

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204399Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Memo

<b>Date</b>	<b>June 3rd, 2014</b>
<b>From</b>	<b>Suresh Kaul, MD, MPH</b>
<b>Subject</b>	<b>Cross-Discipline Team Leader Review</b>
<b>NDA#</b>	<b>204,399</b>
<b>Applicant</b>	<b>Upsher-Smith Laboratories, Inc.</b>
<b>Date of Submission</b>	<b>December 4, 2013</b>
<b>PDUFA Goal Date</b>	<b>June 4, 2014</b>
<b>Proprietary Name / Established (USAN) names</b>	<b>Testosterone Gel Vogelxo</b>
<b>Dosage forms / Strength</b>	<b>Gel for Transdermal use, 50mg &amp;100mg</b>
<b>Proposed Indication(s)</b>	<b>Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone</b>
<b>Recommended:</b>	<b>Approval</b>

### 1. Introduction

The active moiety in Vogelxo is testosterone. Testosterone therapy is available in the United States as several formulations, including: topical gels and solutions, transdermal patch, buccal patch, intramuscular injections and implanted pellets.

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone. Signs and symptoms associated with male hypogonadism include: decreased sexual desire, fatigue, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range. Currently available treatment options for hypogonadism include intramuscular injections, subdermal

implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels which are applied with the hands to the shoulders and upper arms and/or abdomen.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050ng/dL). These replacement therapies are ideally based on short term titration regimens that result in an optimal dose of product for a particular patient.

### **Product Information**

Vogelxo is a clear, translucent, alcohol-based testosterone gel intended for topical administration. Vogelxo contains 1% testosterone in dissolved form and the formulation is intended to release the testosterone for absorption through the skin.

### **Currently approved medications for the treatment of Male Hypogonadism**

Testosterone replacement therapies include: transdermal systems (Androderm 2.5mg & 5mg), gel formulations (AndroGel 1%, AndroGel 1.62%, Testim 1%, Axiron, Fortesta, testosterone Gel), implants (Testopel), a buccally applied product (Striant), intranasal gel (Natesto) and testosterone injections.

## **2. Regulatory Background**

Upsher-Smith Laboratories, Inc. (USL) originally submitted NDA 204399 (testosterone gel for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone) on October 17, 2012. The NDA was submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FDCA) and relies, in part, on the Agency's finding of safety and efficacy for Testim 1% (testosterone gel) (NDA 021454), the reference listed drug (RLD). The patent certification submitted with the NDA included Paragraph IV certifications for each of the ten patents listed in the Orange Book for Testim 1%.

On February 12, 2013, USL submitted an amendment to the NDA notifying the Division that the holder of the NDA for the RLD and the owner of the patents referenced in the patent certification had initiated a patent infringement lawsuit against USL. The lawsuit was still ongoing when the Division issued its action letter for the initial review cycle.

During the initial review cycle, the review team conducted a thorough review of NDA 204399 and concluded that the NDA should be approved. However, because the patent infringement lawsuit had not been resolved, the Division issued a tentative approval letter for the NDA on August 16, 2013. The letter explained that final approval of the NDA could not be granted until (1) expiration of the 30-month stay of approval provided by the Hatch-Waxman Amendments, or (2) the date the court decides that the patents listed in the application's patent certification are invalid or not infringed, or (3) the listed patents expire. The letter also indicated that final approval would be contingent upon there being no new information, since the tentative approval, which would preclude granting final approval of the application.

### **Current Submission**

The current submission (SDN 23), received on December 5, 2013, is a class 2 resubmission that responds to the Division's tentative approval letter issued on August 16, 2013. The submission includes:

- a Memorandum Opinion and Order, pertaining to the patent infringement lawsuit, issued by the U.S. District Court for the District of Delaware on December 4, 2013;
- proposed risk evaluation and mitigation strategy (REMS) for Vogelxo;
- proposed labeling (package insert and Medication Guide) for Vogelxo.

In addition, the submission states that the applicant intends to market an authorized generic<sup>1</sup> with manufacture, packaging and testing that are identical to Vogelxo, and includes proposed REMS and labeling for that product.

### **Patent Infringement Litigation**

In the patent certification for NDA 204399, USL certified that the ten Orange Book listed patents for Testim 1%, the NDA's RLD, would not be infringed by the manufacture, use, or sale of Vogelxo. After submitting the NDA, USL provided Paragraph IV notification to the holder of the NDA for the RLD and to the owner of the Orange Book listed patents. Subsequent to receiving that notification, both parties filed suit against USL for patent infringement in the U.S. District Court for the District of Delaware (Docket #13-CV-148-SLR).

In the current submission, USL submitted two district court documents that pertain to the patent infringement lawsuit: A Memorandum Opinion and an Order both dated December 4, 2013. A third district court document, a Stipulated Final Judgment of Non-Infringement dated December 30, 2013, was submitted on December 31, 2013. The documents dated December 4 granted USL's motion for summary judgment of non-infringement of the Orange Book listed patents, and the document dated December 30 entered a judgment of non-infringement in favor of USL and against the plaintiffs in the lawsuit.

