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RESEARCH**

APPLICATION NUMBER:

202763Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

Date	February 7, 2012
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	202763
Applicant	Teva Pharmaceuticals Inc.
Date of Submission	January 14, 2011
PDUFA Goal Date	February 14, 2012
Proprietary Name / Established (USAN) names	testosterone gel
Dosage forms / Strength	50 mg. (b) (4) mg testosterone applied once daily
Proposed Indication(s)	(b) (4)
Recommended:	<i>Approval</i>

1. Introduction

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for the maintenance of secondary sex characteristics. Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone. Signs and symptoms reported to be associated with male hypogonadism include: erectile dysfunction, decreased sexual desire, fatigue, mood depression, regression of secondary sexual characteristics and osteoporosis.

The active moiety in the proposed product is testosterone. Testosterone therapy is available in the United States as several formulations, including: topical gels and solutions (AndroGel 1%, AndroGel 1.62%, Testim, Fortesta and Axiron), a transdermal patch (Androderm), a buccal patch (Striant), intramuscular injections (testosterone enanthate and testosterone cypionate) and implanted pellets (Testopel). AndroGel 1% is the most widely used testosterone replacement therapy. Approximately (b) (4) patients have used AndroGel 1% since its approval in February, 2000.

Teva Pharmaceuticals (Teva) has developed a testosterone gel intended to be comparable to AndroGel 1%. (b) (4)

(b) (4)

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Teva was unable to submit their application for FDA approval as an abbreviated new drug application (ANDA) to the Office of Generic Drugs (OGD), but rather submitted it as a 505(b)(2) application to the Division of Reproductive and Urologic Products (DRUP).

Thus, on January 14, 2011, Teva Pharmaceuticals submitted their 505 (b)(2) application for testosterone gel, consisting of data from the following 4 studies:

- A single-dose bioequivalence study (Study No. 70343): This was a randomized, open-label, 2-way crossover, bioequivalence study of Teva's testosterone gel and AndroGel 1% (reference) following a 100 mg dose in hypogonadal male volunteers.
- A 21-day, repeat-dose, cumulative irritation and sensitization study (Study No. 10936025): Testosterone gel was applied to the same skin application site once daily for 21 days. Signs and symptoms of irritation were evaluated daily by trained, blinded evaluators. After Day 22, subjects underwent a 14-day washout period when no gel was applied. The subjects returned to the clinical facility on Day 36 where the gels were applied to complementary sites on the opposite arm used in the irritation/induction period. These were removed after at least 48 hours of application and the sites of application monitored over the next 72 hours for signs and symptoms of sensitization reactions
- A hand washing study (Study No. CRI-00018704): This was an open-label, two-period crossover study in healthy adult male subjects comparing the amount of residual drug remaining on the hands after application of the product and a hand washing procedure between the Sponsor's test product testosterone gel and AndroGel 1%.
- An interpersonal transfer study (Study No. M1FX10001): This was an open-label, single-dose, randomized, 4-period, 4-treatment crossover study that assessed the relative bioavailability of the new testosterone gel compared to AndroGel 1% in healthy female subjects following skin-to-skin contact as well as clothed contact with healthy male subjects who received a single topical dose. Potential for transfer was assessed from males to females with males wearing T-shirts and with males not wearing T-shirts.

2. Background

2.1 DESCRIPTION OF PRODUCT

According to the chemist's review dated December 14, 2011, (b) (4)

(b) (4) Isopropyl palmitate is an ester of palmitic acid extracted from coconut oil. (b) (4)

Testosterone gel is clear and colorless and contains 1% testosterone. The inactive ingredients are: (b) (4) dehydrated alcohol 67% (b) (4)

(b) (4) isopropyl palmitate (b) (4) (u) (4) (b) (4) sodium hydroxide (b) (4) (u) (4) and purified water (u) (4) (b) (4)

Originally, the product was to be supplied as 2.5 g and 5 g sachets, as well as (b) (4)

(b) (4) (u) (4). The sachets are

unit-dose, (b) (4) aluminum foil packets containing either 25 mg or 50 mg of testosterone in 2.5 g or 5 g of gel, respectively. The sachets are supplied in cartons of 30.

The product's proposed indicated use is the standard indication for testosterone replacement: in males for (b) (4)

(b) (4) with symptoms of hypogonadism (such as erectile dysfunction, decreased sexual desire, fatigue, loss of energy, mood depression, regression of secondary sexual characteristics, or osteoporosis).

The proposed dose regimen and application instructions are identical to those for AndroGel 1%. The recommended starting dose is 50 mg of testosterone (5 g gel) applied topically once daily to the upper arms/shoulders and/or abdomen. If serum testosterone concentration is below the normal range, the dose may be adjusted from 50 mg to 75 mg (7.5 g gel), and from 75 mg to 100 mg (10 g gel). If the serum testosterone concentration exceeds the normal range, the daily dose should be decreased. If the serum testosterone concentration exceeds the normal range at a daily dose of 50 mg, therapy with Teva's testosterone gel should be discontinued.

2.2 REGULATORY HISTORY

No IND application was opened for this product. Neither pre-NDA meetings nor pre-NDA communications with DRUP occurred prior to submitting the application.

However, there is other relevant regulatory history, as follows:

On December 29, 2008, Teva submitted an ANDA (b) (4) to the Office of Generic Drugs (OGD) for this same product.

(b) (4)

On April 7, 2009, OGD conveyed a Refuse-to-Receive letter to Teva, stating that the ANDA could not be reviewed because Teva's formulation contained different ingredients than those contained in the RLD; (b) (4)

(b) (4)

(b) (4)

On January 13, 2011, the 505(b)(2) NDA for Teva's testosterone gel was submitted to DRUP.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Guodong Fang, stated in his final review, dated January 26, 2011:

"Recommendation on Regulatory Action: From a clinical perspective, this reviewer recommends that Teva, 1% testosterone transdermal gel, be approved for the indication of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- *"Primary hypogonadism (congenital or acquired)" or*
- *"Hypogonadotropic or secondary hypogonadism (congenital or acquired)".*

The Clinical Review Team and other disciplines through their reviews believe that the results from one bioequivalence study, one irritation and sensitization study, one hand washing study, and one bioavailability transfer study included in this 505(b)(2) NDA submission are acceptable. The results of these studies demonstrate that Teva 1% testosterone gel product is effective and safe for the replacement of testosterone in hypogonadal men.

As for all topical testosterone gel products, a Black Box Warning and a Medication Guide addressing the potential for secondary exposure via skin transfer of testosterone to children have been included in labeling and are acceptable."

Dr. Fang provides additional summary comments regarding the contents of the NDA and the study results:

"The basis for the submission of this NDA, under section 505 (b) 2, is the following:

(b) (4)

2. *The active ingredients for the proposed drug product are the same as those of the RLD.*
3. *The route of administration, dosage form and strength of the proposed drug product are the same as those of the RLD.*
4. *Information demonstrating that the proposed drug product provides sufficiently comparable exposures to the RLD drug is provided in the application.*
5. *A skin irritation and sensitization study demonstrating acceptable safety, and no more irritation or sensitization than the RLD is provided in this application.*
6. *Transfer and hand-washing studies have been completed and demonstrate acceptable safety, in addition to comparing the relative bioavailability between the*

proposed drug product and the RLD in female subjects following direct transfer from healthy male subjects.

7. *The labeling for the proposed drug product is the same as that of the reference listed drug, with the exception of information pertaining to the new bioequivalence and transfer studies.”*

3. CMC/Device

The Chemistry Review team, Zhengfang Ge and Moo Jhong Rhee, made the following recommendation in their final review dated December 14, 2011:

“The applicant of this NDA has provided sufficient CMC information to assure identity, strength, purity, and quality of the drug product. However, the Office of Compliance has not issued an overall “Acceptable” recommendation. Labeling issues also have not been resolved as of this review.

Therefore, from the ONQA perspective, this NDA is not recommended for Approval in the present form per 21 CFR 314.25(b)(6),(13) until all pending issues are resolved”.

On January 13, 2012, the overall recommendation from Office of Compliance for the NDA was posted as ACCEPTABLE, based on a satisfactory inspection of the drug product manufacturing site (Cipla, Ltd) in India.

