

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**203098Orig1s000**

**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 REVIEW AND EVALUATION**

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Applicant's letter date: July 4, 2011  
CDER stamp date: July 4, 2011  
Review Completion: January 4, 2012  
Product: Testosterone gel (b) (4)  
Indication: Testosterone replacement in hypogonadal men  
Applicant: Perrigo Israel Pharmaceuticals Ltd.  
Review Division: DRUP  
Reviewer: Jeffrey D. Bray, Ph.D.  
Supervisor: Lynnda L. Reid, Ph.D.  
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# 1 Executive Summary

## 1.1 Introduction

This application is for a testosterone gel <sup>(b) (4)</sup> 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 similar products. 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 published studies of testosterone and the FDA findings of safety and efficacy for AndroGel®, testosterone gel 1% (NDA 21-015) 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. Literature references and a scientific rationale for the reliance on literature were submitted to support the nonclinical sections of the Labeling. While the formulation is different than 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 <sup>(b) (4)</sup> 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

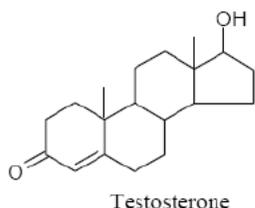
CAS Registry Number: 5949-44-0

Generic Name: testosterone

Chemical Name: (17 $\beta$ )-17-hydroxyandrost-4-en-3-one

Molecular Formula/Molecular Weight: C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>/288.42

Structure or Biochemical Description



Pharmacologic Class: androgen

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

IND 107130	(Perrigo Israel, (b) (4) 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)

(b) (4)

## 2.3 Drug Formulation

Product is delivered as 2.5 and 5 g sachets, or as a meter-dose pump that contains the identical drug product as the sachets. The meter-dose pump provides 1.25 g of drug product/actuation. The recommended starting dose is 5 g corresponding to 50 mg of testosterone and the dose can be titrated up to 10 g/day (100 mg testosterone).

### Composition of Testosterone Gel (b) (4) Product at a Maximal Dosage of 10 g/day

Ingredient	Function	Amount		Maximal Amount in Approved Products*
		mg/g	%w/w	
Testosterone, USP	API	100.0	(b) (4)	--
Alcohol, USP				(b) (4)
Isostearic Acid				
Carbomer 940, NF				
Carbopol 980, NF				
(b) (4) NaOH, NF				
Purified water, USP				

\*In the Inactive Ingredient Database

## 2.4 Comments on Novel Excipients

A consult (b) (4) was performed to determine if the unqualified excipient for a gel product that differed in the applicant drug product from the RLD was of a toxicological concern (#2009-0331). It was deemed that the proposed use of the excipient Isostearic Acid (ISA) (b) (4) was acceptable from a pharm/tox perspective (See Appendix).

## 2.5 Comments on Impurities/Degradants of Concern

Impurities are [REDACTED] (b) (4). They are below the specified limits of NMT [REDACTED] (b) (4).

The sponsor obtained a Letter of Authorization from the holder of [REDACTED] (b) (4) dated May 6, 2011. A review of the DMF shows [REDACTED] (b) (4) with an acceptance criterion of NMT [REDACTED] (b) (4), which exceeds the ICH Q3B(R) guidance qualification limit of NMT 0.15%. The applicant provided a toxicological report in eCTD 3.2.S.4.5-1 that provides adequate characterization. [REDACTED] (b) (4). The drug substance under this DMF has been used in other IND sponsors' clinical trials.

## 2.6 Proposed Clinical Population and Dosing Regimen

Hypogonadal men will self-administer testosterone gel with 2.5 to 10 g of drug product daily to the shoulders/upper arms (abdomen was not evaluated). The starting dose is 5 g with the amount to be titrated based on achieving serum testosterone levels of 300-1000 ng/dL. Sachets can be used in combinations that equal the number of grams of gel prescribed.

