CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204399Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	June 4, 2014
From	Christine P. Nguyen, M.D.
Subject	Deputy Director for Safety Summary Review
NDA #	204-399
Applicant Name	Upsher Smith Laboratories, Inc.
Date of Submission	December 4, 2014
PDUFA Goal Date	June 4, 2014
Proprietary Name / Established (USAN) Name	Vogelxo/Testosterone Gel
Dosage Forms / Strength	Gel (50 mg testosterone tube or packet); metered dose pump (12.5 mg testosterone per actuation)
Proposed Indication(s)	Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Action/Recommended Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Clinical Review	Martin Kaufman, DPM, MBA
Pharmacology Toxicology Review	Lynnda Reid, PhD
CMC Review	Bogdan Kurtyka, PhD Moo Jhong Rhee, PhD
Clinical Pharmacology Review	Li Li, PhD Myong Jin Kim, PhD
CDTL Review	Suresh Kaul, MD, MPH
OSE/DMEPA	Denise V. Baugh, PharmD, BCPS Lisa V. Khosla, PharmD, MHA
OSE/DRISK	Cathy A. Miller, MPH, BSN; Naomi Redd, PharmD Kimberly Lehrfield, PharmC; Cynthia LaCivita, PharmD Claudia Manzo, PharmD
Office of Prescription Drug Promotion	Trung-Hieu Tran, PharmD, MBA Twyla Thompson, PharmC
Division of Medical Policy Program	Shawna Hutchins, RN, BSN, MPH Melissa Hulett, RN, BSN, MSBA
Controlled Substance Staff	Alicja Lerner, MD, PhD Michael Klein, PhD
Project Management Staff	Jeannie Roule Jennifer Mercier

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
CMC=Chemistry, Manufacturing, Controls
CDTL=Cross-Discipline Team Leader

Summary Review

Summary Review and Recommendations of Complete Response

I recommend approval of Vogelxo (testosterone) gel as testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Vogelxo has not been approved for marketing in any country.

This NDA received a 'tentative approval' on August 16, 2013, because of unresolved patent infringement lawsuit against the Applicant. Final approval was contingent upon the final determination by the US District Court or expiry of the affected patents, and the assurance that there have been no changes to the conditions at the time of tentative approval that could impact final approval.

On December 4, 2013, the Applicant submitted a complete response to the August 2013 tentative approval letter. This class 2 resubmission contained a request for final approval for Vogelxo and a proposed REMS that covers for both Vogelxo and its authorized generic. The Applicant notified FDA that, on December 4, 2013, the US District Court for the District of Delaware ruled in favor of the Applicant, and granted summary judgment of non-infringement of all asserted patents. There have been no changes to the conditions at the time of tentative approval that would affect final approval.

The review disciplines (clinical, chemistry, clinical pharmacology, and pharmacology/toxicology; no statistics input was needed) recommended approval of this NDA without required postmarketing studies, and I concur with their recommendations. The Division of Risk Management found acceptable the REMS program that encompasses both the branded Vogelxo product and its authorized generic. Recommendations from the consultants (Division of Medication Errors and Prevention, Division of Medical Policy Program, and the Office of Prescription Drug Promotion) were incorporated. The Controlled Substance Staff (CSS) proposed substantial revisions to Section 9 of labeling that apply to the class of testosterone products. (b) (4) The cross-discipline team leader, Dr. Suresh Kaul, recommended approval of Vogelxo, and I concur with his recommendation (see review dated June 3, 2014).

The labeling for Vogelxo has been agreed to by FDA. Two notable labeling-related issues that arose during the review of this resubmission were:

- Boxed Warning: A Citizen Petition submitted to the FDA on February 25, 2014, requesting the addition of a boxed warning to labeling of testosterone products for cardiovascular (CV) risks. (b) (4) The

Division does not have any evidence that may suggest that the CV risks, if any, with the use of Vogelxo are different from that of other approved testosterone products. Therefore, a boxed warning will not be added to the labeling of Vogelxo at this time. (b) (4)

- A separate Warning for venous thromboembolism (VTE): It is known that testosterone products can cause polycythemia, and this adverse reaction is a class warning. Currently, VTE is labeled as a possible secondary effect of polycythemia. Because there have been postmarketing reports of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in the absence of polycythemia with various formulations of testosterone products, Vogelxo is being approved with a more general warning acknowledging these reports. The Division is requiring the same VTE labeling change for all approved testosterone products.

