

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22309Orig1s000

PHARMACOLOGY REVIEW(S)

Division of Reproductive and Urologic Products
Center for Drug Evaluation and Research

Date: April 26, 2011

From: Jeffrey Bray, Ph.D., Pharmacologist

To: NDA 22-309

Subject: Correction to Pharm/Tox Review

Pharm/Tox has detected two errors in the Review filed to DARRTS on February 1, 2011. In Section 1.1 and 1.3.1, AndroGel 1.62% is incorrectly identified as a “solution”; the correct formulation description for this product is “gel”.

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/s/

JEFFREY D BRAY
04/28/2011

LYNNDA L REID
04/28/2011

ADDENDUM

FOOD AND DRUG ADMINISTRATION

Division of Reproductive Products
Center for Drug Evaluation and Research

Date April 28, 2011

From: Roger Wiederhorn, MD, Medical Officer
Mark Hirsch, MD, Medical Team Leader

To: NDA 22-309

Subject: Final Labeling

Clinical urology has reviewed the final labelling submitted April 26, 2011,
and finds it acceptable.

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/s/

A R WIEDERHORN
04/28/2011

MARK S HIRSCH
04/28/2011
I concur.

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 22-309
Supporting document/s: <\\CDSESUB1\EVSPROD\NDA022309\022309.enx>
Applicant's letter date: October 25, 2010
CDER stamp date: October 27, 2010
Review Completion: January 31, 2011
Product: AndroGel 1.62%
Indication: Testosterone replacement in hypogonadal men
Applicant: Abbott Laboratories
Review Division: DRUP
Reviewer: Jeffrey D. Bray, Ph.D.
Supervisor: Lynnda L. Reid, Ph.D.
Division Director: Scott Monroe, M.D.
Project Manager: Jeannie Roule

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-309 are owned by Abbott Laboratories or are data for which Abbott Laboratories has obtained a written right of reference. Any information or data necessary for approval of NDA 22-309 that Abbott Laboratories 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 22-309.

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1 Executive Summary

1.1 Introduction

The sponsor has re-submitted an application for a topical testosterone 1.62% solution indicated for hypogonadal men. This testosterone solution is to be applied to both sides of the upper arms.

1.2 Brief Discussion of Nonclinical Findings

The sponsor submitted no new nonclinical information with this resubmission. Two nonclinical studies were requested and performed to support the NDA. Previously to support the original application, the sponsor conducted a dermal irritation study in rabbits and a dermal sensitization study in guinea pigs with 1.62% and 4% testosterone formulations. There was mild, dose-dependent dermal irritation in the rabbits. In guinea pigs, there was mild dermal sensitization in all groups, including the placebo gel product. The remainder of the nonclinical application relied upon published findings and nonclinical data submitted under the Sponsor's NDA 21-015 for AndroGel 1%. Testosterone is the predominant male sex steroid produced by the testes and is responsible for adult male sexual characteristics. This topical testosterone 1.62% gel is to be indicated for testosterone replacement in hypogonadal men. 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.

1.3 Recommendations

1.3.1 Approvability

Nonclinical data support Approval of AndroGel 1.62% solution for topical testosterone replacement in hypogonadal men.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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2 Drug Information

2.1 Drug

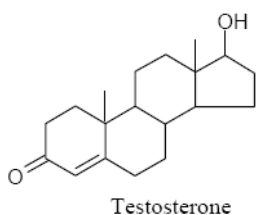
CAS Registry Number: 5949-44-0

Generic Name: testosterone

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

Molecular Formula/Molecular Weight: C₁₉H₂₈O₂/288.42

Structure or Biochemical Description



Pharmacologic Class: androgen

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

IND 50,377 (Solvay, AndroGel® 1.62% testosterone gel)

NDA 21-105 (Solvay, AndroGel® 1% testosterone gel)

NDA 21-454 (Auxillium, Testim® 1% testosterone gel)

NDA 22-504 (Acrux Pharma, 2% testosterone solution)

DMF (b) (4) (b) (4)

2.3 Drug Formulation

AndroGel 1.62% is a transparent (b) (4) gel formulation. The drug product is delivered via a metered pump that administers 20.25 mg of testosterone per actuation. The recommended starting dose is 1.25 g (1 actuation) corresponding to 20.25 mg of testosterone and the dose can be titrated up to 5 g/day or 4 actuations (81 mg testosterone).

