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APPLICATION NUMBER:

204399Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA 204-399
Supporting document/s: EDR:<\\CDSESUB1\EVSPROD\NDA204399\204399.enx>
Applicant's letter date: December 4, 2013
CDER stamp date: December 5, 2013
Product: Testosterone gel 1% (Volgelxo®)
Indication: Testosterone replacement in hypogonadal men
Applicant: Upsher-Smith Laboratories, Inc.
Review Division: DBRUP
Reviewer /Supervisor: Lynnda L. Reid, Ph.D.
Division Director: Hylton Joffe, M.D.
Project Manager: Jeannie Roule

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204399 are owned by Upsher-Smith Laboratories, Inc. or are data for which Upsher-Smith Laboratories, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 204399 that Upsher-Smith Laboratories, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204399.

1 Executive Summary

1.1 Introduction

This new drug application provides for the use of testosterone 1% gel (Vogelxo®) for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. NDA 204-399 was submitted as a 505(b)(2) NDA application on October 18, 2012, with reliance on the FDA's previous findings of safety and efficacy for Testim® (NDA 21-454). The original nonclinical review was performed by Dr. Jeffrey Bray (Filed 4/10/13). Tentative Approval was granted on August 16, 2013, pending patent expiration for the referenced listed drug.

The Sponsor resubmitted the NDA on December 5, 2013.

1.2 Brief Discussion of Nonclinical Findings

This testosterone gel has a different formulation than other FDA-approved testosterone gels, but otherwise has no unique benefits or risks. No new nonclinical studies were submitted.

1.3 Recommendations

1.3.1 Approvability

Nonclinical data support **Approval** of testosterone gel 1% for the treatment of male hypogonadism.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Reliance on the nonclinical sections of the Testim® label are appropriate. The final label submitted on May 27, 2014, is acceptable.

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/s/

LYNNDA L REID
05/28/2014

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
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PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: NDA 204399
Supporting document/s: EDR:<\\CDSESUB1\EVSPROD\NDA204399\204399.enx>
Applicant's letter date: October 17, 2012
CDER stamp date: October 18, 2012
Product: Testosterone gel 1%
Indication: Testosterone replacement in hypogonadal men
Applicant: Upsher-Smith Laboratories, Inc.
Review Division: DRUP
Reviewer: Jeffrey D. Bray, Ph.D.
Supervisor/Team Leader: Lynnda L. Reid, Ph.D.
Division Director: Hylton Joffe, M.D.
Project Manager: Jeannie Roule

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1 Executive Summary

1.1 Introduction

This application is for a testosterone gel 1% indicated for hypogonadal men. The applicant submitted a 505(b)(2) NDA application with reliance on the FDA's previous findings of safety and efficacy for Testim® (NDA 21-454). This testosterone gel has a different formulation than other FDA-approved testosterone gels, but otherwise has no unique benefits or risks.

1.2 Brief Discussion of Nonclinical Findings

The applicant submitted no new nonclinical information, and is relying on the FDA findings of safety and efficacy for Testim®, testosterone gel 1% (NDA 21-454) and published studies on testosterone for Approval. Testosterone is the predominant male sex steroid produced by the testes and is responsible for adult male sexual characteristics. The overall toxicological profile of testosterone is well established. Nonclinical toxicities are not relevant for Approval due to the preponderance of clinical data for testosterone that supersedes any nonclinical findings. Specifically, there was no significant application site toxicities observed. A scientific rationale for the reliance on Testim® supports the nonclinical sections of the Labeling. While the formulation is different from other FDA-approved testosterone gel products, the components are at or below the levels in other FDA-approved products.

1.3 Recommendations

1.3.1 Approvability

Nonclinical data support **Approval** of testosterone gel 1% for testosterone replacement in hypogonadal men.

1.3.2 Additional Non Clinical Recommendations

none

1.3.3 Labeling

Class labeling is appropriate. No significant nonclinical labeling issues were identified nor are significant changes required.

2 Drug Information

2.1 Drug

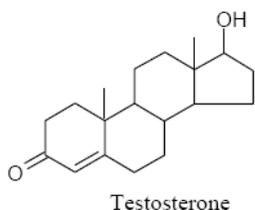
CAS Registry Number: 5949-44-0

Generic Name: testosterone

Chemical Name: (17 β)-17-hydroxyandrost-4-en-3-one

Molecular Formula/Molecular Weight: $C_{19}H_{28}O_2/288.42$

Structure or Biochemical Description



Pharmacologic Class: androgen

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 76654	(Upsher Smith, 1% testosterone gel)
NDA 21-105	(Solvay, AndroGel® 1% testosterone gel)
NDA 22-309	(Abbott Labs, AndroGel® 1.62% testosterone gel)
NDA 21-454	(Auxillium, Testim® 1% testosterone gel)
NDA 22-504	(Acrux, Axiron® 1% testosterone solution)
NDA 202763	(Teva, 1% testosterone gel)
NDA 203098	(Perrigo Israel, 1% testosterone gel)
DMF (b) (4)	((b) (4), testosterone)