The benefit-risk profile of Vogelxo remains favorable. Vogelxo (testosterone) gel should now receive full approval with the resolution of patent infringement lawsuit and acceptable labeling and REMS.

My summary review of the original NDA submission that received a 'tentative approval' is appended below.

Summary Review for Regulatory Action

Date	August 16, 2013
From	Christine P. Nguyen, M.D.
Subject	Deputy Director for Safety Summary Review
NDA #	204-399
Applicant Name	Upsher Smith Laboratories, Inc.
Date of Submission	October 18, 2012
PDUFA Goal Date	August 18, 2013
Proprietary Name / Established (USAN) Name	Vogelxo/Testosterone Gel 1%
Dosage Forms / Strength	Gel (50 mg testosterone tube or packet); metered dose pump (12.5 mg testosterone per actuation)
Proposed Indication(s)	Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
Action/Recommended Action	Tentative Approval (*see sections 11 and 13*)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Clinical Review	Martin Kaufman, DPM, MBA
Statistical Review	Xin Fang, PhD Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Jeffrey Bray, PhD Lynnda Reid, PhD
CMC Review	Bogdan Kurtyka, PhD Moo Jhong Rhee, PhD
ONDQA Biopharmaceutics Review	Tapash Ghosh, PhD Angelica Dorantes, PhD
Clinical Pharmacology Review	Lanyan Fang, PhD Hae-Young Ahn, PhD
Office of Scientific Investigations	Seongeun Julia Cho, PhD Sam Haidar, PhD, RPh
CDTL Review	Suresh Kaul, MD, MPH
OSE/DMEPA	Manizheh Siahpoushan, PharmD Jim Schlick, RPh, MBA
OSE/DRISK	Cynthia LaCivita, PharmD Claudia Manzo, PharmD
Office of Prescription Drug Promotion	Jina Kwak, PharmD
Division of Medical Policy Program	Shawna Hutchins, RN, BSN, MPH Melissa Hulett, RN, BSN, MSBA
Controlled Substance Staff	James Tolliver, PhD Michael Klein, PhD
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DRISK=Division of Risk Management
CMC=Chemistry, Manufacturing, Controls
ONDQA=Office of New Drugs Quality Assessment
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

Upsher Smith Laboratories, Inc. submitted this 505(b)(2) new drug application (NDA) for testosterone gel 1% (tradename Vogelxo), seeking an indication of testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. A variety of dosage forms and routes of administration of testosterone, including topical gel and solution, transdermal patch, buccal tablet, oral capsule and tablet, intramuscular injection, and testosterone implant, are approved for this indication. Testosterone gel and solution products have the unique significant safety risk of skin-to-skin transfer of testosterone from patients to others, especially children, and these products carry a boxed warning and a Medication Guide REMS to address this risk.

The Applicant initially sought in 2007 marketing approval of testosterone gel 1%, hereafter referred to as its tradename Vogelxo, in unit-dose package through the Abbreviated New Drug Application (ANDA) pathway, with the approved testosterone gel 1% (Testim) as the reference listed drug. (b) (4) Because of the need for clinical data, the Office of Generics (b) (4) advised the Applicant to work with the Office of New Drugs.

This 505(b)(2) NDA substantially relies on the Agency's finding of efficacy and safety for Testim, the reference drug. The Applicant submitted bioequivalence data to support therapeutic equivalence of Vogelxo to Testim, and clinical evaluations of skin tolerability and sensitization, hand washing, and secondary skin transfer to address formulation-specific safety concerns of special interest for testosterone gel products.

This memorandum provides the basis for the regulatory action for this application.

2. Background

Testosterone is the predominant circulating androgen in males and is responsible for the development and maintenance of male reproductive functions and secondary sex characteristics. Male hypogonadism, resulting in low serum testosterone concentrations, may be due to primary (testicular failure) or secondary (hypothalamic or pituitary) dysfunctions. Testosterone replacement therapy is used to normalize serum testosterone concentrations in symptomatic hypogonadal men.