## 2.7 Regulatory Background

The applicant previously submitted [REDACTED] (b) (4) on June 15, 2007, for packets containing the same [REDACTED] (b) (4) testosterone drug product. The applicant received a refusal to receive for [REDACTED] (b) (4) on September 26, 2007, and responded plus added information about a multi-dose pump form on November 19, 2007. On January 23, 2008, another refusal to receive letter was sent to the applicant. The applicant responded to the letter on November 27, 2008, and also filed [REDACTED] (b) (4) for multi-dose pump. In May 2009, both ANDAs were accepted for review. In August 2009, the applicant received Complete Response letters for both [REDACTED] (b) (4) with advice to submit an NDA to DRUP. The applicant met with DRUP and then submitted IND 107130 on December 17, 2009. A meeting between the Division and the sponsor was held on May 19, 2010, to discuss the requirements for a 505(b)(2) NDA application.

The applicant submitted Form 356h with the 505(b)(2) box checked and a Reference List Drug listed as Androgel® (testosterone gel) 1%.

## 3 Studies Submitted

No studies were submitted or reviewed. The applicant submitted 16 literature references plus FDA references that establish the nonclinical toxicities of testosterone and support the nonclinical sections of the labeling.

1. FDA Meeting Minutes Dated May 19, 2010

2. Pharmacology Review for AndroGel® NDA 21-015
3. Prescribing Information for AndroGel®
4. Cui,L., Mori,T., Takahashi,S., Imaida,K., Akagi,K., Yada,H., Yaono,M., and Shirai,T. (1998). Slight promotion effects of intermittent administration of testosterone propionate and/or diethylstilbestrol on 3,2'-dimethyl-4-aminobiphenyl-initiated rat prostate carcinogenesis. *Cancer. Lett* 122, 195-199.
5. Han,X., Liehr,J.G., and Bosland,M.C. (1995). Induction of a DNA adduct detectable by 32P-postlabeling in the dorsolateral prostate of NBL/Cr rats treated with estradiol-17 beta and testosterone. *Carcinogenesis*. 16, 951-954.
6. Ho,S.M., and Roy,D. (1994). Sex hormone-induced nuclear DNA damage and lipid peroxidation in the dorsolateral prostates of Noble rats. *Cancer. Lett* 84, 155-162.
7. International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans Vol. 21 (1979).
8. International Agency for Research on Cancer, Androgenic (Anabolic) Steroids (Group 2A), Supplement 7, (1987). [IARC1987a]
9. International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 6, Genetic and Related Effects: An Updating of Selected IARC Monographs from Volume 1 to 42, 506-507, (1987). [IARC1987b]
10. Lasne,C., Lu,Y.P., Orfila,L., Ventura,L., and Chouroulinkov,I. (1990). Study of various transforming effects of the anabolic agents trenbolone and testosterone on Syrian hamster embryo cells. *Carcinogenesis*. 11, 541-547.
11. Magnusson,B., and Kligman,A.M. (1969). The identification of contact allergens by animal assay. The guinea pig maximization test. *J Invest Dermatol* 52, 268-276.
12. Meissner,W.A. and Sommers,S.C. (1966). Endometrial changes after prolonged progesterone and testosterone administration to rabbits. *Cancer. Res.* 26, 474-478.
13. Pollard,M. and Luckert,P.H. (1986). Promotional effects of testosterone and high fat diet on the development of autochthonous prostate cancer in rats. *Cancer. Lett* 32, 223-227. [Pollard1986a]
14. Pollard,M., and Luckert,P.H. (1986). Production of autochthonous prostate cancer in Lobund-Wistar rats by treatments with N-nitroso-N-methylurea and testosterone. *J Natl Cancer. Inst* 77, 583-587. [Pollard1986b]
15. Russo, I.H. and Russo,J. (1996). Mammary gland neoplasia in long-term rodent studies. *Environ. Health Perspect.* 104, 938-967.

16. Sarkar,K., Kinson,G.A., and Rowsell,H.C. (1986). Embryo resorption following administration of steroidal compounds to rats in mid pregnancy. Can J Vet. Res. 50, 433-437.
17. Seraj,M.J., Umemoto,A., Tanaka,M., Kajikawa,A., Hamada,K., and Monden,Y. (1996). DNA adduct formation by hormonal steroids in vitro. Mutat. Res. 370, 49-59.
18. Tsutsui,T., Komine,A., Huff,J., and Barrett,J.C. (1995). Effects of testosterone, testosterone propionate, 17 beta-trenbolone and progesterone on cell transformation and mutagenesis in Syrian hamster embryo cells. Carcinogenesis. 16, 1329-1333.
19. World Health Organization, Guidelines for the Use of Androgens in Men, Geneva, Special Programme of Research, Development and Research Training in Human Reproduction (1992).
20. World Health Organization (WHO) Food Additives Series: 43. Toxicological Evaluation of Certain Veterinary Drug Residues in Food. Fifty-second meeting

## 11 Integrated Summary and Safety Evaluation

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. Nonclinical data support approval of topical testosterone gel (b) (4).