Composition of Androgel 1.62% at Maximum Dosage of 81 mg/day

Ingredient	Function	Amount		Maximal Amount in Approved Products in IID
		mg	%w/w	
Testosterone	API	81	1.62	--
Ethyl alcohol, USP	(b) (4)	(b) (4)	(b) (4)	Yes, 92% Topical
Isopropyl myristate, NF				Yes, 10% Topical
Carbopol C980 NF				Yes, 3.5% Topical
(b) (4) NaOH, NF				Yes, 10% Topical
Purified water				Yes
TOTAL				--

IID, Inactive Ingredient Database

2.6 Proposed Clinical Population and Dosing Regimen

Hypogonadal men will self-administer Androgel 1.62% to the upper arms daily with the amount to be titrated based on achieving serum testosterone levels of 300-1000 ng/dL with a maximum of 4 pump actuations.

2.7 Regulatory Background

The sponsor opened IND 50,377 to evaluate this transdermal testosterone 1.62% product. The sponsor originally submitted NDA 22-309 as a 505(b)(2) application on February 11, 2009. The application review clock was extended 3 months to evaluate an alternative 4 body site application regimen. On March 12, 2010, the Applicant received a Complete Response Letter describing deficiencies pertaining primarily to adequate PK evaluation from 4 application sites and potential transfer of the 4 site application method.

11 Integrated Summary and Safety Evaluation

The overall toxicological profile of testosterone products is well established and both animals and humans exhibit similar toxicities. Testosterone in AndroGel is equivalent to the endogenous male sex steroid and derives its pharmacological activities through binding to the Androgen Receptor. Testosterone replacement in hypogonadal men is approved to alleviate symptoms of testosterone deficiency. There are extensive nonclinical and clinical data with testosterone products including transdermal applications; the safety profile of testosterone gels is well known. The nonclinical studies conducted for this NDA did not identify any new safety concerns associated with the 1.62% Testosterone gel. Nonclinical data support approval.

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/s/

JEFFREY D BRAY
02/01/2011

LYNNDA L REID
02/01/2011
I concur.



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: **22-309**
SERIAL NUMBER: **000**
DATE RECEIVED BY CENTER: **2/12/2009**
PRODUCT: **AndroGel® (Testosterone gel 1.62%)**
INTENDED CLINICAL POPULATION: **hypogonadal men**
SPONSOR: **Solvay Pharmaceuticals**
DOCUMENTS REVIEWED: **\\CDSESUB1\EVSPROD\NDA022309\0000\m4**
REVIEW DIVISION: **Division of Reproductive and Urologic Products**
PHARM/TOX REVIEWER: **Jeffrey Bray, Ph.D., Pharmacologist**
PHARM/TOX SUPERVISOR: **Lynnda Reid, Ph.D., Supervisory Pharmacologist**
DIVISION DIRECTOR: **Scott Monroe, M.D.**
PROJECT MANAGER: **Jeannie Roule**

Date of review submission to Division File System (DFS): August 6, 2009

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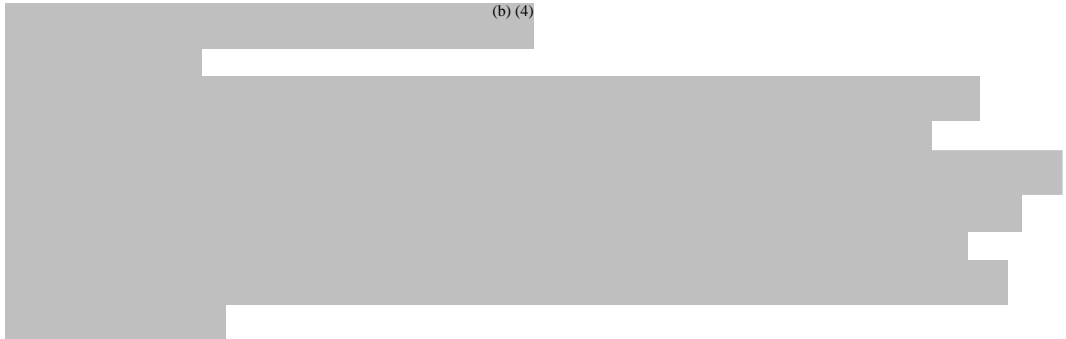
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EXECUTIVE SUMMARY

I. Recommendations

- A. Recommendation on approvability - Nonclinical data support approval.
- B. Recommendation for nonclinical studies - None.
- C. Recommendations on labeling - The main recommendation includes adding a statement to Section 13 Nonclinical Toxicology to include a reference to impact on human carcinogenicity (4, 5.1, and 5.7) and fertility (5.1 and 5.6).