Testim is FDA-approved and is currently marketed by Auxilium Pharmaceuticals, Inc. (NDA 021-454) for testosterone replacement therapy in adult males with conditions associated with a deficiency or absence of endogenous testosterone. A single application of Testim to the skin on the shoulders and/or upper arms provides continuous transdermal delivery of testosterone

during the 24-hour dosing period. Daily application of 5 g or 10 g of Testim contains 50 mg and 100 mg testosterone, respectively. Vogelxo contains the same active ingredient (testosterone) and strength (1%), using the same dosage form (topical gel) and the same route of administration (transdermal) as Testim. Therefore, Vogelxo is pharmaceutically equivalent to Testim and is intended for the same conditions of use as Testim.

Relying on Testim as the reference listed drug, the Applicant submitted in August 2007 an ANDA for its testosterone gel 1% in individual unit-dose packets (ANDA 79-178). (b) (4)

In response to a citizen petition, the Agency determined in 2009 that testosterone gel products that are not qualitatively and quantitatively identical to reference listed drug would need to provide clinical safety data on formulation-specific transfer of testosterone via person-to-person contact. (b) (4) OGD advised the Applicant to work with the Office of New Drugs (OND).

In a Type C guidance meeting held in September 2009, the Division recommended studies of hand washing and person-to-person transferability for testosterone gel 1% to provide clinical data necessary for a 505(b)(2) application. A pre-NDA teleconference was held in August 2011 to discuss the NDA submission.

3. CMC/Device

Vogelxo (testosterone) gel 1% is a clear, alcohol-based testosterone gel intended for topical application. Three container closure systems for Vogelxo will be available: single-use 5 g tubes and packets, and 88 g multiple dose metered pump.

The Biopharmaceutics reviewer (Tapash Ghosh, PhD) found the proposed in-vitro drug release method and acceptance criteria acceptable for product release and on stability. In the review dated August 9, 2013, the CMC reviewer (Bogdan Kurtyka, PhD) concluded that "from the ONDQA perspective, this NDA is now recommended for Approval."

***Comment**: I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months for the unit dose tube and packet dosage forms and 24 months for the multiple dose metered pump at controlled room conditions. There are no outstanding chemistry issues.*

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were requested or submitted to support this application. In the review dated April 10, 2013, the pharmacology/toxicology reviewer (Jeff Bray, PhD) recommended approval of Vogelxo from a nonclinical pharmacology/toxicology perspective.

Comment: *I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.*

5. Clinical Pharmacology/Biopharmaceutics

The Applicant conducted a pivotal bioequivalence (BE) study (P06-011) to establish therapeutic equivalence of Vogelxo to Testim. In addition, two pharmacokinetic (PK) studies were conducted to assess safety regarding skin-to-skin transference (P10-003) and hand and application site washing to remove residual testosterone (P10-002).

Bioequivalence Study (P06-011): This was a single center, open-label, single-dose, open-label, randomized, 2-treatment. 4-way replicate crossover study conducted under fasting conditions comparing equal doses (100 mg testosterone) of the test (Vogelxo) and reference (Testim) products. Treatment phases were separated by a washout period of 7 days. A total of 84 adult males with hypogonadism (an average of two morning total serum testosterone levels ≤ 300 ng/dL [measured on two separate days]) were enrolled. Seventy three (73) subjects completed study, although only 58 subjects contributed to the pharmacokinetic analyses after 15 subjects were excluded for having a mean baseline testosterone serum concentrations > 350 ng/dL during at least one dosing period. The 90% confidence intervals about the ratio of the geometric means of Vogelxo (referred to as USL240 in Table 1) to Testim were within the 80.00% and 125.00% limits for PK parameters C_{max}, $AUC_{0\text{-}24hr}$ and $AUC_{0\text{-}72hr}$ of the ln-transformed baseline-corrected data shown in Table 1.

Table 1: Baseline Corrected BE Analysis (Study P06-011: PK eligible subjects, N=58)

Parameter	USL240 (Test) Mean	Testim® (RLD) Mean	Ratio[1]	90% Geometric CI[2]
C_{max} (pg/mL)	5084.02	4898.21	103.79%	96.90%, 111.18%
$AUC_{0\text{-}24hr}$ (pg*h/mL)	58778.32	53233.56	110.42%	104.55%, 116.61%
$AUC_{0\text{-}72hr}$ (pg*h/mL)	94370.14	85296.16	110.64%	104.19%, 117.49%

CI=confidence interval.
1. Calculated using least-squares means of USL240/Testim®.
2. 90% Geometric Confidence Interval using ln-transformed data.
Source: Primary clinical pharmacology review (7/12/13), Table 1