## 12 Appendix

**DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS  
CONSULTATION (Tracking #69)  
FOR INTERNAL USE WITHIN FDA ONLY**

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DATE: June 17, 2009

From: Jeffrey Bray, Ph.D.  
Pharmacologist, DRUP *UMB JOB 6/17/09*

Through: Lynnda Reid, Ph.D.  
Pharmacology Supervisor, DRUP *L. Reid 6/17/09*

Scott Monroe, Ph.D.  
Division Director, DRUP *sm 7/29/09*

To: Peter Chen  
Consumer Safety Officer, OGD

Date of Consultation: May 12, 2009

RE: Consult No 2009-0331  
Pharmacology/Toxicology Safety Review of Isostearic Acid (ISA)  
*(b) (4)*

Relevant DFM & ANDAs: *(b) (4)* NDA 21-015 (AndroGel®  
1% testosterone gel), DMF# *(b) (4)*

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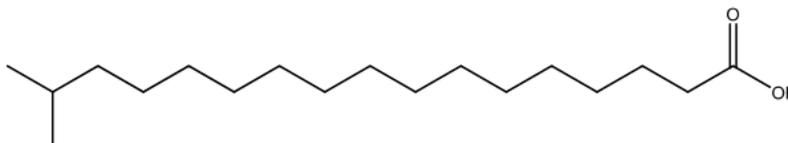
**Recommended Regulatory Action**

From a pharmacology/toxicology perspective, the proposed use of the excipient Isostearic Acid (ISA) at *(b) (4)* is acceptable.

## Introduction

The drug products under review are testosterone gel (b) (4) to treat men with primary and secondary hypogonadism. Perrigo Israel Pharmaceuticals submitted (b) (4) which the Office of Generic Drugs initially refused to file partially based on the inclusion of the excipient Isostearic Acid (ISA) for the proposed topical transdermal gel route of administration since ISA is currently only in approved FDA products as topical creams and ointments. In response, the Sponsor provided a toxicological assessment of ISA prepared by Dr. Ron Filler. The report included the results of an extensive literature and web-based search conducted on the nonclinical toxicology, clinical safety information, and a comparative analysis to chemically similar C18 fatty acids. Also, the response contained a toxicological evaluation by the manufacturer of ISA, (b) (4). The Office of Generic Drugs requested a consult to evaluate the nonclinical data to ensure that the proposed inclusion of (b) (4) ISA in testosterone gel (b) (4) by Perrigo Israel is safe for human use.

Structure of Isostearic Acid



In general, ISA is a blend of branched chain saturated isomers of octadecanoic acid. ISA consists of approximately 80% branched chain C18 isomers of octadecanoic acid and 20% of straight chain isomers C14, C16, and C18 fatty acids. Chemical literature references use the term Isostearic Acid to refer specifically to 16-methylheptadecanoic acid (CAS Number 2724-58-5). ISA is prepared by dimerizing fatty acids from Tall oil, Soybean oil, or tallow in the presence of a catalyst. The reaction mix is fractionated and the monomer fraction is further refined by hydrogenation, solvent separation, and additional distillation.

TABLE 1. Fatty Acid Components of Isostearic Acid.

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Table taken from Ref. 1.

Perrigo Israel Pharmaceuticals is proposing to use ISA instead of isopropyl myristate (b) (4) in its formulation of testosterone gel (b) (4).

The daily exposure using the maximum recommended amount of 10 g AndroGel® 1% would be 20 mg of ISA.