### **3. CMC**

***The Chemistry Review team recommends that NDA 204399 be approved and I concur with their recommendation.***

### **4. Nonclinical Pharmacology/Toxicology**

***The Nonclinical Pharmacology/Toxicology team recommends that NDA 204399 be approved and I concur with their recommendation.***

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<sup>1</sup> An "authorized generic drug" is a listed drug that has been approved under subsection 505(c) of the FDCA and is marketed, sold, or distributed directly or indirectly to retail class of trade with either labeling, packaging, product code, labeler code, trade name, or trade mark that differs from that of the listed drug (21 C.F.R. § 314.3).

## 5. Clinical Pharmacology/Biopharmaceutics

*The Clinical Pharmacology team (DCP3) recommends that NDA 204399 be approved and I concur with their recommendation.*

## 6. Efficacy/Review of Bioequivalence

The efficacy of Vogelxo was not evaluated in a clinical study. Instead, the efficacy of Vogelxo was established by the pivotal bioequivalence study (Study P06-011) showing that it is bioequivalent to Testim, the reference listed drug. Testim is a FDA approved testosterone gel that was shown to be an effective treatment for hypogonadal males. A study showing that Vogelxo provides equivalent blood levels of testosterone to Testim is reasonable support for the conclusion that Vogelxo is also an effective treatment for this indication.

*Detailed review of efficacy can be seen in previous CDTL review memo for Tentative Approval dated August 16, 2013.*

## 7. Safety Update

The current submission contains the applicant's statement confirming that there is no additional safety information for Vogelxo since the tentative approval. This statement is consistent with information provided in the annual reports for IND 76654, the IND USL opened to conduct clinical trials for Vogelxo. The annual reports indicate that (1) all clinical data collected under the IND were submitted in NDA 204399, (2) no clinical trials were ongoing at the time the NDA was submitted, and (3) no clinical trials were initiated since the NDA was submitted.

Although there is no additional safety information specifically for Vogelxo since the tentative approval, additional safety information for the testosterone products in general has become available during this timeframe. (b) (4)

(b) (4) the Division also initiated a Safety Labeling Change for testosterone products since the tentative approval of Vogelxo. On March 26, 2014, and again on May 29, 2014, the Division sent Safety Labeling Change Notification letters to the holders of approved NDAs for testosterone products requesting the addition to labeling of new safety information regarding the risk of venous thromboembolic events (VTE) and testosterone use. The Safety Labeling Change includes changes to the Warnings and Precautions, and Adverse Reactions sections of the package insert; and changes to the Medication Guide.

“Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE.”

The applicant agreed to include the labeling changes required by the Safety Labeling Change in the labeling for Vogelxo.

**CDTL comment:** In my opinion the risk-benefit for Vogelxo has not changed since the tentative approval of NDA 204399 on August 16, 2013, for the following reasons. The clinical trials for Vogelxo were completed when the NDA was initially submitted and the applicant confirms that there is no additional safety information for Vogelxo since the tentative approval. [REDACTED] (b) (4)

[REDACTED] Finally, the new safety information regarding VTE risk with testosterone use, which resulted in a Safety Labeling Change for the approved testosterone products since the tentative approval, is included in the Vogelxo label. Therefore, I conclude that the risk-benefit for Vogelxo has not changed since the tentative approval, and continues to be acceptable.

## 8. Other Relevant Regulatory Issues

### Division of Risk Management (DRISK)

The Division of Risk Management (DRISK) provided a consultation regarding the Sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS).

The current submission contains two proposed REMS documents: one for Vogelxo and one for the authorized generic. Both proposed REMS include a Medication Guide and timetable for submission of assessments 18 months, 3 years, and 7 years after approval of the REMS.

The issue of whether REMS that include both a brand and an authorized generic should have two REMS documents (one for the brand and one for the authorized generic) or a single document for both products was discussed with the Division of Risk Management (DRISK) and the CDER Safety Requirements Team. It was decided that a single REMS document for the brand and authorized generic products would facilitate administrative processes and future REMS modifications. The applicant was informed of this decision and amended the application to include a single REMS supporting document on April 9, 2014, and a single REMS document on May 8, 2014.

DRISK reviewed the proposed REMS for Vogelxo and the authorized generic, including the amendments submitted on April 9 and May 8, 2014, and found it acceptable.

### Controlled Substances Staff (CSS)

In their final review of the NDA, CSS provided recommendations for revisions to Section 9 of the proposed label (Drug Abuse and Dependence). [REDACTED] (b) (4)

## 9. Labeling

The current submission includes proposed labeling (package insert and Medication Guide) for Vogelxo that is identical to that which was tentatively approved on August 16, 2013. During the labeling negotiations, the applicant agreed to include the new safety information regarding

the risk of VTE and testosterone use that the Division requested in the Safety Labeling Change for the approved testosterone products (see Safety Update).

Labeling negotiations for Vogelxo were completed on May 31<sup>st</sup>, 2014 and an agreement was reached between the Division and the applicant on the content of the package insert and Medication Guide.

The authorized generic will have labeling that is materially the same as the labeling approved for Vogelxo.

Recommended changes from all disciplines were incorporated into the label before an agreement was reached with the sponsor. The major safety change made during this review cycle was to include language about association of VTE and Testosterone use to W/P section.

Highlights Section:

“Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients using testosterone products. Evaluate patients with signs or symptoms consistent with DVT or PE.”