Comment*: The clinical pharmacology reviewer finds acceptable that the pivotal BE study was conducted using the 100 mg testosterone dose, despite the fact that the starting dose for Testim and Vogelxo is 50 mg. The reviewer concludes that the use of 100 mg dose could minimize the noise from the endogenous testosterone concentrations in assessing BE between Vogelxo and*

Testim. An earlier pilot bioequivalence/bioavailability study evaluating 3 different formulations of the Applicant's testosterone gel 1% demonstrated that one of the formulations (Vogelxo) showed BE to Testim at the tested dose of 50 mg. These findings and those from the pivotal BE study support BE for Vogelxo at the indicated doses of 50 mg and 100 mg.

The pivotal BE study results satisfy the regulatory requirements for demonstration of bioequivalence of Vogelxo to Testim and may be relied upon to bridge efficacy and general safety of Vogelxo to Testim.

Secondary Skin-to-Skin Transfer Study (P10-003): This was a single-center, open-label, randomized, 3-way crossover study to assess the transferability of Vogelxo during skin-to-skin contact with and without clothing coverage of the application site, and after washing of the application site. A total of 96 healthy subjects (48 male and 48 female subjects) were randomized in pairs (a dosed male was matched with a non-dosed female for the duration of the study). Male subjects applied a single dose of 5 gram of Vogelxo (50 mg testosterone) on the upper arm/shoulder/back in each treatment period. Female subjects rubbed the anterior portion of their forearm over the application site of male subjects. Blood samples were taken from the non-dosed female subjects for determination of serum testosterone concentrations.

In the non-dosed females, direct skin contact at the unclothed application site increased systemic testosterone concentrations by approximately 3-fold from baseline (treatment 1), whereas clothing covering (treatment 2) or washing the application site (treatment 3) prior to skin contact resulted in post-exposure serum testosterone concentrations similar to baseline. Table 2 summarizes results of pre- and post-exposure serum testosterone concentrations in non-dosed females.

Table 2: Percent Change Between Mean Pre- and Post-exposure Testosterone AUC_{0-24} and C_{max} in the Non-dosed Female

Parameter	Treatment 1* (n=47)	Treatment 2* (n=47)	Treatment 3* (n=42)
AUC_{0-24} (mean ± SD) (hr*pg/mL)			
Pre-exposure	3441.8 (1784.8)	3660.0 (2148.4)	3421.0 (1638.7)
Post-exposure	11273.0 (5866.8)	3762.1 (2115.3)	3597.6 (1697.7)
% Change	**+277**	**+4**	**+9**
C_{max} (mean ± SD) (pg/mL)			
Pre-exposure	186.7 (81.9)	198.2 (96.7)	191.4 (82.2)
Post-exposure	793.8 (655.1)	203.8 (103.3)	194.8 (83.1)

*Treatment 1 - without shirt or washing; Treatment 2 – with shirt; Treatment 3 - after washing
Source: Primary clinical pharmacology review (7/12/13); adapted from Table 2.

***Comment**: Washing or covering the application site is effective in decreasing the risk of secondary transfer of testosterone. This information will be included in labeling.*

Hand Washing Study (P10-002): This was a single-center, open-label, randomized, 3-way crossover study in 36 healthy male subjects to quantify residual testosterone on the hand after washing procedure. After applying 5 gram Vogelxo (50 mg of testosterone) to the application site, all subjects underwent 3 hand washing procedures in a cross-over manner: hand air dry

for 3 minutes prior to wash and rinse (treatment A), air dry for 3 minutes prior to wash/rinse and then air dry after wash/rinse (treatment B), or washed and rinsed immediately (treatment C). Skin swab samples of the application hand were collected for testosterone within 15 min prior to dosing, after testosterone application, and after washing.

The testosterone level (micrograms) on the hand surface before and after washing and the percentage of testosterone removed from the skin surface by washing were determined from the skin swab data. Results are shown in Table 3. Hand washing removes approximately 99% of testosterone from the hand skin surface.