AndroGel® 1% (RLD)

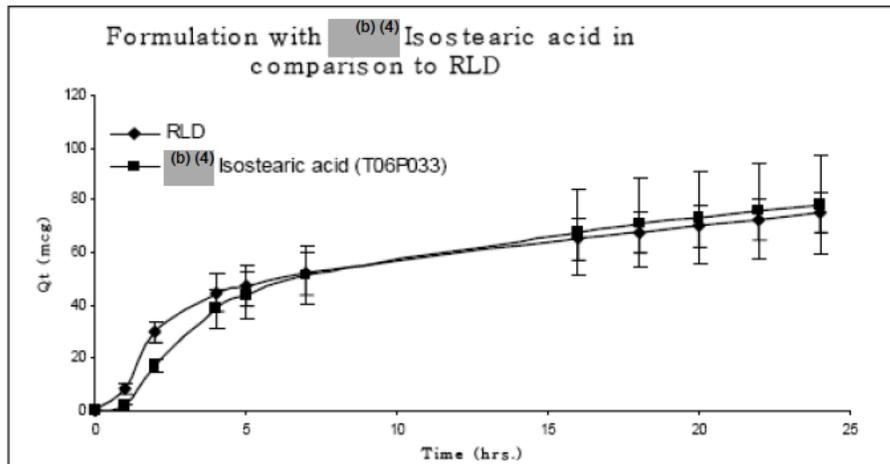
Ingredient	Function	%w/w
Testosterone, USP	API	1.00
Alcohol, USP		(b) (4)
Isopropyl myristate, NF		
Carbopol 980, NF		
(b) (4) NaOH, NF		
Purified water, USP		

Testosterone (b) (4)

Ingredient	Function	%w/w
Testosterone, USP	API	(b) (4)
Alcohol, USP		(b) (4)
Isostearic Acid		
Carbopol 980, NF		
(b) (4) NaOH, NF		
Purified water, USP		

The in vitro Frantz Cell System penetration profile using human cadaver skin (b) (4) is similar between RLD and ISA.

Chart for formulation T06P033 versus the RLD



Review of Safety Data Provided in Assessment

The ISA nonclinical toxicology and irritation and clinical irritation and sensitization studies were originally compiled by the Cosmetic, Toiletry and Fragrance Association (CTFA) before 1983 [1]. A more recent review of the toxicology of ISA was published in 2005 [2].

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### Uses in Topical Drugs and Cosmetics

ISA is present at a concentration of (b) (4) in Aldara® (NDA 20-723, imiquimod 5% cream) [Chollet, 1999], and is listed in the IIG database as approved for the topical route of administration in concentrations of up to 25% . [3]

ISA is listed as an ingredient in topical and vaginal progesterone-containing creams, but the concentrations are not reported. Progesterone cream is categorized as an herbal beauty product, and as such these products are not regulated by the FDA.

ISA is used extensively (b) (4) in moisturizing cosmetics and shows similar physical properties as stearic acid and oleic acid, and is present in a wide variety of cosmetic products. There were 142 formulations reported to the FDA that contained ISA at concentrations from ≤0.1% to 10% in 1981 [1]. In 2005, the Annual Review of Cosmetic Ingredient Safety Assessment for 2002/2003 listed 119 formulations that reported containing ISA at concentrations from 0.003% to 26% [2].

**TABLE 13**  
Historical and current cosmetic product uses and concentrations for Isostearic Acid

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Table taken from Ref. 2.

**Nonclinical Toxicity [from Ref. 1]****Metabolism**

Metabolism was investigated in mitochondrial and microsomal fractions of rat liver homogenate. In general, ISA is metabolized similar to other straight chain fatty acids. However, unlike straight chain fatty acids, ISA is oxidized to a large extent at the  $\omega$  carbon to yield 3-carbon dicarboxylic acids, as well as successively at the  $\beta$  carbon to yield 2-carbon metabolites.

**Acute Toxicity Studies**

Five, single oral dose administration studies were conducted in rats. Three studies used undiluted ISA and 2 other studies used a product formulation containing ISA. The oral LD<sub>50</sub> is between 32 and 64 ml/kg (28.5 g/kg and 57 g/kg). There was mortality observed with clinical signs in a single study evaluating undiluted ISA at the two highest doses (28.5 g/kg and 57 g/kg) showing dose-dependent inhibition of locomotion and debilitation with nasal hemorrhage. Three of five animals died, and the other two were severely debilitated at 57 g/kg. The MTD was set at 28,500 mg/kg and the HED is approximately 28,000 mg/day.

