel", in the highlighted area with the same prominence as the established name and the dosage form statement. The presentation would appear as:

   "**Tradename**
   (testosterone gel)
   50 mg testosterone per packet"

2. Relocate the route of administration statement from the back panel to appear below the statement of strength after revisions (i.e., 50 mg testosterone per packet) on the principal display panel.

4.2.7 Pump Carton Labeling

1. Delete the word [redacted]" that currently appears under the dosage form "testosterone gel".
2. Revisions to the statements [redacted] will be recommended in the steps to follow below.
3. Place the strength statement "12.5 mg of testosterone per pump actuation*" immediately below the established name and dosage form statement (i.e., testosterone gel) in the highlighted area, and with the same prominence as the established name and dosage form statement.
4. Place the statements "*12.5 mg of testosterone per pump actuation*" further down in the white space of the principal display panel followed by the statement "Multi-dose pump capable of dispensing 60 metered pump actuations."

5. You may place a net quantity statement of "2 canisters containing 88 grams each" at the bottom of the principal display panel.

6. Relocate the route of administration statement from the side panel to the principal display panel. Following the revisions, the order of information on the principal display panel would appear as:

   "**Tradename**
   (testosterone gel)
   12.5 mg of testosterone
   Per pump actuation*

   *Each actuation delivers 1.25 grams of gel.
   Multi-dose pump capable of dispensing
   60 metered pump actuations

   For topical use only.

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

   [redacted] (b) (4)

   Dispense the accompanying Medication Guide to each patient

   2 canisters containing 88 grams each"

7. Include a dosing table on the side panel of the pump carton labeling that includes the number of days of supply along with the prescribed daily dose and the number of pump actuations. Including the number of days of supply will help assist the dispensing pharmacist to enter the correct number in the computer as well as to dispense the appropriate number of pumps. The dosing table may appear similar to:

Prescribed Daily Dose	Number of Pump Actuations	Days of Supply
50 mg	4	25
100 mg	8	7

REFERENCES

OSE Review #2011-2653 and #2012-1975, Post Marketing, Label, Labeling and Packaging Review of Testim 1% (Testosterone Gel). Wood-Cummings, T., February 12, 2013.

APPENDICES

APPENDIX A : Database Descriptions

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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

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

/s/

MANIZHEH SIAHPOUSHAN
05/01/2013

CAROL A HOLQUIST
05/01/2013

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 # 204399 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: N/A Established/Proper Name: testosterone gel Dosage Form: topical gel Strengths:		
Applicant: Upsher-Smith Agent for Applicant (if applicable):		
Date of Application: October 18, 2012 Date of Receipt: October 18, 2012 Date clock started after UN:		
PDUFA Goal Date: August 18, 2013	Action Goal Date (if different):	
Filing Date: December 17, 2012	Date of Filing Meeting: December 10, 2012	
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: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s):	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	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)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***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.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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.	Payment of other user fees: N/A ☐ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X		
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)].**		X		
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)]?** ***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 505(b)(2) review staff in the Immediate Office of New Drugs***		X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	X			

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
NDA 21463	Fortesta	NP	Dec 29, 2013
NDA 22504	Axiron	NP	Nov 23, 2013
NDA 202763	Testosterone gel	NP	Feb 14, 2014

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 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***		X		

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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

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

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☐ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Applications in "the Program" (PDUFA V) (NME NDAs/Original BLAs)	**YES**	**NO**	**NA**	**Comment**
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			**X**	
• If yes, were all of them submitted on time?			**X**	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			**X**	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			**X**	
Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
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			

Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)]. ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*				
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***Note:*** *Debarment Certification should use wording in FD&C Act 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…"*	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*: **12/12/12**				

Pediatrics	**YES**	**NO**	**NA**	**Comment**

PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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.*		X		
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?			X	
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? ***If no, request in 74-day letter***			X	
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)? ***If no, request in 74-day letter***			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]			X	
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			Trotextin but DMEPA will not grant
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	X			
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels			

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm
[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

	☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	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	☐ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

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) ***If yes, specify consult(s) and date(s) sent:***				
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** August 2, 2011 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 10, 2012

BLA/NDA/Supp #: NDA 204399

PROPRIETARY NAME: Not at this time

ESTABLISHED/PROPER NAME: testosterone gel

DOSAGE FORM/STRENGTH: topical gel

APPLICANT: Upsher-Smith

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

BACKGROUND: The Applicant has submitted an NDA for a metered dose testosterone gel product (5 g tube, 5 g packet and a 75 g pump each containing 50 mg of testosterone). This NDA is associated with IND 076654.
The application is a 505(b)(2) and the RLD is Testim (NDA 21454)

The submission was originally received as an ANDA 79178 (b) (4) o a Citizen's Petition, that testosterone gel products that are not qualitatively and quantitatively identical to a reference listed drug would need to provide clinical data regarding the transfer of testosterone via person-to-person contact. The 505(b)(2) pathway was believed to be the appropriate pathway for this product.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Jeannie Roule	Y
	CPMS/TL:	Jennifer Mercier	Y
Cross-Discipline Team Leader (CDTL)	Suresh Kaul		Y
Clinical	Reviewer:	Martin Kaufman	Y
	TL:	Donald McNellis	Y

Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	LaiMing Lee	Y
	TL:	Myong-Jin Kim	Y
Biostatistics	Reviewer:	Xin Fang	Y
	TL:	Mahboob Sobhan	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jeffrey Bray	Y
	TL:	Lynnda Reid	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Bogdan Kurtyka	Y
	TL:	Donna Christner	Y
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:	Bogdan Kurtyka	Y
	TL:	Donna Christner	Y
Facility Review/Inspection	Reviewer:		
	TL:		

OSE/DMEPA (proprietary name)	Reviewer:	Alison Park	N
	TL:	Zachary Oleszczuk	N
OSE/DRISK (REMS)	Reviewer:	Cynthia LaCivita	N
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	James Tolliver	N
	TL:	Michael Klein	N
Other reviewers: Biopharmaceutics	Tapash Ghosh		Y
Other attendees			

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☐ Not Applicable ☐ YES ☒ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**: Complete submission	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed?	☐ YES

If no, explain:	☒ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA , include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• Abuse Liability/Potential **Comments**: Schedule III drug	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☒ YES ☐ NO
BIOSTATISTICS	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO

Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**: N/A	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Suresh Kaul, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in "the Program" PDUFA V): N/A

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review

	☐ Priority Review
ACTIONS ITEMS	
☒	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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) • notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for NME NDAs in "the Program")
☐	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 in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	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
02/13/2013

M E M O R A N D U M

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

DATE: January 9, 2013

TO: Chief, Medical Products and Tobacco Inspection Coordinating Branch
Division of Medical Products and Tobacco Inspections
Office of Medical Products and Tobacco Operations

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

SUBJECT: FY 2013, **CDER High Priority User Fee NDA, Pre-Approval Data Validation Inspection**, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 204-399
DRUG: Testosterone Gel 1%
SPONSOR: Upsher-Smith Laboratories, Inc., USA

This memo requests that you arrange for inspection of the analytical portion of the following bioequivalence study. **A DBGLPC scientist with specialized knowledge may participate in the inspection of this analytical site to provide scientific and technical expertise. Please contact DBGLPC point of contact (POC) upon receipt of this assignment to arrange scheduling of this analytical inspection. Following identification of the FDA investigator, background materials will be forwarded directly. Please contact the POC for background materials. Please complete the inspection prior to March 18, 2013.**

Do not identify the application, the study to be inspected, drug names, or the study investigator prior to the start of the inspection. The information will be provided to the sites at the inspection opening meeting.

Study Number: P06-011 ((b) (4) # 60597)

Study Title: "Randomized, Open-label, 2-Treatment, 4-Way Replicate Crossover, Bioequivalence Study of Testosterone 1% Topical Gel Formulation by

Upsher-Smith Laboratories versus Testim® (1% Testosterone, Reference) in Hypogonadal Male Volunteers"

This pivotal BE study was conducted at (b) (4). Based on the results from a previous audit, the review division requested this inspection.

Analytical Site: (b) (4)

Investigator: (b) (4)

Methodology: LC-MS/MS

Please confirm the following during the inspection:

- All pertinent items related to the analytical method used for the measurement of testosterone **concentrations in human serum should be examined.**
- The accuracy of the analytical data provided in the NDA submission by the applicant should be compared with the original documents at the site.
- **The method validation and the actual assay of the subject plasma samples, the variability between and within runs, QC, demonstration of accuracy and precision in matrix using standards and QCs prepared from separate stocks, stability of subject samples covered by validated stability period.**
- **Use of freshly made calibrators and/or freshly made QCs for stability evaluations during pre-study method validation.**
- **At least one demonstration of precision and accuracy from QCs and calibrators prepared from separate stock solutions.**
- **Scrutinize the number of repeat assays of the subject serum samples, and the reason for such repetitions, the SOP(s) for repeat assays and if relevant stability criteria like freeze thaw cycles sufficiently covered the stability of reanalyzed subject samples.**

In addition to the standard investigation involving the source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Additional instructions to ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the DBGLPC POC prior to the inspection. Therefore, we request that the DBGLPC POC be contacted for further instructions before the inspection, and also regarding data anomalies or questions noted during review of study records. The ORA investigator should contact the DBGLPC POC for inspection-related questions or clarifications.

Please fax/email a copy of Form FDA 483 if issued, as soon as possible. If at close-out of the inspection, it appears that the violations may warrant an OAI classification, please notify the POC as soon as possible. At completion of inspection, please remind the inspected entity of the 15 business-day timeframe for submission of a written response to observations listed on Form FDA 483. Please forward written response as soon as you receive it to Dr. Sam H. Haidar and POC (Fax: 1-301-847-8748 or Email: sam.haidar@fda.hhs.gov).

DBGLPC POC: Sripal R. Mada, Ph.D.
sripal.mada@fda.hhs.gov
Tel: (301)-796-4112
FAX: (301)-847-8748

DMPTI POC: Arindam Dasgupta, Ph.D.
arindam.dasgupta@fda.hhs.gov
Tel: (301)-796-3326
FAX: (301)-847-8748

cc:
CDER OSI PM TRACK
OSI/DBGLPC/Haidar/Skelly/Mada/Dejernett
OND/ODE3/DRUP/Roule
OCP/DCP3/Kim/Lee/Bashaw
ORAHQ/OMPTO/DMPTI/BIMO/Arline/Turner/Alexis/Braswell/Johnson/Colon
Draft: SRM 1/8/2013
Edit: MFS 1/8/2013
OSI file BE6409; O:\BE\assigns\bio204399.doc
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/Electronic Archive/BEB
FACTS: (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/

SRIPAL R MADA
01/09/2013

SAM H HAIDAR
01/09/2013