Table 3: Testosterone Level (micrograms) on Hand Skin Surface Before and After Washing Procedures

Treatment	N	Before wash (µg, mean ± SD)	After wash (µg, mean ± SD)	% Removal by washing (mean)
A (air-dry followed by wash/rinse)	36	58.59 ± 38.74	0.64 ± 1.03	98.7%
B (air-dry followed by wash/rinse and air-dry)	35	60.54 ± 41.67	0.52 ± 1.24	99.0%
C (wash/rinse immediately)	35	70.29 ± 43.58	0.16 ± 0.46	99.8%

Source: Primary clinical pharmacology review (7/12/13), Table 3

Comment*: Hand washing under the various scenarios tested, which likely mimic actual use conditions, significantly reduces the risk of secondary transfer via direct skin contact with the patient's hand. This information will be included in labeling to mitigate the risk of transfer of testosterone to others via contact with the patient's hand.*

The clinical pharmacology reviewer (Lanyan Fang, PhD) concluded that:

1. Bioequivalence has been demonstrated for Vogelxo with Testim as the reference drug.
2. Washing or covering the application site with clothing was effective in decreasing the known risk of skin to skin transference of testosterone gel products.
3. Hand washing was effective in removing residual testosterone from the hand and is another effective strategy to decrease the risk of transference via contact with the patient's hand surface.

In the review dated July 12, 2013, the clinical pharmacology reviewer (Lanyan Fang, PhD) concluded that "the overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language."

Comment*: I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.*

6. Clinical Microbiology

Non-applicable.

7. Clinical/Statistical-Efficacy

The efficacy of Vogelxo relies on the successful demonstration of bioequivalence of systemic testosterone exposure with the reference drug Testim in hypogonadal male subjects in study P06-011. The efficacy evaluation included the following pharmacokinetic parameters: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, Kel and $T_{1/2}$ for baseline uncorrected and baseline corrected testosterone. The 90% confidence interval of the ratios of exposure measures (AUC, C_{max}) of Vogelxo compared to Testim were within the BE limit of 80% to 125%, confirming bioequivalence (see Section 5 Clinical Pharmacology/Biopharmaceutics). No other clinical efficacy trials were requested or conducted.

The proposed dosing for Vogelxo is 50 mg testosterone (a single application of one 5-gram gel tube, one 5-gram gel packet, or four metered dose pump actuations [12.5 mg per actuation]) applied once daily to clean, drug intact skin of shoulders and/or upper arms. The daily dose may be increased to 100 mg testosterone (two 5-gram tubes/packets or eight pump actuations), if indicated. Labeling will instruct the use of tube/packet separately from metered dose pump.

The clinical reviewer (Martin Kaufman, DPM, MBA) and CDTL (Suresh Kaul, MD, MPH) concluded that bioequivalence between Vogelxo and Testim has been demonstrated to support the conclusion that Vogelxo is effective as testosterone replacement therapy in the intended population. A statistical review was not necessary for this application.

Efficacy summary: From an efficacy standpoint, the demonstration of bioequivalence between Vogelxo and Testim, together with their known pharmaceutical equivalence, supports a regulatory conclusion of therapeutic equivalence.

8. Safety

The general safety of Vogelxo is supported by a demonstration of bioequivalence to Testim. The overall adverse events reported in the 5 studies conducted with Vogelxo did not raise any new concerns from the known safety profile of testosterone gel products. No deaths or drug-related non-fatal serious adverse events were reported in the development program of Vogelxo.

Formulation-specific safety of Vogelxo was assessed in the skin transference, hand washing, and skin irritation-sensitization studies. Details discussions of the skin transference and hand washing studies are found in Section 5 Clinical Pharmacology/Biopharmaceutics. The following section discusses only the skin irritation-sensitization study.

Skin Sensitization and Irritation Study: This was a single-center, within-subject randomized, double-blind study in 255 healthy adult male subjects to evaluate the cumulative irritation and sensitization produced by Vogelxo compared with Testim. Each subject received all 4 test materials (Vogelxo, Testim, positive irritant, low irritant). The study evaluated skin irritation response during the 21-day induction phase using the Berger/Bowman Skin Irritation Scale. The induction phase was followed by a 2-week no-drug rest phase, after which the

subjects were challenged (dosed) and evaluated for sensitization. Subjects with reactions suggestive of sensitization were rechallenged 3 – 4 weeks after resolution of the original reactions. The actual irritation/sensitization score was a combination of a numerical and letter score. Letter scores were converted into numerical equivalents. A converted score was the sum of the numerical score and the numerical equivalent of the letter score. Assay sensitivity was established with the observation of expected skin reactions with a positive irritant control and a low irritant control.

