CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204399Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III
Division of Bone, Reproductive, and Urologic Products

NDA/BLA #s:	204399/S000
Products:	testosterone gel (authorized generic of Vogelxo)
APPLICANT:	Upshire-Smith Laboratories, Inc.
FROM:	Christine P. Nguyen, MD
DATE:	June 4, 2014

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

Vogelxo (testosterone) gel received a tentative approval on August 16, 2013, because of ongoing patent infringement litigation. On December 4, 2013, the US District Court ruled in favor of the Applicant and on the same date, the Applicant submitted a request for full approval of Vogelxo, proposed REMS for Vogelxo and the authorized generic of Vogelxo (testosterone gel). An authorized generic under the Vogelxo NDA must have an approved REMS prior to marketing. The proposed REMS document addresses the REMS program for both Vogelxo and its authorized generic.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary testosterone gel (authorized generic of Vogelxo) to ensure that the benefits of the drug outweigh the risks of secondary exposure due to drug transfer from adult males using testosterone gel products to children. In reaching this determination, we considered the following:

A. It has been estimated that 4 to 5 million American men have hypogonadism of whom 5 percent receive testosterone therapy. While it is not possible to estimate the size of the population likely to use testosterone gel products, of which Vogelxo (testosterone) gel is a member of the class, these products have the largest market share among

testosterone-containing products. In 2007 alone, approximately (b) (4) prescriptions were dispensed for all formulations of testosterone containing products.

B. Hypogonadism in men is a serious disease resulting from a lack of endogenous testosterone. The aim of testosterone therapy in men with hypogonadism is to restore or normalize male secondary sexual characteristics (such as beard, body hair, voice) and male sexual behavior, and to promote normal male somatic development (muscle mass, bone). The consequences of long term testosterone deficiency in hypogonadal men may include decreased muscle mass and strength, decreased sexual function and osteoporosis.

C. Based on a pivotal bioequivalent study, Vogelxo (testosterone) gel was demonstrated to be bioequivalent to the approved reference drug Testim (testosterone) gel, assuring therapeutic equivalence between Vogelxo and Testim. In phase 3 trial, Testim has been shown to produce serum total testosterone concentrations within the normal range in the majority of hypogonadal men studied. The authorized generic of Vogelxo (b) (4) therefore, its safety and efficacy can be assumed to be same as that of Vogelxo.

D. Testosterone gel will be used for replacement therapy in males with conditions associated with a deficiency or absence of endogenous testosterone. Treatment is expected to continue throughout the patient's lifetime.

E. In addition, to postmarketing reports of secondary exposure of children to testosterone, testosterone gel products, of which testostorone gel is a member of the class, have been associated with various other adverse effects, including gynecomastia, edema, polycythemia, and sleep apnea. In addition, exogenous administration of testosterone may lead to azoospermia.

F. Testosterone gel is not a new molecular entity.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that testosterone gel poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of testosterone gel. FDA has determined that testosterone gel is a product for which patient labeling could help prevent serious adverse effects and that has a serious risk of which patients should be made aware because information concerning the risk could affect patients' decisions to use or continue to use testosterone gel. Under 21 CFR 208, the Applicant is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed testosterone gel.

The elements of the REMS will be a Medication Guide and a timetable for submission of

assessments of the REMS.

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/s/

CHRISTINE P NGUYEN
06/04/2014

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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	May 12, 2014
Reviewer(s)	Cathy A. Miller, M.P.H., B.S.N., Risk Management Analyst Naomi Redd, Pharm.D., Risk Management Analyst Division of Risk Management (DRISK)
Team Leader	Kimberly Lehrfeld, Pharm.D., DRISK Cynthia LaCivita, Pharm.D., DRISK
Division Director:	Claudia Manzo, Pharm.D., DRISK
Drug Name(s):	Vogelxo (testosterone gel) C III & Authorized Generic
Therapeutic class:	Androgen
Dosage forms:	Topical Gel
OND Review Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type/Number:	NDA 204399
Submission # and Date Received	Application Resubmission (eCTD Sequence No. 0020) submitted December 5, 2013; amended (eCTD Sequence No. 0023) submitted April 8, 2014 and May 8, 2014 (eCTD Sequence No. 0024)
PDUFA/Action Date	June 4, 2014
Applicant/sponsor:	Upsher-Smith Laboratories
OSE RCM #:	2013-2867