2.3 Drug Formulation

This testosterone gel 1% product is a 5 g sachet or tube of gel that contains 50 mg of testosterone. This can be titrated up to a maximum of 10 g if the target serum testosterone is not achieved. Also available is a metered dose pump containing 75 g of gel that can dispense 60 doses with each actuation delivering 1.25 g of gel (12.5 mg testosterone) so that 4 actuations equal one sachet.

Table 1 Composition of Testosterone 1% Gel Product at Maximum Dosage of 10 g/day

Ingredient	Function	Amount		Maximal Amount in Approved Products in IID	
		mg	% w/w		
Tesosterone	API	100	1		
Ethyl alcohol	[REDACTED]			(b) (4)	
Glycerin					
Diisopropyl adipate					
Methyl laurate					
Oleyl Alcohol					
Carbomer Homopolymer, Type (b) (4)					
Carbomer Copolymer, Type (b) (4)					
Propylene glycol					
Polyethylene glycol (b) (4)					
Purified water					
Tromethamine					
TOTAL		--	10,000	100	--

IID, Inactive Ingredient Database

Review Note: A previous ANDA filing was rejected [REDACTED] (b) (4). It was communicated to the sponsor in meeting minutes (December 7, 2008) that no further toxicology testing was necessary. [REDACTED] (b) (4).

2.4 Comments on Novel Excipients

none

2.5 Comments on Impurities/Degradants of Concern

The known potential degradation products are [REDACTED] (b) (4). The first 3 are [REDACTED] (b) (4). These are specified at NMT (b) (4) % each, and total impurities are NMT (b) (4) %. These specifications are within range of other testosterone products.

2.6 Proposed Clinical Population and Dosing Regimen

Once daily transdermal gel for hypogonadal men

2.7 Regulatory Background

Originally the sponsor filed an ANDA, but was blocked by a citizen's petition that resulted in the necessity for clinical trials for transdermal gels that used novel excipients in the formulation. The sponsor met with DRUP and OGD on November 8, 2007, to discuss a 505(b)(2) submission (b) (4)

The sponsor again met with DRUP and OGD on September 9, 2009, to discuss a metered dose form of the product. At this meeting, it was agreed that the sponsor would conduct the two Phase 1 hand washing and transfer studies.

3 Studies Submitted

No nonclinical studies were submitted; the sponsor is relying on previous FDA findings of safety and efficacy to support the nonclinical section of the NDA.

11 Integrated Summary and Safety Evaluation

No nonclinical toxicity testing of this drug product was performed. The overall toxicological profile of testosterone products is well established and both animals and humans exhibit similar toxicities. There are extensive nonclinical and clinical data with testosterone products including transdermal applications. Since human clinical exposure of the test article was similar to Testim® (reference drug), the main safety concern was related to application site irritation. The human irritation and sensitization study, and previous evaluation of the drug product components support the argument that nonclinical studies are not necessary.

12 Appendix/Attachments

Dr. Eric Andreasen, Ph.D. performed a risk assessment of the unqualified excipients that was never formally entered into DARRTS. It is enclosed herein with his permission.

Sponsor: Upsher-Smith Laboratories, Inc.
PreIND 76,654
Testosterone Gel 1% for treatment of hypogonadal men
Meetings: Pre-IND 76,654 (Type B) Meeting
Scheduled for November 8, 2007 at 10 AM
Internal meeting scheduled for October 31, 2007 at 10 AM
RE: Questions pertaining to safety of excipients

Introduction

The Sponsor Upsher-Smith Laboratories, Inc. (USL) has submitted a 505(b)(2) NDA for a 1% testosterone gel product for treatment of hypogonadal men. They were precluded from filing this product under an ANDA (b) (4)

Extensive toxicological summaries were submitted by the Sponsor for each of these chemicals. The Sponsor believes that their toxicological assessment and levels of excipients in other topically applied products would assure the safety of each of these excipients at the maximal intended dose of 10g of gel.