Skin irritation: The total numbers of converted irritation evaluation scores received during the induction phase of the study are summarized by treatment in Table 4.

Table 4: Converted Irritation Evaluation Scores by Treatment (Intent to Treat)

Treatment	Scores, n(%)				
	0	1	2	≥3	Total Sites Scored
Vogelxo	2642 (49)	2563 (48)	129 (2)	21 (<1)	5355
Testim	1658 (31)	3342 (62)	302 (6)	53 (1)	5355
Positive irritant*	363 (7)	1003 (19)	3627 (68)	362 (7)	5355
Low irritant*	3310 (62)	1915 (36)	100 (2)	30 (1)	5355

*Positive Irritant Control (0.05% sodium lauryl sulfate); Low Irritant Control (0.9% aqueous sodium chloride)
Source: Primary clinical review (8/12/13), adapted from Table 21

The irritation scores for the test articles were summed across the 21 days of the induction phase to provide a cumulative converted irritation score for each subject and for each test article. Descriptive statistics included the mean values for the test (Vogelxo, μ_T) and reference (Testim, μ_R) products. The statistical plan prespecified that if the upper bound of a one-sided 95% confidence interval (CI) for the difference between the mean values of the test (Vogelxo, μ_T) and 1.25 times the reference (Testim, μ_R) was less than or equal to zero (i.e. $\mu_T - 1.25\ \mu_R \leq 0$), Vogelxo would be deemed non-inferior in irritation to Testim. The upper bound of one-sided 95% CI for the difference between the mean converted cumulative irritation scores of Vogelxo and Testim was -7.9; Vogelxo was non-inferior to Testim in skin irritation.

Skin sensitization: In the challenge phase, any subject with a converted score ≥ 2 at 48 hours post-patch removal was considered to be potentially sensitized; these subjects were to be re-challenged 3 to 4 weeks after the conclusion of the challenge phase to confirm the sensitization reaction. The total numbers of converted sensitization evaluation scores received during the challenge phase of the study are summarized in Table 5.

Table 5: Converted Sensitization Evaluation Scores by Treatment (Per Protocol Population)

Treatment	Scores, n(%)					
	0	0.5	1	2	3	Total Sites Scored
Vogelxo	587 (64)	298 (33)	22 (2)	2 (<1)	7 (1)	916
Testim	557 (61)	317 (35)	31 (3)	7 (1)	4 (<1)	916
Positive Irritant*	554 (61)	339 (37)	23 (3)	0	0	916
Low Irritant*	649 (71)	255 (25)	12 (1)	0	0	916

*Positive Irritant Control (0.05% sodium lauryl sulfate; Low Irritant Control (0.9% aqueous sodium chloride)
Source: Primary clinical review (8/12/13), adapted from Table 24

In the per protocol population of 229 subjects, three subjects (045, 079, 014) had converted score of ≥ 2 at 48 hours post removal at the Testim and Vogelxo test sites, suggesting skin sensitization to both products. Two of the 3 subjects (045, 079) had positive re-challenge to both Testim and Vogelxo; subject 114 was not eligible as a result of being enrolled in another study by the time the re-challenge was to be administered.

In the review dated August 12, 2013, the clinical reviewer (Martin Kaufman, DPM, MBA) concluded that Vogelxo appears to be reasonably safe with respect to skin irritation and sensitization potential; that hand washing was effective in removing residual testosterone after application of Vogelxo; and secondary skin transference can be effectively mitigated by washing or covering the application site with clothing.

The clinical reviewer and CDTL recommended approval of this NDA based on a favorable benefit-risk balance.

Safety summary: Results from the three formulation-specific studies (interpersonal transference, hand washing, and skin irritation-sensitization) support the safety of the inactive ingredients of Vogelxo that differ from Testim. These findings and the demonstration of bioequivalence of Vogelxo to Testim provide evidence of acceptable safety for Vogelxo.

Labeling will contain information about these safety studies and strategies that have been shown to be effective in mitigating the risk of skin transference. Risk management for Vogelxo will be similar to that of other testosterone gel products, including Testim. This strategy will include labeling with a boxed warning for skin transference and a Medication Guide REMS to mitigate this risk.