**Dermal Irritation**

Five studies evaluating the potential for ISA to cause dermal irritation were conducted in rabbits using the Draize skin patch test procedure. Undiluted ISA (2 separate studies), 15% ISA in corn oil, and 3 product formations ranging from 1.24% to 35% were evaluated. In each study, 0.5 ml of test article was applied to bare skin and occluded for 24 h. The site was then graded for erythema and edema using the Draize scale. Undiluted ISA produced minimal irritation and ISA in corn oil was non-irritating. The product formations produced minimal to moderate irritation, and was suggested to be caused by other components of the formulations.

**TABLE 5.** Draize Primary Skin Irritation Tests on Isostearic Acid.

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Table taken from Ref. 1.

### Phototoxicity

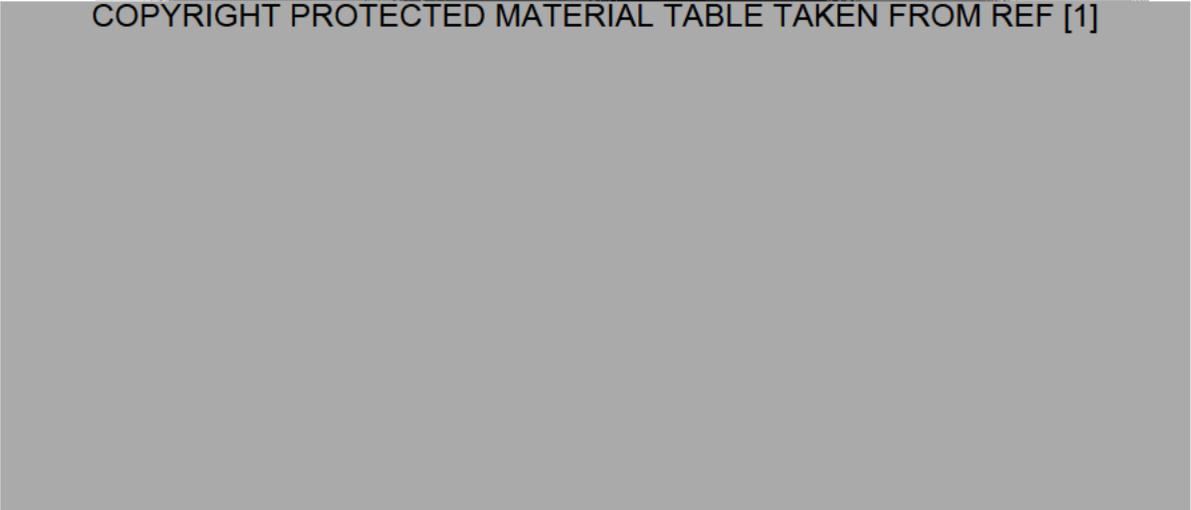
In a separate evaluation of dermal irritation and phototoxicity, 200 mg of undiluted ISA was applied to the dorsal side of New Zealand White rabbits for 2 h under a gauze pad on both sides of the animals. The right side patch was then removed and exposed to  $5 \times 10^7$  ergs/cm black light (320-450 nm) while the left side patch was covered with aluminum foil. The investigators concluded that ISA was mildly irritating without light and moderately irritating with exposure to light, but the difference was not statistically significant.

### Mucous Membrane Irritation (Eye)

Undiluted ISA and four product formulations containing 2-35% ISA were evaluated in modified or standard Draize eye irritation procedures. In each study, 0.1 ml of test article was instilled into the conjunctival sac of one eye of rabbits with no washing, with the untreated eye serving as a control. Irritation was graded according to the Draize scale after 1, 2, 3, 4, and 7 days. The undiluted ISA produced minimal transient irritation and the product formulations ranged from none to moderate, suggesting that other components were the irritant.

TABLE 6. Draize Eye Irritation Tests on Iostearic Acid.

COPYRIGHT PROTECTED MATERIAL TABLE TAKEN FROM REF [1]



### Skin Corrosion Potential

The IntraAgency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) recommends ISA as a non-corrosive agent to use in *in vitro* TER tests used for the assessment of dermal corrosivity for the hazard potential of chemicals.