Full Prescribing Information:

“There have been postmarketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products, such as Vogelxo. Evaluate patients who report signs and symptoms of pain, edema, warmth and erythema in the lower extremity for DVT and those who present with acute shortness of breath for PE. If a venous thromboembolic event is suspected, discontinue treatment with Vogelxo and initiate appropriate workup and management.”

## **10. Recommendations/Risk Benefit Assessment**

**The risk/benefit assessment for Vogelxo is consistent with all previously approved topical testosterone products.**

### **Recommendation**

From a clinical perspective, I recommend that Vogelxo Gel for transdermal use should receive an approval action for the indication of testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: Primary hypogonadism (congenital or acquired), or hypogonadotropic hypogonadism (congenital or acquired).

The recommendation of approval for this 505(b)(2) application is based on the demonstration of bioequivalence (during the first review cycle) between Vogelxo and Testim, a FDA approved testosterone gel, which is the reference listed drug (RLD) for the application. Additionally, the three safety studies conducted by the Sponsor demonstrated an acceptable safety profile for Vogelxo in terms of formulation dependent safety parameters.

**Risk Benefit Assessment**

In my opinion the risk-benefit for Vogelxo has not changed since the tentative approval of NDA 204399 on August 16, 2013, for the following reasons. The clinical trials for Vogelxo were completed when the NDA was initially submitted and the applicant confirms that there is no additional safety information for Vogelxo since the tentative approval. (b) (4)

Finally, the new safety information regarding VTE risk with testosterone use, which resulted in a Safety Labeling Change for the approved testosterone products since the tentative approval, is included in the Vogelxo label. The applicant also submitted a risk evaluation and mitigation strategy (REMS) for Vogelxo and its authorized generic that is acceptable to the Division of Risk Management (DRISK). Labeling negotiations were completed and an agreement was reached on the content and the language in the package insert and Medication Guide. Therefore, I conclude that the risk-benefit for Vogelxo continues to be acceptable.

*In summary, I conclude that the information submitted by the Sponsor is adequate to allow the reasonable conclusion that Vogelxo would be effective and safe for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.*

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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.**  
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/s/  
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SURESH KAUL  
06/03/2014

## Cross-Discipline Team Leader Memo

<b>Date</b>	<b>August 12, 2013</b>
<b>From</b>	<b>Suresh Kaul, MD, MPH</b>
<b>Subject</b>	<b>Cross-Discipline Team Leader Review</b>
<b>NDA#</b>	<b>204,399</b>
<b>Applicant</b>	<b>Upsher-Smith Laboratories, Inc.</b>
<b>Date of Submission</b>	<b>October 17, 2012</b>
<b>PDUFA Goal Date</b>	<b>August 18, 2013</b>
<b>Proprietary Name / Established (USAN) names</b>	<b>Testosterone Gel Vogelxo</b>
<b>Dosage forms / Strength</b>	<b>Gel for Transdermal use, 50mg &amp; 100mg</b>
<b>Proposed Indication(s)</b>	<b>Treatment of Male Hypogonadism</b>
<b>Recommended:</b>	<b><i>Approval</i></b>

### 1. Introduction

The active moiety in Vogelxo is testosterone. Testosterone therapy is available in the United States as several formulations, including: topical gels and solutions, transdermal patch, buccal patch, intramuscular injections and implanted pellets.

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone. Signs and symptoms associated with male hypogonadism include: decreased sexual desire, fatigue, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range. Currently available treatment options for hypogonadism include intramuscular injections, subdermal implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels which are applied with the hands to the shoulders and upper arms and/or abdomen.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050ng/dL). These replacement therapies are ideally based on short term titration regimens that result in an optimal dose of product for a particular patient.

### **Product Information**

Vogelxo is a clear, translucent, alcohol-based testosterone gel intended for topical administration. Vogelxo contains 1% testosterone in dissolved form and the formulation is intended to release the testosterone for absorption through the skin.

### **Currently approved medications for the treatment of Male Hypogonadism**

Testosterone replacement therapies include: transdermal systems (Androderm 2.5mg & 5mg), gel formulations (Androgel 1%, Androgel 1.62%, Testim 1%, Axiron, Fortesta, testosterone Gel), implants (Testopel), a buccally applied product (Striant) and testosterone injections.

## **2. Regulatory Background**

The Sponsor submitted this NDA under section 505b(2) of the Federal Food Drug and Cosmetic Act and is substantially relying on the Agency's findings of safety and efficacy for Testim (NDA 021454), the reference listed drug (RLD). Although both Testim and Vogelxo contain the same active ingredient (testosterone), in the same strength (1%), in the same dosage form (topical gel), and with the same route of administration (transdermal); the composition of each product (Vogelxo and Testim) differs with respect to the inactive ingredients used. Therefore, the Sponsor was required to conduct an irritation and sensitization study (Study P08-001), a hand washing study (Study P10-002), and a skin-to-skin transferability study (Study P10-003) to address formulation dependent safety.

## **3. CMC**

The Chemistry review team concluded that the Sponsor has provided sufficient information on drug substance controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The Sponsor has also provided sufficient stability information on the drug product to assure strength, purity and quality of the drug product during the expiration dating period.

***The Chemistry Review team recommends that NDA 204399 be approved and I concur with their recommendation.***

## **4. Nonclinical Pharmacology/Toxicology**

The toxicology reviewer's opinion is that the nonclinical data support approval of Vogelxo for testosterone replacement in hypogonadal men as a topically applied product.