(b) (4)

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II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Two nonclinical studies were requested and performed to support the NDA. The sponsor conducted a dermal irritation study in rabbits and a dermal sensitization study in guinea pigs with 1.62% and 4% testosterone formulations. There was mild, dose-dependent dermal irritation in the rabbits. In guinea pigs, there was mild dermal sensitization in all groups, including the placebo gel product.

The remainder of the nonclinical application relied upon published findings and previous NDA 21-015.

B. Pharmacologic activity

The nonclinical pharmacology of testosterone products is well established. Testosterone in AndroGel is equivalent to the endogenous male sex steroid and derives its pharmacological activities through binding to the Androgen Receptor (AR). Testosterone replacement in hypogonadal men is approved to alleviate symptoms of testosterone deficiency.

C. Nonclinical safety issues relevant to clinical use

The safety of testosterone gel is well known. The nonclinical studies conducted for this NDA did not identify any new safety concerns associated with the 1.62% Testosterone gel.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-309

Review number: 1

Sequence number/date/type of submission: 000/February 11, 2009/Original

Sponsor and/or agent: Solvay Pharmaceuticals

Manufacturer for drug substance: Solvay Pharmaceuticals, Inc.
901 Sawyer Rd
Marietta, GA 30062

Reviewer name: Jeffrey Bray, Ph.D.

Division name: Division of Reproductive and Urologic Products

HFD #: 580

Review completion date: June 11, 2009

Drug:

Trade name: AndroGel® (1.62% testosterone gel)

Generic name: testosterone gel

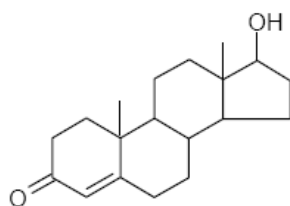
Code name: none

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

CAS registry number: 58-22-0

Molecular formula/molecular weight: C₁₉H₂₈O₂/288.42

Structure:



Testosterone

Relevant INDs/NDAs/DMFs:

NDA 21-105 (AndroGel® (1% testosterone gel))

IND 50,377 (AndroGel® (1.62% testosterone gel))

Drug class: androgen

Intended clinical population: hypogonadal men

Clinical formulation Transparent (b) (4) gel formulation for transdermal administration of testosterone gel. The drug product is supplied in a

pressure-actuated airless pump container that delivers 20.25 mg of drug substance per stroke. Each stroke delivers 6.25 g of drug product.

Ingredient	Function	% w/w	FDA Approved, Up to
Testosterone, USP	API	1.62	
Ethanol, USP	(b) (4)	(b) (4)	Yes, 92% Topical
Isopropyl myristate, NF			Yes, 10% Topical
Carbopol C980 NF			Yes, 3.5% Topical
(b) (4) NaOH, NF			Yes, 10% Topical
Purified water			Yes

Route of administration: transdermal

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Data reliance : Except as specifically identified below, all data and information discussed below and necessary for approval of NDA 22-309 are owned by Solvay Pharmaceuticals or are data for which Solvay Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 22-309 that Solvay Pharmaceuticals 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 described in the drug’s approved labeling. Any data or information described or referenced below from a previously approved application that Solvay Pharmaceuticals does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-309.

Studies reviewed within this submission:

Study Title	Study # and Volume	Conducting laboratory and location	GLP + QA
QIT00001: A primary skin irritation study in rabbits with LVTG	QIT00001	(b) (4)	Yes
QIT00002: A dermal sensitization study in guinea pigs with LVTG	QIT00002		Yes
Development of Improved Testosterone Gel(s)	PD.176.7.09R		No

2.6.2 PHARMACOLOGY

Mechanism of action:

Testosterone is the primary androgen secreted by the testes and is responsible for the development, maturation, and persistence of normal male characteristics, and the testosterone in AndroGel is equivalent to endogenous testosterone. Testosterone has been demonstrated to have a positive effect on male physical attributes, such as increased muscle mass, lean body weight, bone mineral density, sexual function, reduced anemia, and increased libido and feelings of well-being. Dihydrotestosterone is the primary active metabolite and is produced by steroid 5- α -reductase located in non-genital skin, liver, and the urogenital tract of the male and in genital skin of both sexes. Both testosterone and dihydrotestosterone derive their pharmacological activities through binding to the Androgen Receptor (AR).