### Summary of Nonclinical Toxicity Studies with related C18 Fatty Acids

The sponsor proposes that stearic and oleic acids are chemically and structurally similar to ISA, and thus toxicological findings can be used to bridge and support the safety of the closely related ISA. A report compiled <sup>(b) (4)</sup> extensively reviews the toxicology data for stearic acid and oleic acid from the literature.

Stearic acid [4,5,6]:

In rats, approximately 50% of liver radiocarbon was recovered as oleic acid after intravenous administration of <sup>14</sup>C labeled stearic indicating that extensive desaturation occurred. Stearic acid is poorly absorbed.

Acute toxicity was assessed in mice by intraperitoneal injection ranging from 15 to 1500 mg/kg. The only finding of note was a loss of body weight at 1500 mg/kg.

In rats fed a diet of 50% stearic acid for 4 weeks, there were no observed adverse effects. In rats fed a diet of 50% stearic acid for 8 weeks, there were microscopic foreign body-type reactions in adipose tissues. Rats fed stearic acid at 50 g/kg for 24 weeks developed reversible lipogranulomas in adipose tissues. Rats fed 300 ppm of stearic acid for 30 weeks had increased mortality, and exhibited increased anorexia and pulmonary infections and diminished clotting times. Cats administered >5mg of stearic acid had elevated pulmonary but decreased systemic blood pressure with apnea and convulsions leading to death.

Stearic acid was not mutagenic in reverse mutation bacterial systems. Stearic acid was not evaluated in other standard genotoxicity assays.

Evaluation of stearic acid in reproductive toxicity assays was not reported.

Carcinogenicity potential was evaluated in four groups of mice. CFW Swiss Webster mice (n=16/group) were administered subcutaneous stearic acid in tricapylin at 0.05 mg and 0.5 mg weekly for 26 injections. After 18 months, 10 and 6 mice were alive, respectively. Another group of mice (n=15) were administered 1 mg of stearic acid 3 times/week for 10 injections. At 12 and 18 months, there were 8 and 1 mice alive, respectively. Also, BALB/c mice were administered 1 mg of stearic acid 2 times/week for 82 injections. After 18 months, 7 mice were alive. No neoplasms were found in any of these groups.

However, neoplasms were found in 3 other groups BALB/c mice administered stearic acid in this investigation. The first group (n=15) was injected subcutaneously with 0.05 mg stearic acid twice weekly for 104 injections. After 18 months, 13 mice were alive. After 19 months, one pulmonary neoplasm was found. The second group of mice (n=10) received injections of 0.05 mg stearic acid twice weekly for 114 injections. After 18 months, four mice were alive. The incidences of sarcomas were 1, 2, and 1 after 6, 10, and 12 months, respectively, and 1 pulmonary neoplasm and 1 leukemia-lymphoma after 19 months. The third group of mice (n=10) received 0.5 mg stearic acid per subcutaneous injection twice weekly for 114 injections. After 18 months, 9 mice were alive. After 21 months, 1 pulmonary neoplasm and 1 adrenal carcinoma were found.

In a repeat of the first study using the ICR/Ha Swiss Millerton and CFW Swiss Webster mice, and administering subcutaneously stearic acid at 0.05 mg or 0.5 mg in 0.1mL tricapylin. It was determined that stearic acid did not have carcinogenic activity, and that there were no sarcomas observed. The investigators stated that the previously observed sarcomas occurred at the injection sites, suggesting it was related to route of administration, not the stearic acid.

The systemic exposure of 600 mg of stearic acid at 45 h following dermal application seems to be very limited using radioactive stearic acid in rat skin with most of the radioactive material appearing to remain on the surface of the skin.

#### Oleic acid [4,5]:

Oleic acid appears to have limited ability to penetrate the skin of rats and the path is suggested to be via hair follicles. Oleic acid has a  $T_{1/2}$  of approximately 200 days. During the first 4 days following administration, half of the activity is fixed to water and half is stored in adipose tissue.

Acute toxicity was not reported.

Pulmonary findings were observed in dogs receiving weekly injections of 90 mg/kg oleic acid for 1-3 months. Early changes including thromboses and cellular necrosis followed by a repair stage with type 2 cell proliferation and fibrotic foci in subpleural areas. Pulmonary fibrosis was observed later.