On February 1, 2012, in an eMAIL from Zhengfang Ge, I was informed that the only remaining CMC change for the labeling insertion is to add NDC numbers to the How Supplied section of the Package Insert. All the other parts of the PI and MedGuide were acceptable from the ONDQA perspective. Also on February 1, 2012, additional recommended revisions to the container and carton labels were conveyed to Sponsor.

On February 9, 2012, the ONDQA review team completed a final memo stating:

“The NDA is now recommended for approval from the ONDQA perspective.”

The CMC review contained the following items of note:

- *The drug master file (DMF) in support of the drug substance was deemed acceptable.*

 (b) (4)

- *During storage, the content of isopropyl palmitate in the sachets decreases; therefore, the applicant was requested to revise the acceptance criterion of this component to be  of its concentration used in clinical studies. The applicant revised this acceptance criterion accordingly – not less than  ONDQA found this range to be acceptable.*

- Accelerated stability data was provided for 3 batches, 12 months stability data for 5 batches, and 36-month stability data for one batch (Batch X028). In these batches, decrease in isopropyl palmitate content was observed under accelerated and long-term storage conditions; however, that decrease was most prominent in Batch X028. However, Batch X028 was manufactured (b) (4), using a different batch of sachets. Therefore, Batch X028 was considered an outlier and expiration dating was based on stability data from 5 recent batches. In these batches, the predicted isopropyl palmitate content met the acceptance criterion at 18 months. Therefore, the Sponsor's proposed 18 month expiration dating period was deemed acceptable.
- The strength of the product was original expressed as testosterone gel 1%; however, to be consistent with recently marketed testosterone products, ONDQA agreed with the Division of Medication Errors Prevention and Analysis (DMEPA) that the strength will be expressed as 25 mg and 50 mg testosterone per packet.
- One impurity, (b) (4) had an acceptance limit of NMT (b) (4)%, which is above the ICH Q3A guidance for impurity qualification. However, the overall specifications include an acceptance criterion of NMT (b) (4)% for any single impurity, and the RLD, AndroGel 1%, also has an acceptance criterion of NMT (b) (4)% for (b) (4). Therefore, this was considered acceptable.
- The CMC review lists the microbiological attributes of the drug product (Section P.2.5), and there are neither objections nor concerns raised by the micro acceptance criteria.
- The CMC review notes that a proprietary name was not proposed. ONDQA stated that the established name (testosterone gel) was satisfactory
- The revised container and carton labels were deemed satisfactory by ONDQA on February 9, 2012.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Reviewers, Jeffrey Bray and Lynnda Reid, made the following recommendation in their final review dated September 30, 2011:

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

There were no recommendations for additional nonclinical studies. Class labeling was deemed appropriate. No significant labeling issues were identified nor were significant changes required. Literature references and a scientific rationale for the reliance on literature were submitted to support the nonclinical sections of the labeling. The reviewers concluded that while the formulation was different than the other FDA-approved testosterone gel products, the components were at or below the levels in other FDA-approved products.

The only impurities of note were (b) (4) which were below their specified limits of NMT (b) (4)% and (b) (4)%, respectively. The amounts of impurities/degradants over time are below the thresholds for identification and qualification according to ICH Q3B, based on 100 mg testosterone.

5. Clinical Pharmacology/Biopharmaceutics

A final review from the Clinical Pharmacology (ClinPharm) review team of Chongwoo Yu and LaiMing Lee was received on January 19, 2012.

Clinical Pharmacology made the following recommendation:

“The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) reviewed NDA 202763 submitted on January 14, 201, April 21, 2011...(additional dates provided)....and December 5, 2011. The overall Clinical Pharmacology information to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language and the Sponsor agrees on the post-marketing requirement (PMR) recommended below.”

The postmarketing requirement was described as:

“...a study evaluating the effect of washing on removing residual T from the application site.....to support labeling indicating that washing the application site will limit the potential for interpersonal transfer of T. In this study, post-dose control samples before washing should be collected (e.g., use one side as the control and the opposite side as the test) and the recovered T before and after washing and the recovery percentage should be reported, respectively.”

On January 11, 2012, the request for PMR was conveyed to Sponsor, and on January 12, 2012, they agreed to conduct the requested PMR study.

In their final memo, dated February 9, 2012, the Clinical Pharmacology team agreed to the final labeling.

In their “Summary of Important Clinical Pharmacology Findings”, Clinical Pharmacology made the following key comments:

- Re: the BE Study: “This reviewer concludes that BE between T Gel 1% and AndroGel 1% has been established regarding AUC following a single 100 mg dose (2 x 5 g packets) of T to the upper arms/shoulders (5 g gel applied to each side) of hypogonadal males. However, the upper 90% CI of C_{max} was slightly higher (by 1.7%) compared to the BE acceptance range (i.e., 80.00 – 125.00%) but it is still acceptable given there is no concern regarding the lack of efficacy as it is slightly exceeded the upper limit of the 90% CI of the BE acceptance criteria and there were no additional safety signals in the clinical safety studies submitted in this NDA.”
- Re: the Transfer Study: “Study results showed approximately 11% and 16% increase in T AUC (0-24) and C_{max} , respectively compared to baseline of females when males were wearing a T-shirt following a 10 g T Gel 1% application to the upper arm/shoulder of one side (of the male). It should be noted that the interpersonal transfer potential of the topical T applied on the abdomen was not assessed and therefore, the same conclusion cannot be extrapolated to when T Gel 1% is applied to the abdomen. This should be clearly reflected on the product label. (Note: The product label describes the transfer study procedures, including the application sites used). The overall percent difference of the PK parameters for females was much lower when males were wearing a T-shirt during the transfer procedure than without a T-shirt, indicating that there is less exposure to T when a T-shirt was covering the application site.
- Re: the Hand-Washing Study: “The Sponsor did not report the percentage of T removed by the hand washing procedure, as the measurement of residual T on the subjects’ hands (after applying the drug product to the application site) prior to hand washing was not carried out. However, considering that the mean residual amount of T was very small compared to the theoretical dose of 100 mg T (i.e., 2.85%) and that it was comparable to the residual amount following hand washing after application of AndroGel 1%, this reviewer concludes that T from T gel 1% is sufficiently removed from the hands following a hand washing procedure.”

Finally, Clinical Pharmacology did comment upon the Office of Scientific Investigation’s (OSI) audit of (b) (4) where the analytical portion of the pivotal BE study was conducted. The OSI audit found inappropriate conduct of data integration, thus all chromatograms were re-integrated as a result. In addition, OSI recommended to exclude data from 6 subjects as well as data from repeat analyses of 22 samples based upon a single technician’s training deficiency. The BE re-analysis was carried out with these data excluded. The reader is referred to Section 11 of this memo for additional detail about the OSI audit.

Also, on September 11, 2011, the Biopharmaceutics team of Tapash Ghosh and Angelica Dorantes, completed a memo stating:

“Since the provided in-vitro release information does not have regulatory utility, and the in-vitro release test (IVRT) is not part of the product’s quality tests, Biopharmaceutics considers the evaluation of the IVRT information is unnecessary and therefore, ONDQA-

Biopharmaceutics will not provide comments regarding the filing and approvability of this product.”

6. Clinical Microbiology

A Microbiology consult was not requested for this NDA. Microbiology information (acceptance criteria) are shown in Section P.2.5 of the chemist’s review. ONDQA offered neither objections nor concerns regarding the microbiological attributes of the product.

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

The 505 (b)(2) application for Teva’s testosterone gel consisted of data from the following 4 studies:

- A single-dose bioequivalence study (Study No. 70343): This was a randomized, open-label, 2-way crossover, bioequivalence study of Teva’s testosterone gel and AndroGel 1% (reference) following a 100 mg dose in hypogonadal male volunteers.
- A 21-day, repeat-dose, cumulative irritation and sensitization study (Study No. 10936025): Testosterone gel was applied to the same skin application site once daily for 21 days. Signs and symptoms of irritation were evaluated daily by trained, blinded evaluators. After Day 22, subjects underwent a 14-day washout period when no gel was applied. The subjects returned to the clinical facility on Day 36 where the gels were applied to complementary sites on the opposite arm used in the irritation/induction period. These were removed after at least 48 hours of application and the sites of application monitored over the next 72 hours for signs and symptoms of sensitization reactions
- A hand washing study (Study No. CRI-00018704): This was an open-label, two-period crossover study in healthy adult male subjects comparing the amount of residual drug remaining on the hands after application of the product and a hand washing procedure between the Sponsor’s test product testosterone gel and AndroGel 1%.
- An interpersonal transfer study (Study No. M1FX10001): This was an open-label, single-dose, randomized, 4-period, 4-treatment crossover study that assessed the relative bioavailability of the new testosterone gel compared to AndroGel 1% in healthy female subjects following skin-to-skin contact as well as clothed contact with healthy male subjects who received a single topical dose.