Drug activity related to proposed indication: AndroGel is indicated for testosterone replacement therapy in hypogonadal men to alleviate symptoms of testosterone deficiency:

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

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None provided.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

From *in vitro* studies, the proposed 1.62% testosterone gel formulation has (b) (4) the dermal permeation on a $\mu\text{g}/\text{cm}^2$ basis compared to the marketed 1% formulation using Franz diffusion cell chambers on human cadaver skin. The potential for enhanced exposure to dermal testosterone in the clinical trials was adequately addressed by the sponsor.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None.

2.6.6 TOXICOLOGY

General toxicology: The toxicity potential for testosterone has been previously established.

Genetic toxicology: Testosterone was not mutagenic to bacteria and did not induce sperm abnormalities or micronuclei in mice treated *in vivo* (IARC supplement 6 (pp 506-507) and 7 (pp 96-97)). It was reported that testosterone possesses a weak transforming effect in Syrian Hamster embryo (SHE) cells *in vitro* (Lasne et al 1990; Tsutsui et al, 1995).

Carcinogenicity: The carcinogenicity potential for testosterone has been previously established. From the Label of AndroGel® (testosterone gel) 1%: *Testosterone has been tested by subcutaneous injection and implantation in mice and rats. In mice, the implant induced cervical-uterine tumors, which metastasized in some cases. There is suggestive evidence that injection of testosterone into some strains of female mice increases their susceptibility to hepatoma. Testosterone is also known to increase the number of tumors and decrease the degree of differentiation of chemically induced carcinomas of the liver in rat.*

Reproductive toxicology: The reproductive and developmental risk potential for testosterone has been previously established. From the Label of AndroGel® (testosterone gel) 1%: Pregnancy Category X: AndroGel is contraindicated during pregnancy or in women who may become pregnant. It is teratogenic and may cause fetal harm [see Contraindications (4)]. Exposure of a female fetus to androgens may result in varying degrees of virilization. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Local Tolerance: AndroGel caused mild dose-dependent irritation 24 h after dermal application to rabbits. (See Appendix 1)

Special Toxicology: Possible sensitization was observed following dermal application of AndroGel to guinea pigs. (See Appendix 2)

Discussion and Conclusions

The overall toxicological profile of testosterone is well established. There are extensive nonclinical and clinical data with testosterone products including transdermal applications. The sponsor was requested to perform local tolerance studies to demonstrate that the increased testosterone in the product would not increase dermal irritation and sensitivity. AndroGel caused dose-dependent irritation 24 h after dermal application to rabbits. The irritation was not severe and conditions resolved in all animals within 14 days. Possible sensitization was observed following dermal application of AndroGel to guinea pigs that occurred in the challenge, but not the naïve

control animals. This response appears to be due to the vehicle gel system used in the test article formulations as the sensitization response was similar in the placebo and both test article formulations. Sponsor cites literature (Ritz and Buehler, 1980) that suggests irritation is due to ethanol in formulation since irritation was observed with placebo.

2.6.7 TOXICOLOGY TABULATED SUMMARY

None submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Based on extensive clinical experience with transdermal testosterone products, nonclinical studies, and a review of the published literature, Pharmacology recommends approval of AndroGel® (testosterone gel) 1.62% for testosterone replacement in hypogonadal men.

Unresolved toxicology issues (if any): There are no unresolved issues at this time.

Recommendations: None at this time.

Suggested labeling: See Executive Summary, section I. (C).

References:

Lasne C, Lu YP, Orfila L, Ventura L, Chouroulinkov I. Study of various transforming effects of the anabolic agents trenbolone and testosterone on Syrian hamster embryo cells. *Carcinogenesis*. 1990; 11:541-7.

Ritz HL and E.V. Buehler EV. Planning, Conduct and Interpretation of Guinea Pig Sensitization Patch Test in *Current Concepts in Cutaneous Toxicity*, pg. 25-40, 1980.