There were no recommendations for additional nonclinical studies. Class labeling was deemed appropriate. No significant labeling issues were identified, nor were significant changes

required. Literature references and a scientific rationale for the reliance on literature were submitted to support the nonclinical sections of the labeling.

***The Nonclinical Pharmacology/Toxicology team recommends that NDA 204399 be approved and I concur with their recommendation.***

## **5. Clinical Pharmacology/Biopharmaceutics**

Clinical Pharmacology made the following recommendation:

***“The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) reviewed NDA 204399 submitted on October 18, 2012. The overall Clinical Pharmacology information to support this NDA is acceptable.***

### **Summary of Clinical Pharmacology Findings:**

#### **Bioequivalence Study:**

Sponsor conducted an open-label, randomized, 2-treatment, 4-way replicate crossover bioequivalence study (Study P06-011) under fasting conditions comparing equal doses of Vogelxo and Testim® (RLD). Each treatment consisted of a single application of 2 x 5 gram (100 mg testosterone) topical gel using Vogelxo or Testim® applied over a 500 cm<sup>2</sup> area on the upper arms/shoulder. The treatment phases were separated by washout periods of 7 days. The 90% confidence intervals about the ratio of the geometric means of Vogelxo to Testim® were within the 80.00% and 125.00% limits for PK parameters C<sub>max</sub>, AUC<sub>0-24hr</sub> and AUC<sub>0-72hr</sub> of the ln-transformed baseline-corrected data. The results of this study suggest that Vogelxo and the reference product, Testim®, are bioequivalent.

#### **Transfer Study:**

A person-to-person transfer study (Study P10-003) was conducted to assess the transferability of Vogelxo during skin-to-skin contact with and without clothing or after washing an application site. This was a randomized, open-label, 3-way crossover study in ninety-six healthy subjects (48 pairs of dosed male and non-dosed female subjects). Male subjects received a single dose of 5 gram of Vogelxo gel applied on the upper arm/shoulder in each treatment period. Each female subject rubbed the anterior portion of her forearm over the application site of her male partner. Blood samples were taken from the non-dosed female subjects for determination of serum testosterone concentrations.

The results showed that unprotected female partners' mean T serum exposures were approximately 3 folds of the baseline values after direct skin contact with dosed males. In contrast, when a shirt covered the application site or the application site was washed before the contact, female subjects had testosterone levels that were comparable to baseline values. The results of the study indicated that wearing of clothing or the washing of the application site are two effective methods to prevent the transferability of testosterone between dosed and non-dosed individuals.

#### **Effects of Hand Washing**

An open-label, randomized, 3-way crossover study was conducted in 36 healthy male subjects to quantify the amount of T remaining on hands following washing procedure. Subjects self-

applied the entire contents of one tube (5 gram of gel) over the upper shoulder/arm opposite to the subject's dominant hand. Depending upon the treatment groups, subjects washed and rinsed their hands immediately or allowed the hands to air dry for 3 minutes followed by washing and rinsing. Skin swab samples of the application hand were collected for testosterone within 15 min prior to dosing, after testosterone application, and after washing.

The results from this study indicated that independent of the testosterone removal method used, washing hands with or without drying, allowed nearly complete (~99%) removal of Vogelxo from the surface of the skin, thereby greatly reducing the risk of potential cross contamination between individuals.

**Drug-Drug Interactions (DDI):**

No new DDI studies were conducted with Vogelxo Gel. The Sponsor proposed to use publically available information from Testim (RLD) for their product.

**Site Inspections:**

A formal consult to the Office of Scientific Investigations (OSI) was made for clinical and bioanalytical study site inspection of the pivotal BE study (P06-011). OSI's memorandum reveals that the inspection did not identify any incidents in which integrity or accuracy of data was compromised and there are no unresolved issues that would affect the approvability of Vogelxo gel.

**CDTL Comment:**

- 1. The Clinical Pharmacology review team concluded in their review dated July 12, 2013 that the information supplied with the Sponsor's submission adequately supports the bioequivalence of Vogelxo gel and Testim (RLD).*
- 2. The results of the Transfer study indicated that wearing of clothing or washing of the application site are two effective methods to prevent the transferability of testosterone between dosed and non-dosed individuals.*
- 3. The results from Washing study indicated that independent of the testosterone removal method used, washing hands with or without drying, allowed nearly complete (~99%) removal of Vogelxo from the surface of the skin, thereby greatly reducing the risk of potential cross contamination between individuals.*
- 4. There are no unresolved issues regarding the clinical and bio-analytical study site inspections that would affect the approvability of Vogelxo.*

*The Clinical Pharmacology team (DCP3) recommends that NDA 204399 be approved and I concur with their recommendation.*

**6. Clinical Microbiology**

Microbiology consult was not requested for this NDA during the review cycle.

**7. Efficacy/Review of Bioequivalence**

The efficacy of Vogelxo was not evaluated in a clinical study. Instead, the efficacy of Vogelxo was established by the pivotal bioequivalence study (Study P06-011) showing that it is bioequivalent to Testim, the reference listed drug. Testim is a FDA approved testosterone gel

that was shown to be an effective treatment for hypogonadal males. A study showing that Vogelxo provides equivalent blood levels of testosterone to Testim is reasonable support for the conclusion that Vogelxo is also an effective treatment for this indication.