Therefore, the only efficacy study in this NDA is study No. 70343. The other three studies (irritation/sensitization, hand washing and interpersonal transfer) are safety-related.

Study 70343 was a Phase 1, single dose, bioequivalence study, which constitutes the “pivotal BE study” for this application. The primary objective of this study was to compare the rate and extent of absorption of Teva’s testosterone gel 1% and Solvay’s AndroGel 1%, when applied as a single topical dose of 2 x 5 g packets of testosterone gel (each packet containing 50 mg of testosterone for a total of 100 mg of testosterone), under fasting conditions. This was a multi-center, randomized, single-dose, open-label, 2-way crossover bioequivalence study. A

total of 96 hypogonadal men signed the study-specific informed consent form; of these 96 subjects, 93 were enrolled and dosed in the study; 90 of these enrolled subjects completed the study. In each period, subjects reported to the Clinical facility in the morning of Day -1 and remained in the clinical unit until released by the Investigator subsequent to completing the 48-hour post-application blood sample draw. Prior to study commencement, subjects were randomly assigned to a treatment in accordance with the randomization scheme. The two treatments were separated by a washout period of 7 days.

In this study, two 5g packets of testosterone gel were applied (one packet applied on each shoulder and upper arm) to each hypogonadal subject. The dose (2 x 5 g packets of 1 % topical gel) was selected to provide measurable levels of study medication, and the sampling period was selected to allow good characterization of the concentration time profiles.

7.2 DEMOGRAPHICS

Demographics for the subjects who were included in the original pharmacokinetic analyses (n=77) are shown in the following table:

Table 1: Demographic Characteristics of Subjects Included In the Original Pharmacokinetic Analysis in Study 70343

Parameter	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m ²)
Mean±SD	47 ± 10	175.6 ± 5.6	88.5 ± 12.0	28.6 ± 3.2
Range	21 – 68	159.0 – 191.0	64.0 – 118.8	21.7 – 35.4
Median	47	175.5	88.4	28.6

Although the Sponsor did not provide new demographic summary statistics following exclusion of the 6 subjects requested for exclusion by OSI, the demographics in Table 1 adequately reflect the patients in this study.

7.3 DISPOSITION OF SUBJECTS

A total of 93 hypogonadal males were enrolled and received at least one dose of the study medication. A total of ninety (90) individuals completed both treatment periods. Subjects who either were withdrawn or withdrew from the study are shown in Table 2.

Table 2: Subjects Withdrawn from the Study

Subject No.	Reason for withdrawal	Period	Replaced?
04	pre-dose / was withdrawn due to difficulty with catheter insertion	Pre-dose	Yes
12	pre-dose /was withdrawn due to a high blood pressure	Pre-dose	Yes
23	elected to withdraw due to medication taken as treatment for AEs (pain at buttock left side and infected hematoma on left buttock)	1	No
42	was withdrawn due to positive urine drug screen results for benzodiazepines	1	No
91	was withdrawn since medication was found in baggage	1	No

Subjects number 04 and 12 were withdrawn pre-dose but eventually re-entered the study. Thus, only 3 subjects were withdrawn following randomization.

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

Routine pharmacokinetic parameters were assessed for this BE study: AUC_{0-t} , C_{max} and T_{max} for baseline uncorrected and baseline corrected serum testosterone concentrations.

Bioequivalence was determined using the baseline corrected, non-dose-normalized data. As per standard methodology, the 90% geometric confidence interval of the ratio (Test/Reference) of least-squares means from the ANOVA of the ln-transformed AUC_{0-t} , and C_{max} were calculated and were to be within 80% to 125%.

The baseline corrected data was defined as the primary efficacy data and the baseline uncorrected data as supportive data.

7.4.1.1 Primary Efficacy Analysis

Area under the concentration-time curve (AUC) was calculated for each subject and treatment. For the 72 patients included in the final pK analysis, the baseline-corrected serum testosterone concentration mean values (%CV) for AUC_{0-t} were 6590 ng•h/dL (52.65 %) for Teva's testosterone gel and 6114 ng•h/dL (44.53 %) for AndroGel 1%. The baseline-uncorrected serum testosterone concentration mean values (% CV) for AUC_{0-t} were 21821 ng h/dL (20.31 %) for Teva's testosterone gel and 21062 ng•h/mL (20.70 %) for AndroGel 1%.

The peak or maximal serum testosterone concentration (C_{max}) was calculated for each subject and treatment. For the 72 patients included in the final pK analysis, the baseline-corrected serum testosterone concentration mean values (% CV) for C_{max} were 383 ng/dL (64.77 %) for Teva's testosterone gel and 322 ng/dL (48.73 %) for AndroGel 1%. The baseline-uncorrected serum testosterone concentrations mean values for C_{max} were 641 ng/dL (39.54 %) for Teva's testosterone gel and 576 ng/dL (31.17 %) for AndroGel 1%.

The time to reach the peak serum testosterone concentration (T_{max}) was determined for each subject and treatment. For the 72 patients included in the final pK analysis, the baseline-corrected serum testosterone concentration mean (% CV) T_{max} values were 19.6 h (54.74 %) for Teva's testosterone gel and 19.2 h (54.89 %) for AndroGel 1%. The baseline-uncorrected serum testosterone concentrations mean (% CV) T_{max} values were 19.6 h (54.74 %) for Teva's testosterone gel and 19.2 h (54.89 %) for AndroGel 1%.

These data are summarized in the tables below:

Table 3: Summary of Results: Testosterone Baseline-Corrected Re-analysis Dataset Excluding 6 Subjects and Invalid Re-Assay Samples (N=72)

Pharmacokinetic Parameters		Test [Testosterone 2 x 5 g packet of 1% topical gel]			Reference [AndroGel 1%]		
		Mean	SD	CV(%)	Mean	SD	CV (%)
AUC_{0-t}	(ng•h/dL)	6590	3403	51.65	6114	2723	44.53
C_{max}	(ng/dL)	383	248	64.77	322	157	48.73
T_{max}	(h)	19.6	10.7	54.74	19.2	10.5	54.89

Table 4: Summary of Results: Testosterone Baseline-Uncorrected Re-analysis Dataset Excluding 6 Subjects and Invalid Re-Assay Samples (N=72)

Pharmacokinetic Parameters		Test [Testosterone 2 x 5 g packet of 1% topical gel]			Reference [AndroGel 1%]		
		Mean	SD	CV(%)	Mean	SD	CV (%)
AUC_{0-t}	(ng•h/dL)	21821	4432	20.31	21062	4359	20.70
C_{max}	(ng/dL)	641	253	39.54	576	180	31.17
T_{max}	(h)	19.6	10.7	54.74	19.2	10.5	54.89

These data are shown graphically in the figures below:

Figure 1: Baseline-Corrected Mean Serum Testosterone Concentration – Time Profile