Tsutsui T, Komine A, Huff J, Barrett JC. Effects of testosterone, testosterone propionate, 17 beta-trenbolone and progesterone on cell transformation and mutagenesis in Syrian hamster embryo cells. *Carcinogenesis*. 1995; 16:1329-33.

APPENDIX/ATTACHMENTS**Appendix 1: Dermal Irritation in Rabbits**

Study reviewed by Dr. Leslie McKinney (4-26-2006).

Study no. QIT00001: A primary skin irritation study in rabbits with LVTG

Volume #, and page #: CDSESUB1\EVSPROD\NDA022309\0000\m4\42-stud-rep\423-tox\4236-loc-tol\tx-176-0-01cro\ tx-176-0-01cro.pdf

Conducting laboratory and location: (b) (4)

Date of study initiation: January 4, 2006

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, and % purity: Formulation is identical to clinical drug product.

Placebo Testosterone Gel (LVTG-1P), Lot #1652-30-3

Testosterone Gel 4% (LVTG-3A), Lot # 1652-38-3, 99.9%

Testosterone Gel 1.62% (LVTG-1A), Lot #1652-34-3, 99.7%

Methods

Doses: 0, 4%, 1.62% gel

Species/strain: New Zealand White rabbits

Number/sex/group or time point: 6/M/placebo and 4%/ and 6/M/1.62%

Route, formulation, volume: Transdermal, gel, 0.5 mL

Procedure: The day before dosing, fur was removed from dorsal area of the trunk using animal clippers with care not to abrade skin. On Day 0, 0.5 mL of the test material was applied to 2 test sites (1 inch x 1 inch). Test sites were delineated with an indelible marker and one of the test sites was abraded using the back of a No. 40 clipper blade. The abrasions were sufficiently deep to penetrate the stratum corneum, but enough not to cause bleeding. Test material was applied and covered under a gauze patch for 24 h, then removed. The pads were covered and secured to prevent removal and ingestion by the animal. Animals were collared until removal of pad on Day 3 and euthanized after the final scoring interval.

Satellite groups used for toxicokinetics or recovery: none

Age: 11 weeks

Weight: 2.3-2.6 kg

Observation and Times:

Mortality: 2x daily

Clinical signs: 2x daily

Body weights: prior to dosing

Skin: Dermal responses were scored at 1, 24, 48, and 72 h after removal of the patch and up to 14 days after patch removal.

Histopathology: none

Analysis of data: The 1- and 48-hour erythema and edema scores for both the intact and abraded test sites for all animals were added and the total divided by the number of test sites x 2. The calculated Primary Irritation Index (PII) was classified according to according to the Macroscopic Dermal Grading System (based on Draize, 1959): 0-4.99 = nonirritant; ≥ 5 = irritant. (See Appendix 2 of Study Report for details.)

Results:

Placebo gel- Intact skin: Well-defined erythema (4/6) and slight edema (3/6) at 1 h. Test site dermal irritation completely resolved in 1/6 sites by 48 h, 1/6 by 72 h, 1/6 by Day 7, and the remaining site by Day 14. Blanching (1/6) and desquamation (6/6) was also noted.

Placebo gel- Abraded skin: Very slight to well-defined erythema (4/6) and very slight edema (2/6) at 1 h. Test site dermal irritation completely resolved in 1/6 sites by 24 h, 1/6 sites by 48 h, 1/6 by 72 h, and the remaining site by Day 10. Blanching (1/6) and desquamation (6/6) was also noted.

Testosterone gel 1.62% - Intact skin: Well-defined erythema (6/6) and slight edema (4/6) at 1 hr. Test site dermal irritation completely resolved in 2/6 sites by 72 h, 1/6 by 72 h, 3/6 by Day 7, and the remaining site by Day 10. Blanching (1/6) and desquamation (6/6) was also noted.

Testosterone gel 1.62% -Abraded skin: Well-defined erythema (6/6) and slight edema (4/6) at 1 hr. Test site dermal irritation completely resolved in 2/6 sites by 72 h, 3/6 by Day 7, and the remaining site by Day 10. Desquamation (6/6) was also noted.

Testosterone gel 4% - Intact skin: Well-defined erythema (6/6) and slight edema (6/6) at 1 hr. Dermal lesions (eschar) noted at Days 7 and 10, with irritation completely resolved for 5/6 test sites by Day 7 and for the remaining site by Day 14. Blanching (1/6) and desquamation (6/6) was also noted.

