CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202763Orig1s000

SUMMARY REVIEW

Acting Deputy Division Director Summary Review

Date	February 14, 2012
From	Audrey Gassman, MD
NDA #	202763
Applicant name	Teva Pharmaceuticals USA
Date of receipt of original submission	January 14, 2011
Date of receipt of major amendment	September 14, 2011
PDUFA goal date (extended after submission of a major amendment)	February 14, 2012
Proprietary name/established name	None/Testosterone
Dosage Form/strength	Gel/50 mg, (b) (6) mg testosterone applied once daily
Proposed Indication	(b) (4)
Action	Approval

Material reviewed/consulted	Names of discipline reviewers
CDTL Review	Mark Hirsch, MD
Medical Officer Review	Guodong Fang, MD
Statistical Review	Jia Guo, PhD Mahboob Sobhan, PhD
Pharmacology/toxicology Review	Jeffrey Bray, PhD Lynnda Reid, PhD
Clinical Pharmacology Review	Chongwoo Yu, PhD LaiMing Lee, PhD
ONDQA Review	Zhengfang Ge, PhD Moo Jhong Rhee, PhD
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Controlled Substance Staff	James Tolliver, PhD Silvia Calderon, PhD Michael Klein, PhD
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OSI	Sripal Mada, PhD Martin Yau, PhD
SEALD	Jeannie Delasko, RN, MS Laurie Burke RPh, MPH

CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
DMEPA=Division of Medication Error Prevention and Analysis
ONDQA – Office of new Drug Quality Assessment
DMPP=Division of Medical Policy Programs
OPDP= Office of Prescription Drug Promotion
DRISK=Division of Risk Management
OSI=Office of Scientific Investigations
SEALD = Study Endpoints and Labeling Development Team

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1. Introduction

Teva Pharmaceuticals submitted an NDA (202-763) containing a proposed new testosterone transdermal product containing testosterone in a hydroalcoholic gel base for topical application. The indication for this new testosterone gel formulation is testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone including both primary hypogonadism and hypogonadotropic hypogonadism. The goal of this testosterone therapy is to replace testosterone at serum levels within the normal physiologic range.

Multiple testosterone formulations have been previously approved for testosterone replacement therapy. including patches, transdermal gels, a transdermal solution, a buccal tablet and parenteral injections. Teva's testosterone product will be supplied in 2.5 gram and 5 gram sachets. The recommended starting dose of testosterone gel is 5 g once daily (preferably in the morning) to clean, dry, intact skin of the shoulders and upper arms and/or abdomen.

The transfer of topically applied testosterone gel products from patients to others (particularly children) has been recognized as a significant safety concern. This transfer issue was discussed at a Pediatric Advisory Committee meeting held on June 23, 2009. Currently, all topically applied testosterone products have been required to have a Boxed Warning, a Medication Guide, and a Risk Evaluation and Mitigation Strategy [REMS] to address this safety concern related to transfer. As this testosterone product is a topically applied testosterone, a Boxed Warning, a REMS, and a Medication Guide will be required as part of Approval to address the safety issue of interpersonal transfer.

The main objective of this NDA was to demonstrate bioequivalence of the proposed product to a reference listed drug (AndroGel 1%, hereafter referred to as AndroGel), and to demonstrate acceptable safety in the special safety studies required by FDA.

2. Background

Teva Pharmaceuticals USA submitted an original ANDA (b) (4) for the product (testosterone gel) to the Office of Generic Drug (OGD) on December 29, 2008, and received a Refuse to Receive Letter dated April 7, 2009, from the Agency, based on the fact that the formulation of the product contained a different ingredient than those contained in reference listed drug (RLD), (b) (4)

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The Applicant (b) (4) 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) new drug application (NDA) to the Division of Reproductive and Urologic Products (DRUP). No IND application or any pre-NDA communication with DRUP occurred prior to the Applicant submitting the NDA application.

NDA 202-763 was received on January 13, 2011, and contained four clinical studies. The bioequivalence study (70343) was reviewed as the pivotal efficacy study comparing bioavailability of the proposed testosterone product to an RLD product (AndroGel 1%). The other three studies were considered supportive safety studies and included the clinical studies outlined in the 2009 Refuse-to-File letter including: 1) A handwashing study (CRI-00018704), 2) A transferability study (M1FX10001), and; 3) A skin irritation and sensitization study (10936025).

On September 14, 2011, an amendment containing a new clinical and statistical report for the bioequivalence study (Study 70343) was received. The reason for this amendment is outlined in Section 11 of this review. After review of the amendment, it was determined that this submission constituted a major amendment to the application and the user fee goal date was extended to February 14, 2012.

3. ONDQA

The Applicant's proposed testosterone gel contains 1% testosterone. The inactive ingredients are: (b) (4) dehydrated alcohol 67% (b) (4) isopropyl palmitate (b) (4) sodium hydroxide (b) (4) and purified water (b) (4) The Applicant will supply the product as unit-dose sachets 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 Biopharmaceutics review team assessed the submission and concluded in their review dated September 11, 2011, that, "A Biopharmaceutics Review for NDA 202-763 is deemed unnecessary."