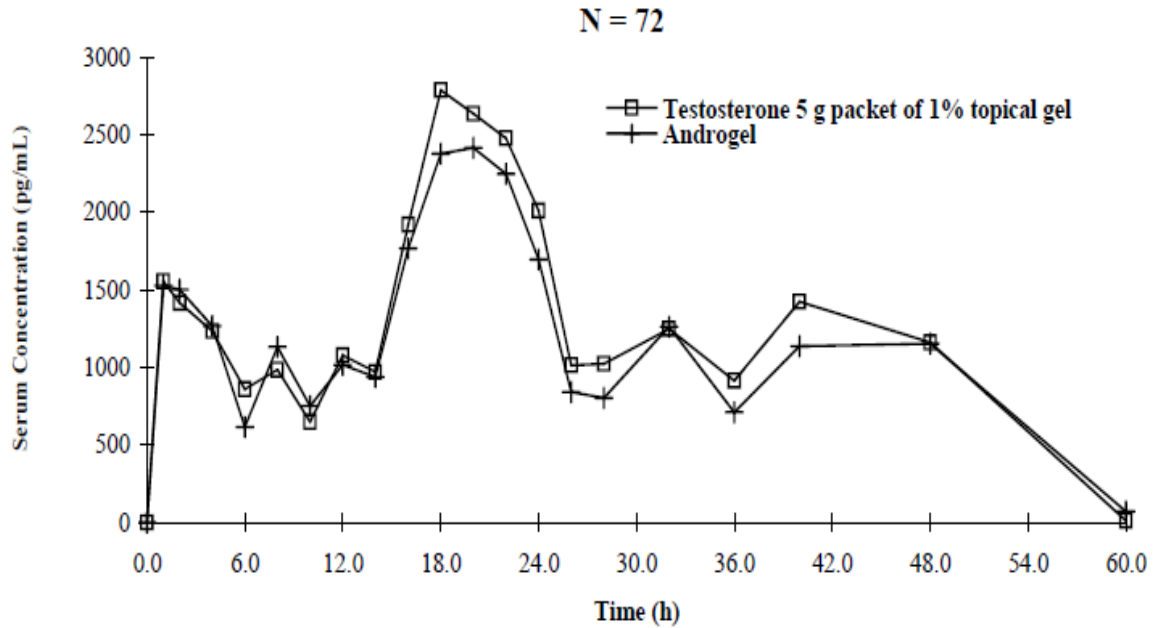
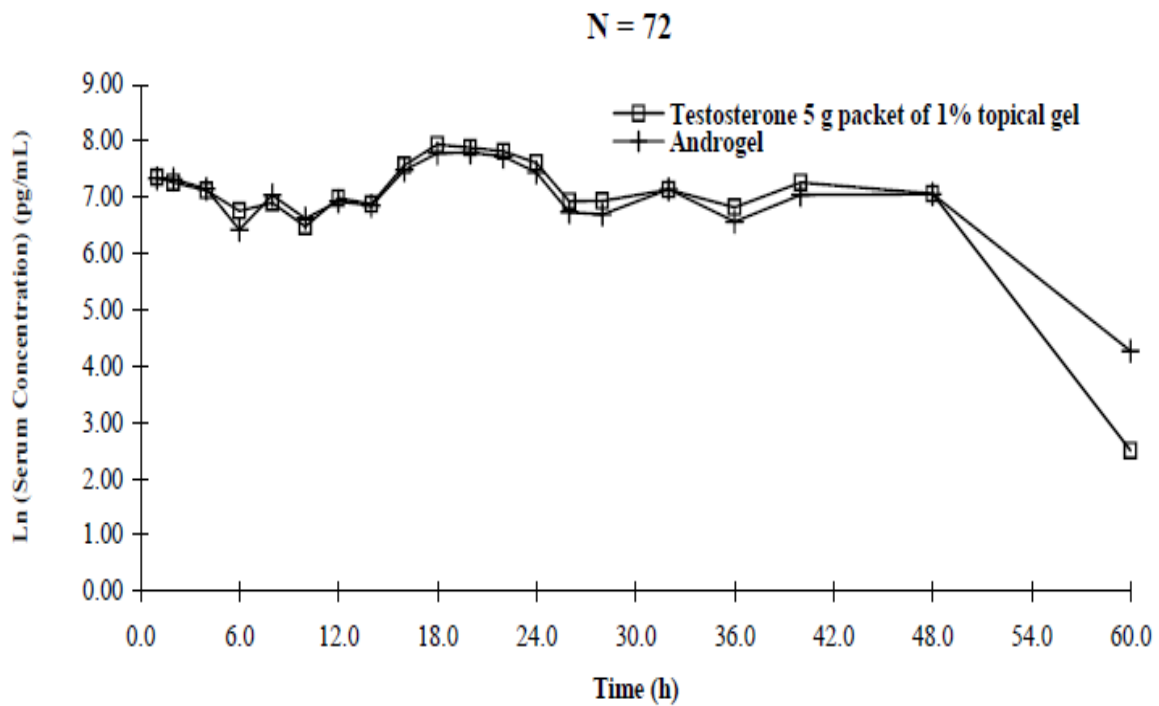


Figure 2: Baseline-Corrected, Ln-Transformed, Mean Serum Testosterone Concentration – Time Profile



The ratios of the AUC and $C_{\max}$ between Teva's testosterone gel and AndroGel 1%, and the 90% confidence interval for those ratios (bioequivalence comparisons) are shown in Table 5 below:

Table 5: Ratios for AUC and $C_{\max}$ for Teva's testosterone gel vs AndroGel 1% for the Baseline-Corrected Re-analysis Dataset Excluding 6 Subjects and Excluding Invalid Re-Assay Samples (N=72)

	AUC _{0-t}	$C_{\max}$
Ratio¹	105.28%	115.72%
90 % Geometric C.I.²	95.82% to 115.67%	105.95 % to 126.40 %
Intra-Subject CV	34.56%	32.29%

¹ Calculated using least-squares means according to the formula:

$$\frac{[\text{Testosterone 5 g packet of 1\% topical gel (A)} - \text{AndroGel (B)}]}{[\text{Testosterone 5 g packet of 1\% topical gel (A)} + \text{AndroGel (B)}]} \times 100.$$

² 90% Geometric Confidence Interval using In-transformed data.

Bioequivalence of AUC between Teva's T gel and AndroGel 1% was established. However, bioequivalence of $C_{\max}$ was not completely established, as the 90% CI for the difference between Teva's T gel and AndroGel 1% was 126.4%, minimally above the 125% criterion. This small difference poses no efficacy nor safety concerns. When assessed using baseline-uncorrected data, the products are bioequivalent for both parameters.

Statistician's Conclusion

In their final memo for this NDA, dated January 24, 2012, the Statistical Review team of Jia Guo and Mahboob Sobhan, stated the following:

"This submission contained information from a bioequivalence study, an irritation and sensitization study, a hand-washing study and a transfer study of testosterone gel 1% for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.

The efficacy evaluation was based on the bioequivalence study, for which the review was conducted by the clinical pharmacology reviewer. No further statistical review for efficacy was conducted by the statistical reviewer."

7.4.2 Overall Assessment of Efficacy

Teva's testosterone gel was shown to be bioequivalent for AUC compared to AndroGel 1% using the baseline-controlled serum testosterone concentrations (ratio 105.28% with 90% CI of 95.82%, 115.67%). For $C_{\max}$, the ratio was higher (115.72%) and the upper limit of the 90% CI just exceeded 125% (105.9%, 126.40%). However, this minor difference does not affect efficacy and there is no reason to conclude a safety concern. Therefore, the Clinical review team concludes that Teva's testosterone gel is sufficiently comparable to AndroGel 1% to support efficacy of the new product.

8. Safety

8.1 SAFETY FINDINGS

The safety data submitted in this NDA come from:

1. The single-dose bioequivalence study (Study No. 70343),
2. The 21-day, repeat-dose, cumulative irritation and sensitization study (Study No. 10936025),
3. An interpersonal transfer study (Study No. M1FX10001), and
4. A hand washing study (Study No. CRI-00018704).

Based on the finding of comparable exposure between Teva's testosterone gel and AndroGel 1%, the extensive safety experience with AndroGel 1% is also relevant to the review of this application.

8.1.1 Deaths, Serious Adverse Events and Discontinuations Due to Adverse Events

No deaths occurred in the 4 studies conducted for this NDA.

A total of 2 serious adverse events were reported in the 4 studies conducted for this NDA: both occurred as part of the contact irritation/sensitization study. One patient was hospitalized for an arm fracture during the washout period between active treatments. The other patient was hospitalized for syncope on Day 41. Both SAEs were judged by the investigator as being unrelated to study treatment.

Only 1 subject withdrew due to an adverse event in the 4 studies conducted for this NDA. This patient in the bioequivalence study fell on the sidewalk immediately before entering the clinical site for study confinement. The patient experienced a buttock hematoma which eventually became infected and which led to his withdrawal from the study.

8.1.2 Other Adverse Events

Overall Adverse Events

In the single-dose, "pivotal", bioequivalence study (Study No. 70343), a total of 208 treatment-emergent adverse events (TEAE) were reported by a total of 80 subjects. In the Teva treatment period, 59 of 93 subjects (63%) reported a TEAE, while in the AndroGel 1% period, 61 of 90 subjects (68%) reported a TEAE.