Testosterone gel 4% - Abraded skin: Well-defined erythema (6/6) and slight edema (6/6) at 1 hr. Test site dermal irritation completely resolved in 2/6 sites by 48 h, 1/6 by 72 h, 1/6 by Day 7, and the remaining sites by Day 14. Blanching (2/6) and desquamation (6/6) was also noted.

The blanching was focal and progressed to desquamation.

Rabbit Dermal Irritation Rating of Testosterone Gel Formulations.

Test Material	P.I.I.	Sponsor's Irritation Rating
Placebo gel	1.13	Nonirritant
Testosterone gel 1.62%	1.92	Nonirritant
Testosterone gel 4%	2.21	Nonirritant

P.I.I.: primary irritation index (total score)

Modified Sponsor Table

Appendix 2: Dermal Sensitization in Guinea Pigs

Study reviewed by Dr. Leslie McKinney (4-26-2006).

Study no. QIT00002 : A dermal sensitization study in guinea pigs with LVTG

Volume #, and page #: CDSESUB1\EVSPROD\NDA022309\0000\m4\42-stud-rep\423-tox\4236-loc-tol\tx-176-0-02cro\ tx-176-0-02cro.pdf

Conducting laboratory and location: (b) (4)

Date of study initiation: January 6, 2006

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, and % purity: Formulation is identical to clinical drug product.

Placebo Testosterone Gel (LVTG-1P), Lot #1652-30-4

Testosterone Gel 4% (LVTG-3A), Lot # 1652-38-4, 99.9%

Testosterone Gel 1.62% (LVTG-1A), Lot #1652-34-4, 99.9%

Methods

Doses: 0, 4%, 1.62% gel

Species/strain: Hartley-derived albino guinea pigs

Number/sex/group or time point: 5M&5F/group

Route, formulation, volume: Transdermal, gel, 0.3 mL

Procedure: The day before treatment, fur was removed from dorsal area of the trunk using animal clippers with care not to abrade skin.

Induction: On Day 0, 0.3 mL of placebo, positive control (1-chloro-2,4-dinitrobenzene; DNCB), or test material placed on a 25 mm Hilltop chamber backed by adhesive tape and quickly applied to the clipped surface of the animal which was then secured with elastic wrap and adhesive tape to prevent removal. The test material was applied 3X/week for 3 weeks (9 total exposures). Animals were reclipped the day before an application to clearly visualize the sites for grading.

Challenge: Based on the results for the Induction study, the 4% test article gel was used at 75% strength due to unexpected primary irritation that was deemed inappropriate for the challenge. Following a 2-week recovery period, a challenge test was performed by applying test articles as follows:

Sponsor-provided Table Describing the Challenge Applications

Group	Material	Concentration (%)	Test Site No.	No. of Animals	
				Male	Female
Test 1	LVTG-3A	75 ^a	2	5	5
Test 2	LVTG-1A	100 ^b	2	5	5
Placebo	LVTG-1P	100 ^b	2	5	5
Common Challenge Control	LVTG-3A	75 ^a	2	4	5
	LVTG-1A	100 ^b	6		
	LVTG-1P	100 ^b	4		
DNCB Test	DNCB	0.1% ^c	2	5	5
		0.05% ^c	4		
DNCB Challenge		0.1% ^c	2	5	5
		0.05% ^c	4		

^aThe vehicle utilized was deionized water.

^bAs received.

^cThe vehicle utilized was acetone/ethanol.

Re-challenge: Based on the results for the Challenge study, the 4% test article gel was increased to 85% strength lack of observed dermal irritation response. The 75% was also retested to bridge the studies. Following a 1-week recovery period, a re-challenge test was performed by applying test articles as follows:

Sponsor-provided Table Describing the Re-Challenge Applications

Group	Material	Concentration (%)	Test Site No.	No. of Animals	
				Male	Female
Test 1	LVTG-3A	85 ^a	6	5	5
	LVTG-3A	75 ^a	4		
Test 2	LVTG-1A	100 ^b	4	5	5
Placebo	LVTG-1P	100 ^b	4	5	5
Rechallenge Control	LVTG-3A	85 ^a	1	5	5
		75 ^a	3		
	LVTG-1A	100 ^b	2		
	LVTG-1P	100 ^b	4		

^aThe vehicle utilized was deionized water.