(b) (4)

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EXECUTIVE SUMMARY

The purpose of this review is to document the Division of Risk Management's (DRISK) evaluation of the proposed Risk Evaluation and Mitigation Strategy (REMS) for Vogelxo (testosterone gel), a topical androgen, new drug application (NDA 204399). This 505(b)(2) application was originally submitted by Upsher-Smith Laboratories (USL) on October 18, 2012, at which time the REMS was reviewed by DRISK and found to be acceptable.[1] The reference listed drug (RLD), Testim 1% (testosterone gel) NDA 21454, upon which this 505(b)(2) application is based, is held by Auxilium Pharmaceuticals. Additional safety studies required for this application were performed by USL under IND 076654.

USL received tentative approval for Vogelxo on August 16, 2013, subject to pending court decisions for a patent infringement suit brought about by the Testim RLD holder, Auxilium. Subsequent to a court decision granting summary judgment of noninfringement of all asserted patents in favor of USL, USL resubmitted their application for final approval, along with the proposed REMS on December 4, 2013.

In their December 4, 2013 resubmission, USL also included a proposed REMS and draft labeling for an authorized generic (AG), identical to the draft labeling for Vogelxo with the exception of the drug product name (testosterone gel) and drug product NDC numbers. USL intends to market both the brand, Vogelxo, and an authorized generic product, testosterone gel.

The goal of the REMS is to inform patients about the serious risks associated with the use of testosterone gel. The elements of the REMS include a Medication Guide (MG) and a timetable for submission of assessments. The resubmission of the MG for Vogelxo and the AG is currently under review by the Division of Medical Policy Programs Patient Labeling Team (PLT) under a separate cover. FDA determined a REMS was necessary for all topical testosterone gel products after receiving cases of virilization in children who were secondarily exposed to testosterone due to drug transfer drom adult males using testosterone gel products. The final proposed REMS for Vogelxo and the AG, received on December 4, 2013, amended on April 8, 2014, and May 8, 2014 contains the agreed upon elements consistent with the approved REMS for Testim. DRISK finds the proposed REMS for Vogelxo and the AG testosterone gel, NDA 204399, acceptable.

1 INTRODUCTION

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested the Division of Risk Management (DRISK) review the proposed REMS for NDA 204399, Vogelxo (testosterone) gel and authorized generic (AG). This review documents DRISK's evaluation of the proposed REMS for Vogelxo and the AG testosterone gel.

1.1 BACKGROUND

Vogelxo is an androgen proposed for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone with

[1] DRISK REMS Review of Vogelxo dated July 22, 2013 (C. LaCivita)

primary hypogonadism (congenital or acquired) or hypogonadotropic (congenital or acquired). The recommended starting dose for adult males is 50 mg of testosterone (one tube or one packet or 4 pump actuations) applied topically once daily at approximately the same time each day. If the morning pre-dose serum testosterone concentraton is below the normal range, the dose may be increased to 100 mg. Vogelxo is supplied in unit-dose tubes in cartons of 30 and unit-dose packets in cartons of 30. Each tube or packet contains 50 mg testosterone in 5 g of gel. Vogelxo is also supplied in a metered-dose pump that delivers 12.5 mg of testosterone per complete pump actuation. Each 88 g metered-dose pump is capable of dispensing 75 g of gel or 60-metered pump actuations. Each pump actuation delivers 1.25 g of gel. The metered-dose pump is supplied in cartons of two.