The most commonly reported TEAEs were related to study drug application site, with "Application site erythema" reported by 42% and 43% of subjects in the Teva and AndroGel 1% groups, respectively, and "Application site pruritus" reported by 9.7% and 7.8% of subjects in the Teva and AndroGel 1% groups, respectively. None of these application site TEAEs were significant and only one led to an abnormality on physical examination (one patient with superficial erythema and a pimple at the application site).

The only other TEAE reported by more than 4 patients in a treatment period was "blood pressure increased"; reported by 8.6% and 7.8% of subjects in the Teva and AndroGel 1%

groups, respectively. All TEAES of “blood pressure increased” were mild in severity, transient, and none led to a blood pressure outside the normal range in any case.

Table 6 below shows the overall adverse events in the bioequivalence study.

Table 6: Treatment Emergent Adverse Events in Study No. 70343

MedDRA; Preferred Term	A (Teva 1% T gel)	B (AndroGel)
Number of subjects dosed	93	90
Eye disorders	1 (1.1%)	
Conjunctivitis	1 (1.1%)	
Gastrointestinal disorders	2 (2.2%)	1 (1.1%)
Abdominal distension		1 (1.1%)
Diarrhoea		1 (1.1%)
Dyspepsia	1 (1.1%)	
Nausea		1 (1.1%)
Toothache	1 (1.1%)	
General disorders and administration site conditions	43 (46.2%)	45 (50.0%)
Application site erythema	39 (41.9%)	39 (43.3%)
Application site irritation	2 (2.2%)	
Application site papules	2 (2.2%)	1 (1.1%)
Application site pruritus	9 (9.7%)	7 (7.8%)
Application site reaction	2 (2.2%)	1 (1.1%)
Asthenia		1 (1.1%)
Energy increased		1 (1.1%)
Feeling cold	1 (1.1%)	
Peripheral coldness		1 (1.1%)
Pyrexia		1 (1.1%)
Infections and infestations	2 (2.2%)	1 (1.1%)
Folliculitis	1 (1.1%)	1 (1.1%)
Hematoma infection	1 (1.1%)	
Injury, poisoning and procedural complications	8 (8.6%)	11 (12.2%)
Post procedural complication	1 (1.1%)	
Post procedural discomfort	1 (1.1%)	1 (1.1%)
Post procedural hematoma	1 (1.1%)	4 (4.4%)
Post procedural swelling	2 (2.2%)	4 (4.4%)
Procedural pain	1 (1.1%)	4 (4.4%)
Procedural site reaction	3 (3.2%)	
Scratch	1 (1.1%)	1 (1.1%)
Skin laceration	1 (1.1%)	
Wound		1 (1.1%)
Investigations	9 (9.7%)	11 (12.2%)
Blood pressure increased	8 (8.6%)	7 (7.8%)
Gamma-glutamyltransferase increased		1 (1.1%)
Heart rate increased	1 (1.1%)	3 (3.3%)
Prostatic specific antigen increased		1 (1.1%)
Red blood cells urine positive		1 (1.1%)
Musculoskeletal and connective tissue disorders	3 (3.2%)	1 (1.1%)
Back pain	1 (1.1%)	
Muscle spasms		1 (1.1%)

Musculoskeletal pain	1 (1.1%)	
Pain in extremity	1 (1.1%)	
Nervous system disorders	3 (3.3%)	4(4.4%)
Dizziness		1 (1.1%)
Headache	2 (2.2%)	3 (3.3%)
Somnolence	1 (1.1%)	
Psychiatric disorders		1 (1.1%)
Nervousness		1 (1.1%)
Renal and urinary disorders	1 (1.1%)	1 (1.1%)
Pollakiuria	1 (1.1%)	1 (1.1%)
Reproductive system and breast disorders	1 (1.1%)	
Testicular pain	1 (1.1%)	
Respiratory, thoracic and mediastinal disorders	1 (1.1%)	3 (3.3%)
Cough		1 (1.1%)
Pharyngolaryngeal pain		2 (2.2%)
Respiratory tract irritation	1 (1.1%)	
Rhinorrhoea		2 (2.2%)
Skin and subcutaneous tissue disorders	10 (10.8%)	5 (5.6%)
Blister		1 (1.1%)
Dermatitis acneiform	1 (1.1%)	
Dry skin	2 (2.2%)	1 (1.1%)
Erythema	2 (2.2%)	1 (1.1%)
Pruritus	2 (2.2%)	
Rash	1 (1.1%)	
Rash papular		1 (1.1%)
Skin lesion	4 (4.3%)	1 (1.1%)
Total	59 (63.4%)	61 (67.8%)

In the 21-day cumulative irritation and sensitization study (Study No. 10936025), a total of 231 TEAEs were reported by a total of 110 (of 265 total) subjects. All but two of these TEAEs were mild in severity; the other two have been described previously.

Of the 231 TEAEs, a total of 71 TEAEs were classified as “localized” to the application of the test article, while a total of 160 were classified as “non-localized” TEAEs. The most frequently reported “localized” TEAE was “application site pruritis”; reported by equal numbers (n=8) of subjects in the Teva testosterone gel and AndroGel 1% groups. The most frequently reported “non-localized” TEAEs were: blood pressure increased, blood pressure decreased, headache, and “open wound”. All blood pressure changes were in a minor range and occurred variably during treatment.

Table 7 below shows all “non-localized” adverse events in the contact sensitization/irritation study.

Table 7: Non-Localized Adverse Events in Study No. 10936025

MedDRA SOC	MedDRA Preferred Term	N ¹ = 265	
		n ²	% ³
Gastrointestinal disorders	Abdominal pain upper	1	.38
Gastrointestinal disorders	Dyspepsia	1	.38

Gastrointestinal disorders	Nausea	1	.38
Gastrointestinal disorders	Stomach discomfort	2	.75
Gastrointestinal disorders	Vomiting	1	.38
General disorders & administration site conditions	Energy increased	2	.75
General disorders & administration site conditions	Inflammation	1	.38
General disorders & administration site conditions	Oedema peripheral	1	.38
General disorders & administration site conditions	Pain	1	.38
Injury, poisoning & procedural complications	Face injury	1	.38
Injury, poisoning & procedural complications	Open wound	14	5.28
Injury, poisoning & procedural complications	Scratch	1	.38
Injury, poisoning & procedural complications	Skin laceration	5	1.89
Injury, poisoning & procedural complications	Upper limb fracture	1	.38
Investigations	ALT increased	1	.38
Investigations	AST increased	2	.75
Investigations	Blood ALKP increased	1	.38
Investigations	Blood ALKP increased	1	.38
Investigations	Blood bilirubin increased	1	.38
Investigations	Blood glucose abnormal	4	1.51
Investigations	Blood glucose increased	3	1.13
Investigations	Blood pressure decreased	12	4.53
Investigations	Blood pressure increased	22	8.30
Investigations	Heart rate increased	1	.38
Musculoskeletal & connective tissue disorders	Arthralgia	1	.38
Musculoskeletal & connective tissue disorders	Musculoskeletal stiffness	1	.38
Musculoskeletal & connective tissue disorders	Pain in extremity	2	.75
Nervous system disorders	Dizziness	1	.38
Nervous system disorders	Headache	12	4.53
Nervous system disorders	Insomnia	1	.38
Psychiatric disorders	Anxiety	2	.75
Renal and urinary disorders	Pollakiuria	1	.38
Reproductive system & breast disorders	Spontaneous penile erection	1	.38
Respiratory, thoracic and mediastinal disorders	Nasal congestion	4	1.51
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	3	1.13
Respiratory, thoracic and mediastinal disorders	Sneezing	2	.75
Respiratory, thoracic and mediastinal disorders	Throat irritation	1	.38
Skin and subcutaneous tissue disorders	Acne	1	.38
Skin and subcutaneous tissue disorders	Ecchymosis	1	.38
Skin and subcutaneous tissue disorders	Erythema	1	.38
Skin and subcutaneous tissue disorders	Excoriation	4	1.51
Skin and subcutaneous tissue disorders	Pruritus	10	3.77
Skin and subcutaneous tissue disorders	Skin erosion	2	.75
Surgical and medical procedures	Wound drainage	1	.38
Vascular disorders	Hypotension	1	.38
Vascular disorders	Syncope	2	.75

¹ N = Total number of subjects dosed

² n = Number of subjects reporting adverse event

³ % calculated as (number of subjects reporting adverse event / Total number of subjects dosed) x 100

8.1.3 Special Safety Study Results

8.1.3.1 Contact Irritation/Sensitization Study

Study 10936025 was a multiple site, multiple-application, randomized, double-blind, two-phase study to evaluate the cumulative skin irritation and sensitization potential of two formulations of Teva's testosterone gel compared to AndroGel 1% and Testim, respectively, in healthy male subjects.