Eighty-four (84) subjects began the study and 73 subjects completed the clinical portion of the study in its entirety. Fifteen (15) subjects had a mean baseline testosterone serum concentration greater than 350ng/dL during at least one dosing period. Therefore, these subjects were excluded from the pharmacokinetic analysis. The serum samples from 58 subjects with a mean baseline testosterone concentration < 350 ng/dL (3500 pg/mL) during all four dosing periods were included in the determination of bioequivalence.

The results for the In-transformed baseline-corrected data for Vogelxo (Test A) and Testim (Test B) are summarized in Table 1 below.

**Table 1: Summary of Transformed PK Parameters (Study P06-011)**

	Ratio <sup>1</sup>	90% Geometric CI <sup>2</sup>	
		Lower	Upper
AUC <sub>0-t</sub>	110.64%	104.19%	117.49%
AUC <sub>0-24</sub>	110.42%	104.55%	116.61%
C <sub>max</sub>	103.79%	96.90%	111.18%

<sup>1</sup>Calculated using least-squares means.

<sup>2</sup>90% Geometric CI using In-transformed data

Source: NDA 204399, Module 5.3.1.2, CSR P06-011

The 90% confidence intervals about the ratio of the test (Vogelxo) geometric mean to the reference (Testim) geometric mean were within the 80.00% to 125.00% limits for AUC<sub>0-t</sub>, AUC<sub>0-24</sub> and C<sub>max</sub>.

#### ***CDTL comment***

***Based on the data shown in Table 1, it is my opinion that this study provided reasonable and acceptable evidence of bioequivalence of Vogelxo and Testim. I believe that demonstration of equivalent blood levels of total testosterone between the two products provides adequate support for Vogelxo, to be an effective treatment for hypogonadal males.***

## **8. Safety**

The safety of Vogelxo was not evaluated in a clinical trial. Instead, the safety of the drug product was established by demonstrating its bioequivalence to Testim, the reference listed drug (RLD), in the pivotal bioequivalence study (Study P06-011).

In addition, because the formulation of Vogelxo differs from the RLD with respect to only inactive ingredients, three safety studies were conducted to assess formulation dependent areas of safety. Study P08-001 evaluated the cumulative irritation and sensitization of the skin produced by Vogelxo compared with Testim, Study P10-002 evaluated the removal of Vogelxo from the hand used for application after washing with soap and water, and Study

P10-003 evaluated the transfer of testosterone from a treated male to an untreated female via skin contact.

### Transfer Study

The primary objective of this study was to determine the extent of skin-to-skin testosterone transfer from male subjects dosed with Vogelxo to non-dosed female subjects under the following conditions: (1) in the presence and absence of clothing on the application site (Treatments A and B, respectively) and (2) after the application site had been washed (Treatment C).

Tables 2, 3, and 4 summarize the pre-exposure, uncorrected post-exposure, and baseline corrected post-exposure  $AUC_{0-24}$  and  $C_{max}$  for testosterone, respectively, for the 48 non-dosed female subjects included in the PK population.

**Table 2: Pre-exposure Testosterone  $AUC_{0-24}$  and  $C_{max}$**

Parameter		Treatment A (n=47)	Treatment B (n=47)	Treatment C (n=42)
$AUC_{0-24}$ (hr*pg/mL)	Mean (SD)	3660.0 (2148.4)	3441.8 (1784.8)	3421.0 (1638.7)
	Range	719.7 - 10963.9	725.4 - 10740.2	771.3 - 9713.0
$C_{max}$ (pg/mL)	Mean (SD)	198.2 (96.7)	186.7 (81.9)	191.4 (82.2)
	Range	72 - 532.2	82.7 - 521.3	85.8 - 459.7

Treatment A - with shirt; Treatment B - without shirt or washing; Treatment C - after washing

Source: NDA 204399, Module 5.3.3.1,

*Comment: The pre-exposure testosterone levels as reflected by the  $AUC_{0-24}$  and  $C_{max}$  were similar in each of the three treatment groups.*

**Table 3: Post-exposure Uncorrected Testosterone  $AUC_{0-24}$ ,  $RD_{AUC}$ , and  $C_{max}$**

Parameter		Treatment A (n=47)	Treatment B (n=47)	Treatment C (n=42)
$AUC_{0-24}$ (hr*pg/mL)	Mean (SD)	3762.1 (2115.3)	11273.0 (5866.8)	3597.6 (1697.7)
	Range	676.5 - 11230.1	3692.4 - 37710.1	1116.3 - 10198.7
$RD_{AUC}$ (%)	Mean (SD)	4.0 (11.7)	277.0 (217.4)	8.7 (21.7)
	Range	-33.6 - 30.3	28.2 - 1178.4	-38.7 - 103.1
$C_{max}$ (pg/mL)	Mean (SD)	203.8 (103.3)	793.8 (655.1)	194.8 (83.1)
	Range	76.1 - 530.6	229.2 - 4736.57	94.8-514.1

Treatment A - with shirt; Treatment B - without shirt or washing; Treatment C - after washing