Weanling rats fed a diet of 15% oleic acid for 10-16 weeks had no adverse growth effects. Four females became pregnant, two died in parturition; one litter was cannibalized at birth and the remaining litter dies within 3 days of birth after the dams were fed 15% oleic acid for 16 weeks. Female rats (n=7) fed a diet of 15% oleic acid for 16 weeks and then mated produced offspring, 44 of which survived 1 week and 11 of which survived 3 weeks. Findings of note were retarded mammary development and ovarian cysts. No lesions were found in non-reproductive organs.

Oleic acid was not mutagenic in reverse mutation bacterial systems. Oleic acid increased aneuploidy in the D<sub>6</sub> strain of *S. cerevisiae* up to 50 µg/ml and V79 CHL fibroblasts at 2.5, 5 and 100 µg/ml.

Oleic acid was evaluated for carcinogenic potential in two investigations. In the first study, Swiss Webster mice (n= 15) given subcutaneous injections of 0.1 mg of 1 mg/ml oleic acid in tricaprilyn 3 times/week for 10 injections. After 12 months, 9 mice were alive, and after 18 months, 1 mouse was alive. No neoplasms were observed after this treatment. In the second investigation, Swiss-Webster mice (n=16) were administered 0.5 mg oleic acid with 2 injections /week for 33 injections. After 12 months, 8 mice were alive, and after 18 months, 4 were alive. One mammary gland carcinoma was found after 9 months. Oleic acid was deemed to be noncarcinogenic.

### **Summary and Assessment of Nonclinical Toxicology Results**

In general, topically applied ISA, undiluted or as part of a product formulation, was minimally irritating in standard assays that evaluate dermal irritation. There was no evidence of phototoxicity or eye irritation. The acute oral toxicity of ISA is low in rats requiring very large amounts before morbidity and mortality were observed (HED is approximately 27,600 g). The human daily dermal exposure is 0.02 mg, thus representing low overall exposure compared to animal testing. However, the pharmacokinetics, the chronic toxicology, and the potential genotoxicity, carcinogenicity, and reproductive/developmental toxicology of ISA have not been

directly assessed. A computational toxicology consult determined that ISA is predicted to have potential genotoxicity in some models and mouse sperm toxicity. Of interest, ISA was specifically predicted to have low or no toxicity in most common toxicity assays and models. The sponsor provided a safety assessment of the related C18 fatty acids, stearic acid and oleic acid. These are minor components in the ISA formulation (Table 1, page 2). In general, the toxic potential of stearic acid and oleic acid appears low and the most significant findings were related to pulmonary findings after chronic oral or parenteral, but not topical, administration.

### **Clinical Studies with ISA[1]**

#### **Dermal Irritation**

Five clinical studies evaluating the potential for ISA to cause dermal irritation were conducted using the 24 h dermal occlusion patch test procedure. One study used undiluted ISA with 100 subjects and the other studies used product formulations containing 0.44% to 35% ISA. All amounts are at least 2X the amount proposed by the sponsor. The undiluted ISA was graded to be negative in causing dermal irritation. A single study was graded as minimal irritation, possibly caused by other components of the formulation.

**TABLE 7.** Clinical 24-Hour Single Insult Patch Tests with Isostearic Acid.

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Table taken from Ref. 1.

#### **Sensitization**

Four clinical studies evaluating the potential for ISA to cause dermal irritation and sensitization were conducted using a repeated insult patch test procedure. The amount of ISA used in these studies ranged from 5 to 30 mg. Two studies used ISA diluted in mineral oil and two studies used product formulations containing 0.2% and 0.44% ISA. The methodologies of the first two studies were slightly different. In the first study, 0.1 ml of 35% ISA was applied on the back of subjects at 48 h intervals for 3/week for 3 weeks before removal. The area was occluded for the

first 24 h, then washed. The test sites were graded at 48 h, then a fresh application was placed on the site. Following a 3-week nontreatment period, the test site and another previously untreated site had test article applied as above. The sites were graded at 24, 48, and 72 h. There were transient reactions observed, but the evaluators concluded that that ISA was not an irritant or a sensitizer. In the second study using 10% ISA in mineral oil, Test article was applied to the back and semi-occluded for 48 h (or 72 h on weekends). The patch was removed, the site graded and test article reapplied. This was repeated 10 times, followed by a nontreatment period of 2 weeks. There was a rechallenge as above, then the site was graded. The evaluators reported no irritation or sensitization. The formulation studies observed no irritation or sensitization.