During the irritation/induction period, 0.1 mL of each gel (0.025 mL/cm² of gel - which is equivalent to 0.25 mg/cm² of testosterone) was applied on an area of 2 cm x 2 cm and replaced once daily to the same application sites for a total of 21 days. Each of the four gels was applied to application sites on the upper arm at least 1 cm away from each other. During the irritation/induction period, half of the subjects had the gels applied to the right arm and the other half to the left arm. After the gels had been applied and allowed to dry, the application sites were covered by a standard occlusive patch. On Day 22, the Day 21 applications were removed and no new product applied. Signs and symptoms of irritation were evaluated by trained, blinded, validated evaluators daily during the irritation/induction period. Standardized rating scales were utilized.

Following Day 22 removal and assessments, subjects underwent a 14 day washout period when no gels were applied. The subjects returned to the clinical facility on Day 36 where the gels were applied to complementary sites on the opposite arm used in the irritation/induction period. These applications were removed on Day 38 and the sites of application monitored over the next 72 hours for signs and symptoms of possible sensitization reactions using the same rating scales as for the induction/irritation period.

A scale of 0-7 was used to evaluate skin irritation (0 = no evidence of irritation, 7 = strong reaction spreading beyond test (i.e. application) site), based upon a previous FDA Guidance for conducting such studies. However, the Sponsor pointed out that this scale works well when mild irritation is present; however, if irritation is not present at all (e.g., scores of 0) it produces a skewed outcome. In this study, most irritation scores were 0 or 1. In order to resolve this issue, the analyses were conducted using a modified scale, where 1-8 is the same as 0-7. The original definitions of skin irritation remained the same (i.e., 1 = no evidence of irritation, 8 = strong reaction spreading beyond test site).

A total of 5,407 individual irritation assessments were made for each drug (n=4 test articles) in a total of 265 subjects during the irritation phase. No applications were halted because of excessive irritation for any subject for any study drug. The percentages of individual observations that had an unadjusted score > 1 (minimal erythema, barely perceptible) were 2.3% for Teva's testosterone gel and 2.1% for AndroGel 1%. The adjusted mean cumulative total irritation score are shown in Table 8 below:

Table 8: Mean Cumulative Total Irritation Scores (Sum of Irritation + “Other Effects” Scores on Days 1 through 22) Using the Adjusted Irritation Scale of 1–8.

	Product*	N	Mean (SD)	Min.	Median	Max.
Mean Total Irritation Score Day 1 through Day 22	A	233	23.79 (4.12)	22.00	22.00	51.00
	C	233	23.72 (4.39)	22.00	22.00	50.00

* **Test Formulation A:** 0.1 ml of testosterone 1% topical gel (Manufactured by Cipla Ltd. (Goa) India for TEVA Pharmaceuticals USA).

* **Reference Formulation C:** 0.1 ml of AndroGel® (testosterone gel) 1% (Manufactured by Laboratories Besins International for Unimed Pharmaceuticals, LLC [Unimed]).

Comparative analyses were conducted demonstrating that Teva’s testosterone gel was statistically non-inferior to AndroGel 1% for cumulative total irritation.

In regard to testing for hypersensitivity reaction, if at either the 48 hour or 72 hour post removal evaluation on Day 38, the scoring of total irritation (irritation + “other effects” scores) was greater than 1 and was greater than a maximum single daily score observed during the irritation/induction phase of the study for that subject then the subject was considered to have demonstrated a potential sensitization response to that specific product(s). No cases of sensitization were observed for any of the four products tested.

8.1.3.2 Interpersonal Transfer Study

Study No. M1FX10001 was an open-label, single-dose, randomized, 4-period, crossover study comparing the transfer potential of Teva’s testosterone gel to AndroGel 1% from a male subject to a female subject.

Female subjects reported to the clinic on Day -2, at least 48 hours prior to dosing of male subjects. Females stayed for 26 hours after dosing of the male subject (and subsequent “transfer procedure”). Male subjects reported to the clinical site on Day -1 at least 10 hours prior to dosing (and subsequent “transfer procedure”). Males stayed for at least 4 hours after dosing. Male subjects were unclothed from the waist up (without T-shirts) in treatment periods A (Teva testosterone gel) and C (AndroGel 1%). In treatment periods B (Teva testosterone gel) and D (AndroGel 1%), males wore a 100% cotton long-sleeved T-shirt. Starting at 2 hours after dosing, each couple was to engage in total of 15 minutes of close physical contact in a vertical position. Blood sample collections were obtained on Day -1 from female subjects at pre-dose, 2, 4, 6, 8, 10, 12, 16 and 24 hours. These sampling times were relative to the time of the “transfer procedure” conducted on Day 1. On Day 1, blood samples were collected from females subjects within 10 minutes prior to dose transfer (0 hour) and after dose transfer at 2, 4, 6, 8, 10, 12, 16 and 24 hours.

The key comparison in this study was testosterone systemic exposure in women who had physical contact with men using Teva’s testosterone gel without a T-shirt (Treatment Period A) compared to men using Teva’s product with a T-shirt (Treatment Period B). Comparisons were also made for AndroGel 1% with and without a T-shirt, as well as between Teva testosterone gel and AndroGel 1%.

The results of this study demonstrated that in men without T-shirts, both products did “transfer” to females (n=47 couples). For Teva’s testosterone gel, AUC increased almost 200%, and C_{max} increased by 272%.

However, the results confirmed that T-shirts substantially mitigated transfer. In women who had 15 minutes of close physical contact with men wearing a T-shirt and using Teva’s testosterone gel (n=45 couples), AUC increased by approximately 11%, and C_{max} increased by 15.5%.

These data are shown in Table 9:

Table 9: Teva’s Testosterone Gel - % Difference of Testosterone C_{max} and AUC_{0-t} Pre-Transfer vs. Post-Transfer - With and Without T-Shirts

Parameter (Mean±SD)	Without T-Shirt (N = 47)			With T-Shirt (N = 43)		
	24-hr Pre- Transfer	24-hr Post- Transfer	% Difference	24-hr Pre- Transfer	24-hr Post- Transfer	% Difference
C _{max} (ng/dL)	27.4±18	102±86	+272	24.5±17	28.3±16	+15.5
AUC _{0-t} (ng•h/dL)	462±184	1378±984	+198	478±275	530±322	+10.8

Similar results were observed with AndroGel 1%, such that no significant differences were observed between interpersonal transferability potential with Teva’s testosterone gel and AndroGel 1% when the male user is wearing a T-shirt.

8.1.3.3 Handwashing Study

Study No. CRI-00018704 was a study to evaluate the residual amount of testosterone on normal skin of the hand, in healthy adult male subjects following hand washing.

This was an open-label, two-period, crossover, study that compared the amount of the residual drug product remaining on the hands between Teva’s testosterone gel and AndroGel 1% following a hand-washing procedure. On study days 1 (Period I) and 15 (Period II), subjects entered the clinic, had their hands washed and wiped each with three ethanol dampened gauze (blank control sample). Subsequently, each subject had 10 g of testosterone gel (2 x 5 g doses, totaling 100 mg testosterone) applied to their dominate hand. The subject distributed each 5 g dose to areas of the upper arm and posterior and anterior shoulder. The subjects were then required to follow a hand washing procedure, as follows:

- The subjects wet their hands with warm tap water (35°C ± 5°C) for 10 seconds.
- 2 mL of liquid soap was dispensed to the hands (same brand of soap was used throughout the study)
- Subjects washed their hands with a controlled hand scrubbing procedure for 20 seconds
- Subjects rinsed their hands with warm tap water for 20 seconds
- Subjects dried their hands with a dry cotton towel for 30 seconds

The subjects performed this hand-washing procedure following the application of both products. Each dosing was separated by a 14 day washout period. Following the hand wash, the subjects’ hands were wiped with three ethanol dampened gauze per hand, the palm, fingers, and back of each hand were wiped with gauze (2” x 2”) dampened with approximately

2 mL of ethanol (1 to palm, 1 to fingers, and 1 to back of hand) to collect any residual testosterone left on the skin surface. The samples taken following the hand-washing procedure were evaluated for testosterone content.