Testim 1% (testosterone gel), NDA 21454, Auxillium Pharmaceuticals, is the RLD upon which this 505(b)(2) application is based. Testim was originally approved on October 31, 2002. Since the time of approval, the Agency became aware through spontaneous postmarketing adverse event reports and peer-reviewed biomedical literature, of cases of secondary exposure of children to testosterone due to drug transfer drom adult males using testosterone gel products. The Agency considered this information to be "new safety information" as defined in the Food and Drug Administration Amendments Act (FDAAA). On April 22, 2009, the Agency requested that Auxillium submit safety labeling changes, along with a REMS, to address the identified safety risks. Auxillium subsequently submitted a REMS for Testim to address the risk of secondary chronic exposure in children and adults, which was approved on September 18, 2009.[2]

The 505(b)(2) application for Vogelxo NDA 204399 was originally submitted by Upsher-Smith Laboratories (USL) on October 18, 2012 at which time the REMS, reviewed by DRISK on July 22, 2013, and the MG, reviewed by the Office of Medical Policy Patient Labeling Team (PLT) on July 30, 2013, were found to be acceptable. USL received tentative approval for Vogelxo on August 16, 2013, subject to pending court decisions for a patent infringement suit brought about by the Testim RLD holder, Auxilium. Subsequent to a court ruling in favor of USL, the application was resubmitted on December 5, 2013, amended April 8, 2014 and May 8, 2014, included a proposed REMS for brand Vogelxo and an authorized generic (AG) testosterone gel. USL intends to market both the brand and the AG.

The goal of the REMS for all testosterone topical products[3] is to inform patients about the serious risks associated with the use of testosterone gel. The elements of the REMS for brand Vogelxo and the AG are identical and each include a Medication Guide (MG), a timetable for submission of assessments including REMS Assessment submissions to FDA at 18 months, 3 years and 7 years from the date of approval of the REMS, along with one supporting document and one REMS document that each incorporate both the brand name Vogelxo and the AG testosterone gel together.

[2] Division of Reproductive and Urologic Products Prior Approval Supplement(S-008) Approval Letter for Testim, NDA 21454 dated September 18, 2009.

[3] List of currently approved individual REMS, including all testosterone topical products (Androgel 1%, Androgel 1.62%, Axiron, Fortesta, Testim, Testosterone Gel)

1.2 REGULATORY HISTORY

The following is an overview of the regulatory history for Vogelxo (NDA 204399):

- **10/18/2012:** Upsher-Smith Laboratories (USL) submitted 505(b)(2) new drug application (NDA 204399) for testosterone gel including their proposed REMS (**eCTD** Seq. No. 0000)
- **12/21/2012**: DBRUP issued a Filing Communication for NDA 204355 including request for labeling reformatting
- **1/22/2013**: USL submitted an Amendment to Filing Communication Request (**eCTD** Seq. No. 004), including the proposed REMS and supporting document reformatted as requested by DBRUP
- **7/22/2013**: DRISK completed review of Vogelxo REMS finding the REMS acceptable[4]
- **8/16/2013**: USL received tentative approval (TA) for Vogelxo pending final judgement of lawsuit filed by the RLD holder, Auxilium Pharmaceuticals, for patent infringement
- **12/4/2013**: USL resubmitted NDA 204399 to the Agency in their Request for final approval, proposed REMS and the addition of an authorized generic (AG), subsequent to a court ruling in favor of USL, granting summary judgment of noninfringement of all asserted patents for the RLD, Testim NDA 21454
    - **4/8/2014*:*** USL submitted an amendment to their resubmission, which included one Supporting Document that incorporates both the brand name, Vogelxo, and the AG, testosterone gel in the same document.
    - **05/08/2014:** USL submitted an amendment to their resubmission, in response to an email communication from DBRUP on 4/28/2014, requesting a revised REMS document that incorporates both the brand name, Vogelxo, and the AG, testosterone gel in the same document.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

The following submissions, listed by date submitted, were reviewed from NDA 204399 for the proposed Vogelxo and AG, testosterone gel REMS.