Source: NDA 204399, Module 5.3.3.1

**Table 4: Post-exposure Baseline Corrected Testosterone AUC<sub>0-24</sub> and C<sub>max</sub>**

Parameter		Treatment A (n=47)	Treatment B (n=47)	Treatment C (n=40)
AUC <sub>0-24</sub> (hr*pg/mL)	Mean (SD)	307.1 (196.0)	7793.6 (5276.5)	364.8 (226.0)
	Range	8.6 - 651.9	913.42 - 33374.0	43.6 - 839.0
C <sub>max</sub> (pg/mL)	Mean (SD)	50.1 (29.0)	648.6 (640.6)	53.7 (26.7)
	Range	5.3 - 158.1	109.8 - 4555.9	10.7 - 110.2

Treatment A - with shirt; Treatment B - without shirt or washing; Treatment C - after washing

Source: NDA 204399, Module 5.3.3.1

**CDTL Comment:**

*When the application site was clothed (Treatment A) or washed (Treatment C) prior to contact, none of the female subjects had a maximal testosterone concentration greater than the upper limit of the normal range of testosterone (700 pg/mL) for healthy females during the 24 hour period following skin-to-skin contact with their dosed male partner. By comparison, when the application site was neither clothed nor washed (Treatment B), 18 (38%) female subjects had a maximal testosterone concentration that was greater than the normal range.*

*Therefore, it is reasonable to conclude that in the absence of clothing or application site washing, a nearly 3-fold increase in testosterone levels was observed in non-dosed females following skin-to-skin contact with dosed males. When the application site was clothed or washed before contact, the post-exposure maximum serum testosterone levels of each of the non-dosed female subjects was within the normal range for healthy women.*

**Residual Testosterone after Washing**

This study quantified the amount of Vogelxo remaining on a subject's hand after applying the drug to the application site, both before and after washing the hand with soap and water. Three treatment groups were defined based on drying time after application of the drug and drying method after washing. The treatment groups are summarized in Table 5.

**Table 5: Treatment Groups (Study P10-002)**

Treatment	A	B	C
Drying time after application of drug (mins.)	3	3	0
Drying method after washing and rinsing hands	Cloth towel	Air dried (9 mins)	Cloth towel

Testosterone levels obtained from the skin swab samples at baseline, before washing, and after washing are summarized in Table 6.

**Table 6: Testosterone Level ( $\mu\text{g}$ ) Obtained From Skin Swab Samples**

		Treatment A	Treatment B	Treatment C
Baseline	N	36	35	35
	Mean (SD)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
	Range	0.0 – 0.0	0.0 – 0.0	0.0 – 0.0
Before Washing	N	36	35	35
	Mean (SD)	58.59 (38.74)	60.54 (41.67)	70.29 (43.58)
	Range	11.23 – 141.86	7.57 – 185.74	10.75 – 174.98
After Washing	N	36	35	35
	Mean (SD)	0.65 (1.03)	0.52 (1.24)	0.16 (0.46)
	Range	0.00 – 3.95	0.00 – 6.61	0.00 – 1.64

Source: NDA 204399, Module 5.3.3.1.3

#### ***CDTL Comment***

***Mean testosterone levels of the hand after washing were 0.65, 0.52, and 0.16  $\mu\text{g}$  for Treatments A, B, and C, respectively. Washing reduced the testosterone level remaining on the hand after application of the gel by 98.65%, 99.02%, and 99.77% for Treatments A, B, and C, respectively.***

***Therefore, it is reasonable to conclude that washing was effective in removing approximately 99% of the testosterone remaining on the skin of the hand used to apply Vogelxo. This result was consistent regardless of whether or not the gel remaining on the hand after application was allowed to dry for 3 minutes, or dried with a towel or air dried. For a detailed review of this study, see the MO and CP reviews.***

#### **Skin Sensitization Study**

Results from the sensitization data were collected for all subjects that were qualified to continue to the challenge phase of the study (N=229). In the challenge phase any subject with a converted score of 2 or more at 48 hours post-patch removal was considered to be potentially sensitized and was re-challenged at least 3 to 4 weeks after the conclusion of the challenge phase to confirm the sensitization reaction.

The total number of converted sensitization evaluation scores received during the challenge phase of the study are summarized by treatment in Table 7.

**Table 7: Total Converted Sensitization Evaluation Scores (Study P08-001)**

Treatment	Scores, n(%)					Total Sites Scored
	0	0.5	1	2	3	
A	587 (64.1%)	298 (32.5%)	22 (2.4%)	2 (0.2%)	7* (0.8%)	916
B	557 (60.8%)	317 (34.6%)	31 (3.4%)	7 (0.8%)	4** (0.4%)	916
C	554 (60.5%)	339 (37.0%)	23 (2.5%)	0	0	916
D	649 (70.9%)	255 (24.6%)	12 (1.3%)	0	0	916

Treatment A: Vogelxo

Treatment B: Testim

Treatment C: Positive Irritant Control (0.05% sodium lauryl sulfate)

Treatment D: Low Irritant Control (0.9% aqueous sodium chloride)

There were no reaction scores greater than 1 for the positive irritant control and the low irritant control at the 48 hour post-patch removal time point during the challenge phase of the study. Following administration of Vogelxo and Testim, three (1.3%) of 229 subjects had reaction scores greater than 1 at the 48 hour post-patch removal time point during the challenge phase of the study. These were identified as being the same three subjects (Subjects 045, 079, and 114) for both products. All three subjects demonstrating a reaction were contacted for a confirmatory re-challenge. One subject (Subject 114) was not eligible to participate in the re-challenge phase as a result of being enrolled in another study. The other two subjects were re-challenged with Vogelxo and Testim (greater than 14 days after the initial challenge). Following re-challenge both subjects demonstrated reaction scores of 3 at 0.5, 24, and 48 hours post-patch removal, and a reaction score of 2 or greater 72 hours post-patch removal.