The results of this study, conducted in 48 subjects, demonstrated that a total of 285 µg and 287 µg (<0.3 mg) of testosterone remained on the hands following application of Teva's testosterone gel and AndroGel 1%, respectively. Teva's testosterone gel was found to be statistically non-inferior to AndroGel 1%. These results demonstrate that very little testosterone is left on the hands after application of both Teva's testosterone gel and AndroGel 1% to the application sites and hand-washing.

8.1.4 Overall Assessment of Safety Findings

Based on the results of the single-dose bioequivalence study, the 21-day irritation/delayed contact sensitization study, the interpersonal transferability study, and the handwashing study, Teva's testosterone gel demonstrated acceptable safety.

The bioequivalence study demonstrated an acceptable level of exposure comparability. The irritation/sensitization study demonstrated little, if any, evidence of cumulative irritation potential and no hypersensitivity reactions were observed. The interpersonal transfer study demonstrated that a T-shirt effectively mitigated interpersonal transfer from the application sites of male users to female partners. The handwashing study demonstrated very little testosterone remaining on the hands following application of the gel and handwashing. There were no unexpected adverse events observed in these 4 studies. The extensive experience with AndroGel 1% is relevant to Teva's testosterone gel and provides robust support for safety.

Additionally, labeling has been successfully negotiated with Sponsor, including the package insert, the Medication Guide and the container/carton labeling. The Division of Medication Errors Prevention and Analysis has deemed the labeling acceptable, including the established name, testosterone gel. The REMS associated with the Medication Guide is also acceptable.

Finally, the Sponsor has agreed to conduct an application site washing study as a postmarketing requirement in order to determine the amount of residual testosterone on the skin of the application site, and the wash-off percentage, following washing of the application sites.

9. Advisory Committee Meeting

An Advisory Committee was not held for this application.

10. Pediatrics

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

11. Other Relevant Regulatory Issues

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

A consultation regarding labeling for the new indication was requested and completed by OPDP. In their final consult report dated January 30, 2011, Janice Maniwang and Jina Kwak provided comments on various sections of the label, including Highlights, Indications and Usage, Dosage and Administration (D &A), Contraindications, Warnings & Precautions, Adverse Reactions, Use in Specific Populations, and Clinical Pharmacology. The OPDP team also provided several comments on the Medication Guide.

All the OPDP comments and recommendations were carefully considered. Some were addressed through internal discussions amongst the primary review team and through successful negotiations with Sponsor. Several DDMAC recommendations were not taken, based on the differing overall recommendations made by the other review team members. For example:

- In the Highlights section, OPDP recommended that DRUP consider adding the (b) (4) (b) (4). This issue had been discussed at length amongst Clinical, Clinical Pharmacology, ONDQA, and DMEPA, resulting in a decision not to present the (b) (4) (b) (4) but rather present the dosage in terms of mg of testosterone per sachet.
- In the Dosage and Administration (D &A) section, OPDP noted that the male figure showing the proper application sites could overstate the efficacy of the product through “defined biceps and pectoral muscles”. It was decided to leave the figure as is, based upon its previous use in the AndroGel 1% label, and its utility in patient instructions for safe use.
- In the Dosage and Administration (D &A) section, OPDP asked whether the label should state to (b) (4). These items could not be clarified for the Teva labeling, as the labeling for this 505(b)(2) application was derived from AndroGel 1% and these stipulations were not part of the clinical studies nor labeling for that product.
- In the Contraindications section, OPDP asked whether it was appropriate to (b) (4). It was decided not to include this statement as it is theoretical without evidence of hypersensitivity in clinical studies nor in clinical practice, and we were therefore advised by SEALD not to include this statement in Contraindications.
- In the Warnings & Precautions section, OPDP asked DRUP to consider adding specific times for assessing prostate specific antigen, rather than the current statement regarding evaluation of patients for prostate cancer before and during treatment. It was decided to keep the statement as is, lacking specific data to support specific PSA testing times.
- In the Clinical Pharmacology section, OPDP recommended to remove a sentence regarding the signs and symptoms of male hypogonadism. This sentence was deemed important for appropriate product use and it was retained.

- In the MedGuide, OPDP asked whether the new “Limitation of Use” should be added to the MedGuide. This issue was discussed amongst the entire review team who believed that current statements in the MedGuide were sufficient to guide patients (e.g., use only the doses and instructions prescribed by your physician, etc).

Office of Scientific Investigation (OSI)

At the request of the Division of Pharmacology 3, OSI audited the clinical and analytical portions of the bioequivalence study 70343.

The clinical portion of the study was conducted at three sites: (b) (4). The analytical portion of the study was conducted at (b) (4). While arranging times and dates for inspections, it became clear that both the (b) (4) sites were closed; thus, all materials related to the clinical assessment were transferred to (b) (4) where audit of the analytical portion was also conducted.

The final OSI memorandum, by Sripal Mada and Martin Yau, dated July 1, 2011, concluded:

- *“Runs #58PQM and 71PQM containing plasma samples data for subjects # 60, 61, 62, 92, 93 and 94, and Run #74PQM containing plasma sample data after repeat analysis is not assured. DBGC (Division of Bioequivalence and GLP Compliance) recommends that the data from subjects # 60, 61, 62, 92, 93 and 94, and the re-assayed samples in Run #74PQM be excluded from the final BE evaluation.*
- (b) (4) *should re-process all the chromatograms for both validation and subjects samples using integration parameters established in the method SOP.*
- *The data in the clinical portion are acceptable for your review.”*

Based on the results of the OSI inspections, conducted from June 6 to June 21, 2011, Form-483 was issued. The key issues noted in the Form-483 that led to the DSI conclusions were:

1. *Re: Runs #58PQM and #71PQM:* The DSI evaluation described a technician who was not properly trained. Training records indicated that this technician could not handle pipettes properly. Runs #58PQM and #74PQM (production runs) were affected by this technician’s practice
2. *Re: Re-processing all the chromatograms:* The OSI evaluation noted that technical writers who did not work in the bioanalytical laboratory were given inappropriate permission to edit chromatograms in the lab’s Analyst software. In addition, there was a common access procedure to access the computer workstation and Analyst software. OSI noted that integration parameters for many chromatograms in validation and analytical runs were modified and the reasons for these modifications were not documented nor captured in the audit trail. Therefore, OSI recommended that all chromatograms generated during method validation and production runs be re-processed.

Following receipt of the Sponsor's responses to the Form-483 deficiencies, Sripal Mada and Martin Yau completed another memo, dated July 30, 2011. In that final memo, the OSI concluded:

"Following our evaluation of (b) (4) response to the Form FDA-483, DBGC's recommendation to DRUP in our July 1, 2011, EIR review remains unchanged".

Therefore, based on the OSI recommendation, DRUP asked Sponsor to exclude the data from subjects # 60, 61, 62, 92, 93 and 94 and any data generated for the re-analyzed samples in Run #74PQM. The Sponsor complied with this request and submitted a revised report on September 15, 2011, and an improved, substantially revised report on November 3, 2011.

Financial Disclosure

Financial disclosures were submitted for the investigators in the pivotal BE study 70343. A total of 11 investigators provided disclosures and none had any relevant financial disclosure information to declare. There was no missing financial disclosure information for investigators in the studies noted.

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

The Division of Risk Management (DRISK) provided a consultation regarding the Sponsor's proposed Risk Evaluation and Mitigation Strategy (REMS). On January 31, 2012, Robert Shibuya and Claudia Karwoski of DRISK provided their final consult, concluding:

"DRISK reviewed the topical Testosterone Gel 1% proposed REMS and finds it acceptable with minor revisions. The detail of the distribution of the Medication Guide is more appropriate for the REMS Supporting Document."