Composition of Upsher-Smith's 1% Testosterone Product and Maximal Dosage 10 g/day					
Ingredient	Upsher-Smith Formulation		Testim®	AndroGel®	Maximal Amount in Approved Product (IID)
Testosterone	1.0 %	100 mg	1.0 %	1.0 %	
Ethyl Alcohol					(b) (4)
Diisopropyl Adipate					
Methyl Laurate					
Oleyl Alcohol					
(b) (4) (Carbomer (b) (4) Copolymer, Typ (b) (4)					
(b) (4) (Carbomer (b) (4) Homopolymer Type (b) (4)					
Polyethylene Glycol (b) (4)					
Glycerin					
Propylene Glycol					
Tromethamine					
Table adapted from the Sponsor. IID- Inactive Ingredient Database, a database with the listed maximal level of excipients in FDA approved products. X = unknown concentration. Ingredients are listed as a percentage of total dose and the quantity in a 10 g gel dosage. (b) (4)					

Summary Safety Assessments

Ethyl Alcohol (Ethanol)

The toxicity of ethanol has been extensively studied ((b) (4) summary; (1)). Acute ethanol exposure has been linked with CNS depression, cardiotoxicity, hypothermia, hypoglycemia, acidosis, electrolyte imbalances, hemorrhaging of the GI and fetal intoxication. Chronic exposures have been associated with physical dependency, CNS affects, cardiomyopathy, hepatotoxicity, GI hemorrhaging, pancreatitis and cancer.

The maximal concentration from the USL product is (b) (4)

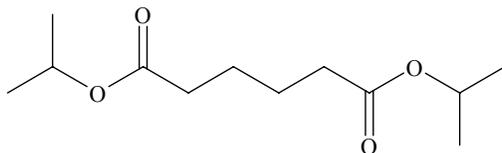
A consensus on a no affect level for oral exposure to ethanol has not been reached. However comprehensive reviews of the literature suggest that potential beneficial health affects are out weighed by increased adverse health affects at an oral dose of around 20 g/day (2;3). The maximal possible dose of ethanol (b) (4) in the gel product would equate with a dose of (b) (4) of ethanol in a 60 kg human assuming complete absorption. This is well below the oral dose of 20 g/day (0.33 g/kg) that was estimated to elevate the potential for low-risk harm in humans (2;3). The resulting **safety margin would be (b) (4)** times the maximal dose of the testosterone gel product. **However the safety margin is undoubtedly greater** since dermal absorption is not as efficient as oral absorption. Ethanol was not detected in the blood of humans sprayed with 9.7 g of with 70% ethanol product within one hour of exposure (4). Additionally *in vitro* absorption studies with uncovered pig and guinea pig skins found that less than 3% of the applied ethanol was absorbed within 19 hrs exposure (4;5).

Since absorption is expected to be low, the main concern is for application site toxicity. However this may not be a major concern. In the Sponsor's preliminary clinical study, USL's 1% T gel was well tolerated and no serious adverse events were reported following a single maximal dose (10g of gel) (study P06-011). The most frequent adverse events considered possibly or probably related to drug after a single application of the maximal dose (10g of gel) were application site erythema (13.6%) and application site reaction (6.2%). The incidences of these findings were just slightly more frequent that in the Testim dosed population (12.3% and 2.5% respectively).

The concentration of ethyl alcohol in the Sponsor's product is not likely to cause adverse affects other than mild application site erythema and site reactions. These affects can be monitored for and the application sites could be varied to avoid repeated daily irritation. Additionally the concentration proposed is below that used in topical gels.

Diisopropyl Adipate

Diisopropyl adipate (DIPA), a diester of isopropyl alcohol, (b) (4). The metabolism of DIPA is unknown but it is suspected to be broken down into isopropanol and adipic acid by esterases.



There is very little toxicity data regarding DIPA. DIAP is not acutely toxic with an estimated oral LD₅₀ in rats of > 3000 mg/kg (6). Repeat dose studies with DIAP have not been conducted. It is not know whether DIPA is genotoxic, carcinogenic, or has the potential for reproductive or developmental toxicity. However the Sponsor provided toxicology information for structurally similar chemicals and the anticipated metabolites isopropanol and adipic acid and concluded that there is little concern for these toxicities. Although doctyl adipate, a structurally similar compound, was not found to be mutagenic or carcinogenic in rats it was carcinogenic in mice due to slight increased hepatocellular carcinomas in females and perhaps in males causing hepatocellular adenomas (7). The Sponsor postulated that the carcinogenic outcomes were due to proliferation of peroxisomes mediated by ethylhexanol a known peroxisome proliferator and

moiety of doctyl adipate. Since DIAP does not contain this moiety, the Sponsor surmised that carcinogenic outcomes of doctyl adipate are not relevant.