- 12/5/2013: Resubmission of NDA 204399 including proposed REMS for Vogelxo and AG (**eCTD** Sequence No. 0020)
    - 4/8/2014: Amendment to Resubmission of NDA 204399 including revised Supporting Document for Vogelxo/AG combined (**eCTD** Sequence No. 0023)

[4] DRISK REMS Review of Vogelxo dated July 22, 2013 (C. LaCivita)

- 05/08/2014: Amendment to Resubmission of NDA 204399 including revised REMS document for Vogelxo/AG combined (**eCTD** Sequence No. 0024)

- 7/24/2013: USL revised PI sent to DBRUP via email
- 10/18/2012: Original Submission of NDA 204399 including proposed REMS (**eCTD** Sequence No. 0000)
  - 7/30/2013: Amendment to Original Submission including revised REMS (**eCTD** Sequence No. 0018)

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Approved REMS for other testosterone topical products (NDAs 21015, 22309, 22504, 21463, 202763, 21454)[5]
- 7/22/2013: DRISK REMS Review of Vogelxo (C. LaCivita)
- 7/18/2013: DBRUP red-lined PI sent to USL|for revision
- 7/30/2013: PLT Review of the original submission Vogelxo MG (S. Hutchins)
- 8/16/2013: DBRUP Tentative Approval Letter for Vogelxo (NDA 204399)

3 RESULTS OF REVIEW OF PROPOSED BRAND VOGELXO AND AUTHORIZED GENERIC REMS

The resubmission dated December 5, 2013 by USL did not include a supporting document therefore, an information request was sent to USL via email on April 7, 2014, requesting the missing supporting document. DRISK asked that the sponsor provide clarification on their intention to have one supporting document that incorporated both the brand name Vogelxo and the AG, testosterone gel in the same document, or two separate supporting documents, one for Vogelxo and one for the AG testosterone gel. USL subsequently submitted an amendment to the resubmission dated April 8, 2014, which included a single Supporting Document, clarifying the provision of a REMS Supporting Document that "includes both the brand, Vogelxo (testosterone) gel and the Authorized Generic, Testosterone Gel" in one document.

Following additional discussions between DBRUP, DRISK and the CDER Safety Requirements Team (SRT) on formatting of REMS for products that include a brand and an authorized generic, a decision was made that to better facilitate administrative processes and future REMS modifications, both the brand name and the AG product should be incorporated into one REMS document. Subsequently, DBRUP sent a request to USL on April 29, 2014 to submit an amendment to the REMS submission, incorporating one single REMS document that includes both the brand name and the authorized generic name as opposed to separate documents for each. On May 8, 2014 USL submitted an amendment to their resubmission (eCTD Seq. No. 0024) that included

[5] List of currently approved individual REMS, including all testosterone topical products (Androgel 1%, Androgel 1.62%, Axiron, Fortesta, Testim, Testosterone Gel

a revised REMS document incorporating both the brand and generic name in one document as requested.

The proposed REMS for NDA 204399 submitted December 5, 2013, and amended April 9 and May 8, 2014, consists of one REMS document with the brand name Vogelxo and authorized generic name testosterone gel in one document, along with (b) (4)

The elements of the proposed REMS is consistent with the approved REMS for Testim and includes a Medication Guide and a timetable for submission of assessments. The MG for is currently under review by the Division of Medical Policy Programs PLT) under a separate cover.

4 DISCUSSION

An "authorized generic drug" is a listed drug, as defined in CFR, Title 21, Part 314.3, that has been approved under subsection 505(c) of the [Food, Drug, and Cosmetic] act and is marketed, sold, or distributed directly or indirectly to retail class of trade with either labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark that differs from that of the listed drug. Therefore, an authorized generic drug under an NDA is required to have the same labeling and approved REMS as the innovator product prior to marketing.

The proposed REMS' for NDA 204399 was resubmitted on December 5, 2013, and amended April 8, 2014 and May 8, 2014, for Vogelxo and the AG testosterone gel. In their resubmission, USL stated that the two products (b) (4) and the NDA includes only a single dosage form (topical) and strength. They further clarified that "USL intends to market both the brand and an authorized generic drug product…the manufacture, packaging and testing of the authorized generic is identical to Vogelxo.

Recently, the Agency became aware of an additional safety concern with testosterone use and issued "Safety Labeling Change Notification" letters to applicant holders of all approved testosterone products[6] to add safety language to the PI and MG related to risks of VTE and DVT. While this information does not directly impact the REMS document, it will impact the MG which is an element of the REMS.