9. Advisory Committee Meeting

No Advisory Committee meeting was necessary for this application. To date, the Agency has approved six testosterone gels (Androgel 1%, Androgel 1.62%, and Testim, Fortesta, Teva's testosterone gel, Perrigo's testosterone gel) and one testosterone solution (Axiron) as testosterone replacement therapy in hypogonadal men. A Pediatric Advisory Committee was convened in June 2009 to discuss the safety concern of secondary skin transference of testosterone, especially to children. Based on the Committee's feedback, all currently approved testosterone gel and solution products contain a boxed warning and a Medication

Guide under the REMS to mitigate the transference risk. The same labeling and Medication Guide REMS will apply to Vogelxo.

10. Pediatrics

The Applicant requested a full pediatric waiver. Because it does not involve a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, this application does not trigger PREA requirements.

11. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI): At the request of the Office of Clinical Pharmacology, OSI inspected the analytical portion of the pivotal BE study (P06-011). OSI concluded "although inconsistent integration in chromatogram processing is objectionable, the inspection did not identify any incidents in which integrity or accuracy of the data was compromised." The final determination was "VAI."

Office of Compliance: Compliance determined that inspections of the drug substance and drug product manufacturing and testing operations are acceptable (December 31, 2012).

Office of Surveillance and Epidemiology

- *Division of Medication Error Prevention and Analysis (DMEPA):* DMEPA found the tradename Vogelxo, and the container and carton labeling acceptable.
- *Division of Risk Management (DRISK):* DRISK found the Risk Evaluation and Mitigation Strategy (REMS) acceptable.

Controlled Substance Staff (CSS): Vogelxo will be a Schedule III controlled substance, as with other testosterone products. CSS found acceptable the labeling under Section 9 (Drug Abuse and Dependence), which was identical to the language recommended by CSS in April 2012 for the Testosterone Gel 1% under NDA 203-098.

Financial Disclosure*:* The Applicant certified that no clinical investigator participating in studies with Vogelxo had disclosable financial interest. The clinical team did not identify any concerns regarding financial disclosures for this NDA.

Litigation: The NDA holder of the reference drug Testim, Auxilium Pharmaceuticals Inc., has initiated a patent infringement suit against the Applicant in the US District Court for the District of Delaware (Auxilium Pharmaceuticals Inc. et al v. Upsher-Smith Laboratories Inc. Docket#: 13-CV-148). Therefore, final approval cannot be granted at this time.

Comment: *The ongoing infringement suit is the only unresolved regulatory issue at this time.*

12. Labeling

Labeling negotiations are completed. Labeling for Vogelxo is now consistent with that of Testim and with other previously approved testosterone gel products with respect to secondary transfer potential, including a boxed warning and Medication Guide. (b) (4) The Office of Prescription Drug Promotion (OPDP) recommended revisions the prescribing information, and OPDP and the Division of Medical Policy Programs provided revisions to the Medication Guide. These recommendations were considered and incorporated into the approved labeling. The final labeling was acceptable to the Study Endpoints and Label Development Team, after minor formatting revisions.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

I agree with the CDTL and the review teams that Vogelxo should be approved as testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

Because of ongoing patent infringement litigation against Vogelxo, however, this NDA will receive a ***tentative approval*** at this time. Final approval is contingent upon the final determination by the US District Court or expiry of the affected patents, and the assurance that there have been no changes to the conditions at the time of tentative approval that could impact final approval.

- **Risk Benefit Assessment**

Vogelxo is pharmaceutically equivalent to Testim in testosterone content and has been shown to be bioequivalent to the reference drug Testim. Therefore, therapeutic equivalence, and general safety, between Vogelxo and Testim has been established. Formulation-specific safety issues were adequately assessed in the studies of skin transference, hand washing, and comparative skin irritation-sensitization with Testim. Findings from the skin transference and hand washing studies show that specific actions effectively mitigated the risk of secondary transfer of testosterone, and these actions will be conveyed in labeling. The skin irritation and sensitization potential of Vogelxo was comparable to that of Testim. Overall, I believe that the benefit of Vogelxo outweighs its risks in the intended population.

- **Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies**

At the time of final NDA approval, a Medication Guide REMS will be required to mitigate the risk of secondary testosterone skin transference to others, especially women and children. This requirement is a class REMS for all currently approved testosterone gel or solution products.

- **Recommendation for other Postmarketing Requirements and Commitments:**

None.

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/s/

CHRISTINE P NGUYEN
06/04/2014