**TABLE 8.** Clinical Repeated Insult Patch Tests with Isostearic Acid.

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Table taken from Ref. 1.

### **Phototoxicity**

In the same sensitization study that used 35% ISA, phototoxicity was examined in 28 subjects. The procedure was the same as above except the forearm was used as the test site. The subjects were divided into 2 groups that received UVA only (n=19) or UVA and UVB light (n=9). Those receiving UVA had UVA light (320-400 nm) was applied to the test site for 15 min at 4.4  $\mu\text{W}/\text{cm}^2$  at the skin surface. Those receiving both had UVB light applied to the test site at two times the mean erythema dose (280-320 nm) and also received UVA for 5 min as previously described. There were transient reactions observed, but the evaluators concluded that that ISA was not phototoxic.

### **Conclusion:**

Below are the conclusions from the published safety assessments of ISA.

“On the basis of the available information presented in this report, the Panel concludes that Isostearic Acid is safe as a cosmetic ingredient in the present practice of use.” [1]

“A safety assessment of Isostearic Acid was published in 1983 with the conclusion: “safe as a cosmetic ingredient in the present practice of use” (Elder 1983). Studies available since that safety assessment was completed, along with updated information regarding uses and concentrations were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.” [2]

ISA is a common ingredient in hundreds of cosmetic products with decades of human use up to 200 times the proposed concentration. Fatty acids including ISA are a component of many vegetable and animal food products. The limited nonclinical toxicology data (mainly dermal) and clinical safety data support the findings that ISA appears to be safe for use as an excipient in all manners of topical formulations with similar findings. In fact, 100% ISA was often found to be less of an irritant or sensitizer than formulations that had much lower concentrations. Further, two closely related fatty acids that are found in ISA as minor components did not appear to have significant nonclinical toxicities.

From a Pharm/Tox perspective, there is adequate nonclinical and clinical safety information to support the use of Isostearic Acid (b) (4) in testosterone (b) (4) gel.

### References

1. Final Report on the Safety Assessment of Isostearic Acid *J Am Coll Toxicol*. 1983 2(7):61-74.
2. Annual Review of Cosmetic Ingredient Safety Assessments--2002/2003. *Int J Toxicol* 2005; 24 Suppl 1:1-102.
3. Chollet JL, Jozwiakowski MJ, Phares KR, Reiter MJ, Roddy PJ, Schultz HJ et al. Development of a topically active imiquimod formulation. *Pharm Dev Technol* 1999; 4(1):35-43.
4. National Library of Medicine, TOXNET, Hazardous Substance Data Bank
5. Final Report on the Safety Assessment of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid. *J. Am. Coll. Toxicol.* 6(3), 1987, 321-402.
6. Butcher EO. Penetration of radioactive stearic acid into the skin of the rat. *J Invest Dermatol* 1953; 21(4):243-247.

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/s/  
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JEFFREY D BRAY  
01/27/2012

LYNNDA L REID  
01/30/2012  
Concur.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

**NDA Number: 203098**

**Applicant: Perrigo**

**Stamp Date: July 5, 2011**

**Drug Name: testosterone gel <sup>(b) (4)</sup> NDA Type: 505(b)2**

**60-Day Filing Review Date: September 3, 2011**

**74-Day Letter Date: September 17, 2011**

**Expected Date of Draft Review: December 1, 2011**

**PDUFA Goal date: May 5, 2012**

On **initial** overview of the NDA application for RTF:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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 with literature to support the nonclinical sections of the labeling. Reference listed drug: AndroGel 1%
2	Is the pharmacology/toxicology section of the NDA indexed and paginated in a manner allowing substantive review to begin?	n/a		See above.
3	On its face, is the pharmacology/toxicology section of the NDA legible so that substantive review can begin?	n/a		See 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 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		
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		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR A NEW NDA/BLA

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
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/m2 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 FDA-approved products.
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. 9/1/2011  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

Lynnda Reid, Ph.D. 9/1/2011  
 \_\_\_\_\_  
 Team Leader/Supervisor Date

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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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JEFFREY D BRAY  
09/01/2011

LYNNDA L REID  
09/01/2011