A review was published by The Cosmetic Ingredient Review which included an abundance of dermal toxicity data in animals and humans (6). Undiluted DIPA was found to be minimally to mildly irritating in three dermal irritation studies in rabbits (6). When diluted to 5 or 21% DIPA was also minimally irritating in rabbits (6). In humans DIAP was not irritating in a 24 hr patch test but was moderately irritating in a 21 day irritation assay (6). In another clinical study a 20% formulation of DIPA was minimally to mildly irritating did not cause skin sensitization or photosensitization (6).

Skin Irritation Studies in Rabbits with DIPA		
N	Dose of DIPA	Findings
9	0.1 ml (undiluted)	Minimal erythema
9	0.1 ml (5% DIPA)	Minimal erythema at 24 hrs
9	0.1 ml (20.75% DIPA)	Minimal erythema at 24 and 48 hrs
Table adapted from the Sponsor with data derived from the CIR review (6)		

The maximal DIAP exposure from USL's 1% T product is (b) (4) assuming 60 kg human and complete absorption). Since the oral toxicity of DIAP has not been extensively studied and there is little evidence of dermal toxicity, the Sponsor proposed a dose limiting NOAEL based upon most potentially toxic metabolite isopropanol. Decreased male fertility was observed in rats dosed with at 100 mg/kg of isopropanol. This is a human equivalent dose of 968 mg of isopropanol or a molar equivalent of 1855 mg of DIAP. This would result in a safety margin of 12.3 times the maximal potential dose in humans assuming complete absorption of DIAP and full metabolism to isopropanol.

References

- (1) International Agency for Research on Cancer (IARC). Alcohol drinking, summary of data reported and evaluation. Volume 44. 1-21-1998. World Health Organization, IARC.
Ref Type: Report
- (2) Australian Commonwealth Department of Health and Aged Care. Evidence regarding the level of alcohol consumption considered to be low-risk for men and women. 1999.
Ref Type: Report
- (3) Anderson P, Cremona A, Paton A, Turner C, Wallace P. The risk of alcohol. *Addiction* 1993; 88(11):1493-1508.
- (4) Pendlington RU, Whittle E, Robinson JA, Howes D. Fate of ethanol topically applied to skin. *Food Chem Toxicol* 2001; 39(2):169-174.
- (5) Gummer CL, Maibach HI. The penetration of [14C]ethanol and [14C]methanol through excised guinea-pig skin in vitro. *Food Chem Toxicol* 1986; 24(4):305-309.

- (6) The Cosmetic Ingredient Review (CIR). Final report on the safety assessment of dioctyl adipate and diisopropyl adipate. *J Am Coll Toxicol* 1984; 3(3):101-130.
- (7) National Toxicology Program (NTP). Carcinogenesis bioassay of di(2-ethylhexyl) adipate (CAS No. 103-23-1) in F344 rats and B6C3F mice (feed study). 212. 1982. Ref Type: Report

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/s/

JEFFREY D BRAY
04/10/2013

LYNNDA L REID
04/10/2013
I concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204399

**Applicant: Upsher-Smith
Laboratories, Inc.**

Stamp Date: October 18, 2012

Drug Name: testosterone gel 1% NDA Type: 505(b)2

60-Day Filing Review Date: December 17, 2012

74-Day Letter Date: December 31, 2012

Expected Date of Draft Review: February 1, 2013

PDUFA Goal date: August 18, 2013

On initial overview of the NDA application for RTF: Fileable

	Content Parameter	Yes	No	Comment
1	On its face, is the pharmacology/toxicology section of the NDA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	X		The applicant performed no nonclinical studies, but submitted a justification for the 505(b)(2) pathway relying upon the listed drug: Testim® (testosterone gel)
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?		n/a	See #1 above.
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?		n/a	See #1 above.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility, juvenile studies, acute and repeat dose adult animal studies*, animal ADME studies, safety pharmacology, etc)?	X		See #1 above.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		n/a	Clinical cumulative skin irritation and sensitization study were conducted instead.
6	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route?		n/a	See #5 above.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	Content Parameter	Yes	No	Comment
7	Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	n/a		
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	n/a		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?	X		Labeling consistent with other testosterone gels will be applied.
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)	n/a		No issues have been identified; sponsor is using excipients ≤ amounts in FDA Inactive Ingredient Database or providing a toxicology evaluation for (b)(4)
11	Has the sponsor addressed any abuse potential issues in the submission?	X		Ensure consistency among transdermal T products in labeling on potential abuse.
12	If this NDA is to support a Rx to OTC switch, have all relevant studies been submitted?	n/a		
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	X		

Any Additional Comments: none

Jeffrey Bray, Ph.D. 12/3/2012

 Reviewing Pharmacologist Date

Lynnda Reid, Ph.D. _____

 Team Leader/Supervisor Date

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/s/

JEFFREY D BRAY
12/12/2012

LYNNDA L REID
12/12/2012