Both subjects demonstrated reactions at the challenge and re-challenge study phases, which is suggestive of sensitization to both Vogelxo and Testim. Results from the sensitization data for all subjects indicate that both Vogelxo and Testim demonstrate a low, but equal propensity for inducing sensitization (i.e., allergic contact dermatitis).

***CDTL Comment***

***Based on the results of the challenge and re-challenge phase of the study, I agree with the clinical reviewer that the sensitization potential of Vogelxo is similar to that of Testim.***

**Skin Irritation Study**

This study included application of Vogelxo, Testim, a positive control, and a low irritant control, that were applied under occlusive conditions to 4 sites on both upper outer arms and evaluated for irritation response for 21 days. Following a rest phase, the subjects were dosed with all four treatments on four sites on the upper back, which were evaluated for sensitization to Vogelxo and Testim.

**Table 8: Intent-To-Treat Population (N = 255)**

Variable	Hypotheses	Upper Bound of One-Sided 95% CI	Description of Observed Response
Converted Cumulative Irritation Evaluation Scores	$H_0: \mu_T - 1.25 \mu_R > 0$ $H_1: \mu_T - 1.25 \mu_R \leq 0$	-7.9230	This suggests the test product is non-inferior to the reference product in irritation.

Source: NDA 204399, Module 5.3.3.1.1

**CDTL Comment**

*The null hypothesis was rejected for the hypothesis test comparing Vogelxo to Testim for the cumulative irritation evaluation scores (the upper bound of the one-sided 95% confidence interval is less than or equal to zero). Therefore, the test product (Vogelxo) was found to be non-inferior to the reference product (Testim) in irritation” in the Intent-To-Treat population.*

**Adverse Events**

A total of 121 treatment emergent adverse events (TEAEs) were reported by 67 (26.3%) subjects during the study. No deaths or TEAEs leading to discontinuation were reported. One subject reported 2 SAEs (ruptured spleen and broken clavicle due to bicycle accident) during the study that was considered to be not related to treatment. All TEAEs were mild or moderate in severity. The most commonly reported TEAEs were application site pruritus (7.5%), pharyngolaryngeal pain (4.3%), and headache (3.9%).

Of the 121 TEAEs reported, 36 were judged to be at least possibly related to the study medication. The possibly related TEAEs are summarized in Table 9.

**Table 9: Treatment-related Adverse Events (Study P08-001)**

Preferred Term	Safety Population	
	Overall	
	N=255	
	n (%)	Events
Application site hyperaesthesia	1 (0.4)	1
Application site irritation	2 (0.8)	2
Application site pain	2 (0.8)	2
Application site pruritus	19 (7.5)	22
Fatigue	1 (0.4)	1
Musculoskeletal stiffness	1 (0.4)	1
Myalgia	2 (0.8)	2
Dysgeusia	1 (0.4)	1
Headache	1 (0.4)	1
Paraesthesia	1 (0.4)	2
Mood altered	1 (0.4)	1

Source: NDA 204399, Module 2.7.4

***CDTL Comment:***

***The adverse events reported during Study P08-001 were similar to those seen with other testosterone products and do not raise any new safety issues. Most treatment-related adverse events were treatment site related as expected.***

**Overall Assessment of Safety Findings**

*Based on the results of the interpersonal transferability study, the hand washing study, skin sensitization and irritation study, Vogelxo Gel demonstrated acceptable safety.*

**9. Advisory Committee Meeting**

No advisory committee meeting was held to discuss this product as there were no outstanding issues that required outside input.

**10. Pediatrics**

The Applicant stated that a request for waiver of pediatric studies is not applicable, as this NDA does not seek a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. This is acceptable and consistent with guidance that the Division has received previously from PeRC for other testosterone gel products.

**11. Other Relevant Regulatory Issues**

**Division of Professional Drug Promotion (DPDP) in the Office of Prescription Drug Promotion (OPDP)**

A consultation regarding labeling was requested and completed by OPDP. All the OPDP comments and recommendations were carefully considered. Recommendations were addressed through internal discussions amongst the primary review team and through successful negotiations with Sponsor.

**Office of Scientific Investigation (OSI)**

At the request of the Division of Pharmacology 3, OSI audited the clinical and analytical sites of the bioequivalence study. OSI's memorandum reveals that the inspection did not identify any incidents in which integrity or accuracy of data was compromised and there are no unresolved issues that would affect the approvability of Vogelxo gel.

**Financial Disclosure**

Financial disclosures were submitted for the investigators in the pivotal BE study.

**Office of Surveillance and Epidemiology: Division of Risk Management (DRISK)**

The Division of Risk Management (DRISK) provided a consultation regarding the Sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS).

DRISK reviewed the Vogelxo proposed REMS and finds it **acceptable** with minor revisions.