A revised REMS document, showing annotated changes, was provided to DRUP and subsequently conveyed to Sponsor. Sponsor accepted all FDA-recommended changes.

In addition to providing the Sponsor with edits to the REMS, DRISK also provided Sponsor with 20 comments relevant to a future REMS Assessment Plan

Office of Medical Policy Initiatives/ Division of Medical Policy programs (DMPP)

On January 20, 2012, Shawna Hutchins, Melissa Hulett and LaShawn Griffiths of DMPP provided a final consult regarding the Sponsor's proposed Medication Guide. DMPP concluded:

"The MG is acceptable with our recommended edits."

DMPP pointed out that their review of the Medication Guide was based on the "substantially complete" PI that was forwarded to them on January 20, 2012. DRISK provided a number of edits to the Medication Guide, most of which were intended to update the document to be consistent with the most recent Medication Guide used by other topical testosterone products. All edits were conveyed to Sponsor, and all were ultimately agreed upon by Sponsor.

Office of Surveillance and Epidemiology: Division of Medication Error Prevention and Analysis (DMEPA)

On November 3, 2011, Jibril Abdus-Samad, Todd Bridges and Carol Holquist from DMEPA provided a final review of the carton/container labeling, the PI and the Medication Guide from the Medications Errors perspective.

The DMEPA reviewer noted that the Agency has previously revised the strength presentation of topical testosterone products from percentage strength (e.g., 1%) to milligrams of testosterone per packet (b) (4). This was done because medication errors had been reported due to health care practitioners believing that 1% strength of one product was equivalent to 1% strength of another product. DMEPA stated that using milligrams of testosterone per packet (b) (4) allows the prescriber to communicate the dose based on the strength presentation.

DMEPA also described several medication error reports that they had retrieved from AERS for already approved testosterone gel products which may reflect: secondary exposure to testosterone (n=7), prescribing error (n=3), wrong site of administration (n=2) and accidental exposure in eye (n=1). Of the 7 reports of secondary exposure, one was already known to DRUP, one was compounded estrogen and testosterone cream, one lacked any details, and two were identical (describing twins). The review of these cases is ongoing. In the three prescribing error cases, all were told by their physicians to apply the drug to their chests. One person applied testosterone gel to his face for poison ivy and one person applied Testim to his abdomen, instead of to his arms/shoulders only.

For this application, DMEPA advised:

- Strength presentation should be milligrams of testosterone per packet.
- The labeling should clearly state that testosterone products are not interchangeable with one another.

DMEPA stated that they had considered different methods for preventing inappropriate interchange of topical testosterone products. They stated:

“Different proprietary names for topical testosterone provides some distinction between these products, however the proprietary name does not inform the user of the differences between these products and the lack of interchangeability. Therefore, labeling topical testosterone products with the revised strength presentation (milligrams of testosterone per packet (b) (4)) and highlighting these products are not interchangeable should minimize the risk of inappropriate product exchange. Additionally, the topical testosterone products must comply with the required Medication Guide to provide further instruction for patients and caregivers”

Therefore, DMEPA’s recommendations were accepted in full by DRUP, and we conveyed those to Sponsor in revised PI and MedGuide and container/carton labeling.

- The (b) (4) (b) (4) was deleted and replaced with milligrams of testosterone per packet, and

- A new “Limitations of Use” was added to the Indications and Use section stating, *“Topical testosterone products may have different doses, strengths, or application instructions that may result in different exposure.”*
- The Patient Counseling section of the PI states: *“Testosterone gel should be used only in the prescribed doses and application instructions.”*
- The MedGuide states: *“It is important that you apply testosterone gel exactly as prescribed by your healthcare provider. Your healthcare provider will tell you how much testosterone gel to apply and when to apply it.”*

It is important for the reader to be aware that Teva Pharmaceuticals did not propose a tradename for this product, (b) (4). The established name of the product is “testosterone gel”. This was discussed with all disciplines on the review team. At the NDA mid-cycle meeting on June 13, 2012, and again at the NDA “wrap-up” meeting on September 15, 2011, DMEPA advised that the lack of a tradename was acceptable and safe based on the clarifying statements in labeling that DMEPA had recommended are incorporated into final labeling.

On January 19, 2012, a large group meeting was held to discuss the issue of lack of tradename. DMEPA again recommended that a proprietary name itself would not preclude drug errors, nor would adding the modifier “1%” to the established name. DMEPA continued to advise their previous labeling recommendations, which had already been incorporated into labeling, as the best means to avoid medication errors. We were also notified that from a regulatory perspective, there was no means to compel Sponsor to select a proprietary name. Therefore, with this in mind, the large group review team agreed that the name “testosterone gel” was acceptable, when coupled with DMEPA’s labeling recommendations, which were instituted.

On February 8, 2012, DMEPA conveyed an eMAIL accepting the final container and carton labeling. On February 9, 2012, DMEPA accepted the final PI and Medication Guide with very minor edits which Sponsor accepted.

Office of Compliance

On January 13, 2012, the Office of Compliance provided an “Acceptable” recommendation via EES.

Controlled Substances Staff (CSS)

In their final review of the original NDA, dated September 14, 2011, James Tolliver, Silvia Calderon and Michael Klein of CSS confirmed that AndroGel 1.62% is in Schedule III of the Controlled Substances Act (not the Anabolic Steroids Control Act). CSS also provided specific recommendations for revisions to Section 9 of the proposed label (Drug Abuse and Dependence). The revisions include information that anabolic steroids, such as testosterone, are abused. CSS stated that while drug dependence has not been documented in individuals using therapeutic doses for approved indications, dependence has been observed in some individuals using high doses of anabolic steroids.

The labeling recommendations from CSS were conveyed to Sponsor during the labeling negotiations and all CSS recommendations were implemented.

12. Labeling

Labeling discussions were commenced towards the latter part of the review cycle and were successful in producing a Package Insert and Medication Guide acceptable to all members of the FDA review team and the Sponsor. The final container and carton labeling were also found acceptable by DMEPA and ONDQA.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that this new drug application be Approved.

13.2 Risk Benefit Assessment

The risk/benefit assessment for Teva's testosterone gel is consistent with all previously approved topical testosterone products.

In terms of *efficacy*, Teva's testosterone gel was shown to be bioequivalent for AUC compared to AndroGel 1% using the baseline-controlled serum testosterone concentrations (ratio 105.28% with 90% CI of 95.82%, 115.67%). For C_{max} , the ratio was higher (115.72%) and the upper limit of the 90% CI just exceeded 125% (105.9%, 126.40%). However, this minor difference does not affect efficacy and there is no reason to conclude a safety concern. Therefore, the Clinical review team concludes that Teva's testosterone gel is sufficiently comparable to AndroGel 1% to support efficacy of the new product.

In terms of key *safety* issues, these are also all consistent with previously approved topical testosterone products. There was no evidence of chronic irritation and no sensitization reactions were observed. A T-shirt effectively mitigates secondary exposure to testosterone from a primary user. Hand-washing largely removes the product from the user's hands after application of the gel.

In regard to general safety issues, the comparable exposure is taken to mean that the adverse reactions for Teva's testosterone gel are the same as AndroGel 1%, and reflect well-known testosterone-related pharmacological adverse effects.

Finally, the labeling has been successfully negotiated with Sponsor, including the package insert, the Medication Guide and container/carton labeling. Despite the lack of a proprietary name, the labeling makes it clear that testosterone products have different doses, application instructions and exposures. Further, (b) (4) replacement with milligrams of testosterone was advised by DMEPA and is expected to improve compliance. The REMS, which pertains to the potential risk of secondary exposure to children and women, is acceptable.

13.3 Recommendation for Postmarketing Risk Management Activities

All postmarketing risk management requirements and activities that apply to the currently approved testosterone gels also apply to Teva's testosterone gel. The Sponsor will conduct appropriate REMS Assessments.

13.4 Recommendation for other Postmarketing Study Commitments

The Sponsor has committed to conduct an application site-washing study as a postmarketing requirement. The study will assess the amount of testosterone remaining on a user's application site before and after washing. The Sponsor has committed to specific dates to submit the final study protocol, to complete the study, and to submit a final study report.

13.5 Recommended Comments to Applicant

There are no additional comments for Sponsor at this time.

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/s/

MARK S HIRSCH
02/10/2012

AUDREY L GASSMAN
02/10/2012