In order to align the safety labeling changes requested of all approved testosterone product application holders with the pending Vogelxo application, DBRUP requested that USL incorporate the revisions into the Vogelxo PI and MG in an email sent July 18, 2013. The revisions were subsequently agreed upon by USL and resubmitted to DBRUP via email on July 24, 2013. Accordingly, the December 5, 2013 resubmission of Vogelxo and AG incorporated the agreed upon safety labeling changes to the PI and MG, incorporating DBRUP's requested safety labeling change language related to venous thromboembolism (VTE) and deep vein thrombosis (DVT) risks.

[6] DBRUP Safety Labeling Changes Notificaton Letter to all testosterone application holders dated March 26, 2014.

USL's final proposed REMS for Vogelxo and AG testosterone gel contains one REMS document and one supporting document that incorporate both the brand name Vogelxo and and the AG testosterone gel. DRISK believes that this will allow REMS modifications that would affect both of these products to be handled through a single REMS document in a more comprehensive manner. We acknowledge, however, that each product will have a separate package insert and MG, one for Vogelxo and one for the AG testosterone gel.

5 CONCLUSION/RECOMMENDATIONS

DRISK compared the proposed REMS for Vogelxo, NDA 204399, to the approved REMS' documents for other approved testosterone topical products while additionally referencing the original REMS review conducted by DRISK for Vogelxo and found the Vogelxo REMS to be acceptable on July 22, 2013.

DRISK finds the proposed REMS for Vogelxo and the authorized generic testosterone gel, NDA 204399, acceptable.

ATTACHMENT

Final REMS Document for NDA 204399 Brand Vogelxo and Authorized Generic testosterone gel

Initial REMS Approval: XX/XXXX

NDA 204399

VOGELXO (testosterone) gel CIII

and Authorized Generic (testosterone gel) CIII

Class of Drug: Androgen

UPSHER-SMITH LABORATORIES, INC.

6701 Evenstad Drive

Maple Grove, MN 55369

763-315-2000

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL:

The goal of this REMS is to inform patients about the serious risks associated with the use of testosterone gel.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each testosterone gel prescription in accordance with 21 CFR 208.24.

The Medication Guide is part of the REMS.

B. Timetable for Submission of Assessments

Upsher-Smith Laboratories, Inc. (USL) will submit REMS Assessments to the FDA for testosterone gel at 18 months, 3 years and 7 years from the date of initial approval of the VOGELXO (testosterone gel) REMS.

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. USL will submit each assessment so that it will be received by the FDA on or before the due date.

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/s/

CATHY A MILLER
05/12/2014

CLAUDIA B MANZO
05/12/2014
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
Office of Drug Evaluation III
Division of Reproductive and Urologic Products

NDA/BLA #s:	204399
Products:	Vogelxo (testosterone) gel
APPLICANT:	Upshire-Smith Laboratories, Inc.
FROM:	Christine P. Nguyen, MD
DATE:	August 15, 2013

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Vogelxo (testosterone) gel to ensure that the benefits of the drug outweigh the risks of secondary exposure due to drug transfer from adult males using testosterone gel products to children. In reaching this determination, we considered the following:

A. It has been estimated that 4 to 5 million American men have hypogonadism of whom 5 percent receive testosterone therapy. While it is not possible to estimate the size of the population likely to use testosterone gel products, of which Vogelxo (testosterone) gel is a member of the class, these products have the largest market share among testosterone-containing products. In 2007 alone, approximately (b) (4) prescriptions were dispensed for all formulations of testosterone containing products.

B. Hypogonadism in men is a serious disease resulting from a lack of endogenous testosterone. The aim of testosterone therapy in men with hypogonadism is to restore or normalize male secondary sexual characteristics (such as beard, body hair, voice) and male sexual behavior, and to promote normal male somatic development (muscle mass, bone). The consequences of long term testosterone deficiency in hypogonadal

men may include decreased muscle mass and strength, decreased sexual function and osteoporosis.