**Division of Medical Policy programs (DMPP)**

Shawna Hutchins of DMPP provided a final consult regarding the Sponsor's proposed Medication Guide. DMPP concluded: The MG is acceptable with the recommended edits.

### **Controlled Substances Staff (CSS)**

In their final review of the NDA, CSS provided specific recommendations for revisions to Section 9 of the proposed label (Drug Abuse and Dependence). The revisions include information that anabolic steroids, such as testosterone, are abused.

### **12. Labeling**

This is a 505(b)2 application and approvability determination requires that Vogelxo be bioequivalent to the reference related drug (RLD) Testim. The clinical reviewer, Marty Kaufman recommended that the label be similar to the current Testim label, but that the Sponsor needed to include a clinical section of the label with the BE study data and also update the safety section with the Transfer, Hand washing and Skin Sensitization and Irritation data respectively. These and other recommended changes were incorporated into a completed and finalized agreed upon label.

The Indications and Usage section was revised to include the following Limitation of Use:

- Safety and efficacy of Vogelxo in males less than 18 years old have not been established.
- Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.

The Dosage and Administration section was revised to include administration instructions for the packet and multi-dose metered pump.

### **13. Recommendations/Risk Benefit Assessment**

**The risk/benefit assessment for Vogelxo is consistent with all previously approved topical testosterone products.**

#### **Recommendation**

**From a clinical perspective, I recommend that Vogelxo Gel for transdermal use should receive an approval action for the indication of testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: Primary hypogonadism (congenital or acquired), or hypogonadotropic hypogonadism (congenital or acquired).**

**The recommendation of approval for this 505(b)(2) application is based on the demonstration of bioequivalence between Vogelxo and Testim, a FDA approved testosterone gel, which is the reference listed drug (RLD) for the application. Additionally, the three safety studies conducted by the Sponsor demonstrated an acceptable safety profile for Vogelxo in terms of formulation dependent safety parameters.**

### **Risk Benefit Assessment**

This NDA was submitted as a 505(b)(2) application, which relied on the Agency's previous finding of safety and efficacy for Testim, the reference listed drug (RLD). The Sponsor conducted a pivotal bioequivalence study (Study P06-011) to establish the "bridge" between Vogelxo and Testim. Establishing bioequivalence was considered sufficient to support the conclusion that Vogelxo would be effective for the same indication as the RLD.

However, because the inactive ingredients of Vogelxo are not identical to those of the RLD, bioequivalence alone was not considered sufficient to establish the safety of Vogelxo. In addition to bioequivalence, the Sponsor was required to address the formulation dependent safety concerns of skin irritation and sensitization, ability of washing to remove the gel from the hand used to apply the gel, and interpersonal transfer of testosterone from dosed men via skin contact.

The Sponsor conducted Study P06-011 to demonstrate that Vogelxo and Testim are bioequivalent. Based on the results of this study, bioequivalence of Vogelxo with Testim was established.

The Sponsor conducted Study P08-001 to evaluate the cumulative irritation produced by Vogelxo compared to the cumulative irritation produced by Testim on intact skin of healthy adult male subjects. The study also evaluated the sensitization potential of Vogelxo compared to Testim. Statistical analysis of the data comparing the converted cumulative irritation evaluation scores indicated that Vogelxo is no more irritating than Testim when topically applied over a continuous 21-day period. Results from the sensitization data for all subjects indicate that both Vogelxo and Testim demonstrate an equal propensity for inducing sensitization.

Based on the results of this study, it is reasonable to conclude that the irritation and sensitization potential of Vogelxo is similar to that of Testim.

The Sponsor conducted Study P10-002 to determine if washing the hands following application of Vogelxo removed testosterone from the surface of the skin. This study showed that washing was effective in removing approximately 99% of the testosterone remaining on the skin of the hand used to apply Vogelxo. The result was consistent regardless of whether or not the gel remaining on the hand after application was allowed to dry for 3 minutes, or dried with a towel or air dried.

The Sponsor conducted Study P10-003 to determine the extent of skin-to-skin testosterone transfer from male subjects dosed with Vogelxo to non-dosed female subjects under the following conditions: in the presence of clothing, in the absence of clothing, and after the application site had been washed. The study demonstrated that testosterone is transferred from a male treated with Vogelxo to a non-dosed female through skin-to-skin contact. Based on the data obtained, it is reasonable to conclude that covering the application site with clothing or washing the application site before contact are effective methods for preventing clinically significant testosterone transfer from a treated male to a non-treated female.

From a safety perspective, Vogelxo was shown in the safety studies (Transfer, Washing of Hands and Skin sensitization and irritation) to be reasonably safe for its intended use from a clinical perspective. The general pattern of adverse events for Vogelxo was reasonable and was likely to be similar to other drugs in the class. The most common adverse events for drugs in this class are: application site erythema and irritation, nasopharyngitis, increase in hematocrit, headache, diarrhea and vomiting. In regard to general safety issues, the comparable exposure is taken to mean that the adverse reactions for Vogelxo gel are the same as Testim and reflect well-known testosterone-related pharmacological adverse effects.

***In summary, I conclude that the information submitted by the Sponsor is adequate to allow the reasonable conclusion that Vogelxo would be effective and safe for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.***

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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.**  
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/s/  
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SURESH KAUL  
08/12/2013