^bAs received.

Test article was removed 6 hours after chamber application. The binding materials were removed and the area was wiped with gauze moistened with deionized water. The test sites were graded for dermal irritation at approximately 24 h and 48 h following the chamber applications.

Satellite groups used for toxicokinetics or recovery: none

Age: 6-7 weeks

Weight: M: 339-456 g, F: 322-433 g

Observation and Times:

Clinical signs: 2x daily

Body weights: The day prior to induction, challenge, and re-challenge applications.

Skin: Dermal responses were scored at 24 h and 48 h after removal of the chamber.

Analysis of data: Sensitization potential is based on the dermal responses observed on the test and control animals at challenge. Dermal scores of ≥ 1 in the test animals and scores of 0 to \pm in the controls are considered indicative of sensitization. Dermal scores of 1 in both test and control animals are generally considered equivocal unless a higher dermal response (≥ 2) is observed in the test animals. Group mean dermal scores were calculated for challenge.

Results:

Mortality: A Challenge control male was euthanized moribund on day 6 for humane reasons with impaired mobility and left forelimb cool to touch. Gross necropsy included pale spleen and all lung lobes mottled dark red/red. Findings were not considered test article related.

Clinical signs: Nothing relevant

Body weights: No test article-related change

Skin: Dermal Sensitization in Guinea Pigs Treated with Testosterone Gel Products

Treatment	# with grades ≥ 1 (total #for M/F, with 24 & 48 h data combined)	
	Challenge test group	Challenge control group
75% T Gel-4%	0/10	0/9
100% T Gel-1.62%	1/10	0/9
	Placebo test group	Challenge control group
100% Placebo	2/10	0/9
	Re-challenge test group	Re-challenge control group
75% T Gel-4%	2/10	0/10
85% T Gel-4%	4/10	0/10
100% T Gel 1.62%	1/10	0/10
	Placebo test group	Re-challenge control group
100% Placebo	0/10	0/10

Positive Control		
	DNCB test group	DNCB control
0.05% DNCB	10/10	0/10
0.1% DNCB	10/10	0/10

Modification of Dr. McKinney's table
Data excerpted from sponsor's tables

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22309	----- ORIG 1	----- UNIMED PHARMS	----- ANDROGEL

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/s/

JEFFREY D BRAY
08/06/2009

LYNNDA L REID
08/07/2009
I concur. Nonclinical data support approval.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-309

**Applicant: Solvay
Pharmaceuticals**

Stamp Date: February 12, 2009

**Drug Name: AndroGel 1.62% NDA Type: 505(b)2
(testosterone gel)**

45-Day Filing Review Date: March 31, 2009

74-Day Letter Date: April 27, 2009

Expected Date of Draft Review: June 20, 2009

PDUFA Goal date: December 12, 2009

On initial overview of the NDA application for RTF:

	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		
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	X		
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	X		
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		Two nonclinical studies were requested and performed to support the NDA. The sponsor conducted a dermal irritation study in rabbits and a dermal sensitization study in guinea pigs with 1.62% and 4% T formulations. The remainder of the nonclinical application relied upon published findings and previous NDA 21-015.
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).	X		The formulation used in the nonclinical studies was similar to the marketed formulation.
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?	X		

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?	X		
8	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?	X		see Comments
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	X		Format and class labeling alterations may be needed.
10	If there are any impurity – etc. issues, have these been addressed? (New toxicity studies may not be needed.)	X		No issues have been identified.
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?		NA	
13	From a pharmacology/toxicology perspective, is the NDA fileable? If ``no`` please state below why it is not.	X		

Any Additional Comments: AndroGel caused dose-dependent irritation 24 h after dermal application to rabbits. The irritation was not severe and resolved in all animals and conditions within 14 days. Sensitization was observed following dermal application of AndroGel to guinea pigs. Sponsor cites literature that suggests irritation is due to ethanol in formulation since irritation was observed with placebo.

Jeffrey Bray, Ph.D.

3/30/2009

Reviewing Pharmacologist

Date

Team Leader/Supervisor

Date

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this page is the manifestation of the electronic signature.**

/s/

Jeffrey Bray
4/21/2009 03:18:35 PM
PROJECT MANAGER FOR QUALITY

Lynnda Reid
4/21/2009 03:22:50 PM
PHARMACOLOGIST