C. Based on a pivotal bioequivalent study, Vogelxo (testosterone) gel was demonstrated to be bioequivalent to the approved reference drug Testim (testosterone) gel, assuring therapeutic equivalence between Vogelxo and Testim. In phase 3 trial, Testim has been shown to produce serum total testosterone concentrations within the normal range in the majority of hypogonadal men studied.

D. Vogelxo (testosterone) gel will be used for replacement therapy in males with conditions associated with a deficiency or absence of endogenous testosterone. Treatment is expected to continue throughout the patient's lifetime.

E. In addition, to postmarketing reports of secondary exposure of children to testosterone, testosterone gel products, of which Vogelxo (testosterone) gel is a member of the class, have been associated with various other adverse effects, including gynecomastia, edema, polycythemia, and sleep apnea. In addition, exogenous administration of testosterone may lead to azoospermia.

F. Vogelxo (testosterone) gel is not a new molecular entity.

In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Vogelxo (testosterone) gel poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Vogelxo (testosterone) gel. FDA has determined that Vogelxo (testosterone) gel is a product for which patient labeling could help prevent serious adverse effects and that has a serious risk of which patients should be made aware because information concerning the risk could affect patients' decisions to use or continue to use Vogelxo (testosterone) gel. Under 21 CFR 208, the Applicant is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Vogelxo (testosterone) gel.

The elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

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/s/

CHRISTINE P NGUYEN
08/15/2013

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

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	July 22, 2013
Reviewer:	Cynthia LaCivita, Pharm.D. Risk Management Analyst, Team Leader Division of Risk Management
Division Director	Claudia Manzo, Pharm.D. Director, Division of Risk Management
Drug Name(s):	Vogelxo (testosterone gel) C III
Therapeutic Class:	Androgen
Dosage and Route:	Topical
Application Type/Number:	NDA 204399
Applicant/sponsor:	Upsher Smith Laboratories, Inc.
OSE RCM #:	2012-2945

1 INTRODUCTION

This review provides the Division of Risk Management (DRISK) evalution of the proposed Risk Evaluation and Mitigation Strategy (REMS) submitted by Upsher Smith Laboratories, Inc., for New Drug Application (NDA) 204399, Vogelxo (testosterone gel) C III, a topical androgen. Vogelxo is an androgen indicated for testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone with primary hypogonadism (congenital or acquired) or hypogonadotropic hypogonadism (congenital or acquired).

The subject of this review is the REMS document. The MG will be reviewed by the Division of Medical Policy Programs (DMPP) under separate cover.

2 MATERIALS REVIEWED

- October 18, 2012 - Upsher Smith Laboratories, Inc submissionfor New Drug Application (NDA) 204399, testosterone gel C III
- January 23, 2013, Proposed REMS, supplement 004
- Approved REMS for Testosterone topical products (NDAs 21015, 22309, 22504, 21463, 202763)
- Product labeling submitted by the sponsor as supplement 0013, and found in DARRTS on May 3, 2013

3 PROPOSED TESTOSTERONE GEL C-III REMS

The proposed REMS was submitted on January 23, 2013, as supplement 004 and includes a Medication Guide (MG) and a timetable for submission of assessments.

4 RECOMMENDATIONS

Reference to the product formulation (b) (4) was removed from the REMS document to accurately reflect dosing and administration in the FDA's proposed product labeling. The product labeling does not include the strength as a percentage; dosing units are in milligrams.

DRISK compared the proposed REMS document for Vogelxo, NDA 204399 to the approved REMS' documents for other approved testosterone topical products. DRISK finds the proposed REMS acceptable providing that Upsher Smith Laboratories, Inc., makes all the necessary changes that are identified in track changes version of the attached REMS document. Please make the corresponding changes to the REMS Supporting Document. Upsher Smith Laboratories, Inc., should submit the revised REMS, MG and REMS Supporting Document for approval.

Attached - REMS document in WORD with track changes.

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/s/

CYNTHIA L LACIVITA
07/22/2013

CLAUDIA B MANZO
07/22/2013
concur