The Chemistry Review (ONDQA) 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.

In an addendum to the December, 2011, ONDQA review, finalized on February 9, 2012, the ONDQA review team stated that, "This NDA is now recommended for approval from the ONDQA perspective."

Comments:

1. *I concur with the recommendations of the ONDQA review team that there are no outstanding CMC issues.*
2. *The strength of the product was original expressed as testosterone gel 1%; however, to be consistent with recently marketed testosterone products, ONDQA, The Division of Medication Errors Prevention and Analysis (DMEPA) and the clinical team agreed that the strength should be expressed as 25 mg and 50 mg*

testosterone per packet. Labeling and carton/container changes were implemented to reflect this recommendation.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology review team stated in their review dated September 30, 2011, that "Nonclinical data supports Approval of testosterone gel 1% for testosterone replacement in hypogonadal men."

Comment: I concur with the recommendations of the pharmacology/toxicology review team. There are no outstanding pharmacology/toxicology issues.

5. Clinical Pharmacology

The Clinical Pharmacology review team evaluated three of the four submitted studies (Bioequivalence Study 70343, Study CRL-00018704 and Study M1FX10001). The Clinical Pharmacology reviewer stated that these studies were evaluated because they had relevant clinical pharmacology data. The Clinical Pharmacology reviewer concluded that the Applicant had successfully demonstrated comparable bioavailability of testosterone between the proposed testosterone gel product and the RLD product (AndroGel 1%) in Study 70343. The other two safety studies containing data on hand-washing (CRL-00018704) and transfer potential (M1FX10001) were also reviewed and no new safety signals were identified by the Clinical Pharmacology review team. Additional comments on the Clinical Pharmacology data are also included in Section 7 of this review.

Clinical Pharmacology made the following recommendation in their review dated January 19, 2012: "The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) reviewed NDA 202763 ……...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 Clinical Pharmacology team subsequently outlined the postmarketing requirement (PMR) 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."

The proposed PMR recommended by the Clinical Pharmacology team was conveyed to the Applicant on January 12, 2012. The Applicant provided concurrence with the PMR and provided PMR milestones on January 12, 2012.

In an Addendum to their January 19, 2012 review, finalized on February 9, 2012, the Clinical Pharmacology team stated that, "The DCP3, OCP finds NDA 202763 acceptable from the Clinical Pharmacology perspective."

Comment: I concur with the recommendations of the clinical pharmacology review team. There are no outstanding clinical pharmacology issues.

6. Clinical Microbiology

Microbiology consult was not requested by ONDQA. Outstanding issues related to microbiology were addressed in the ONDQA review (See ONDQA review dated December 14, 2011).

7. Efficacy/Statistics

The principal study to support the efficacy of the Applicant's proposed testosterone gel product that was submitted to the NDA is Study 70343. Because the Applicant demonstrated comparable exposure of their product to the approved comparator (AndroGel), efficacy for the Applicant's testosterone product could be bridged to the efficacy data for AndroGel. The other submitted studies (irritation/sensitization, hand washing and interpersonal transfer) were considered safety-related and are briefly outlined in section 8 of this review.

Bioequivalence Study 70343:

The "pivotal study" reviewed to determine efficacy of this testosterone gel was bioequivalence Study 70343. The objective of Study 70343 was to compare the rate and extent of absorption of the Applicant's testosterone product to a currently approved testosterone product (AndroGel) when applied as a single topical dose of 2 x 5 gram packets of testosterone gel (each packet corresponding to 50 mg testosterone for a total dose of 100 mg), under fasting conditions. Study 70343 was a multi-center, randomized, single-dose, open-label, two-way crossover bioequivalence study. A total of 93 hypogonadal male subjects were enrolled and dosed in the study; 90 of these enrolled subjects completed the study. The trial was performed at three sites in Canada, with a fourth satellite site used for screening and/or return visits for some of the subjects in this study.

A single topical dose of testosterone as 2 x 5 gram packets of either the Applicant's testosterone gel or an approved testosterone product was administered in each study period. The treatment phases were separated by a washout period of 7 days. Blood samples were collected prior to drug application, immediately before drug application, and post-dose in each treatment period. The efficacy evaluation included the following pharmacokinetic parameters: AUC0-t, Cmax and Tmax for baseline uncorrected and baseline corrected testosterone. Adverse events, vital sign measurements, physical examination and laboratory evaluations were also collected and analyzed as safety parameters.

Demographics:

The study population included hypogonadal men who were 18 years of age or older and were in compliance with the inclusion and exclusion criteria described in the protocol. The demographics and baseline characteristics for the 77 subjects who were included in the pharmacokinetic analysis (based on the Applicant's submission dated September 8, 2011) are outlined in the table below.

Table 1* Demographics for the Subjects Included in the Pharmacokinetic Analyses (n=77):

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

*Table 1 obtained from Table 6.6 from the Medical Officer's review dated January 26, 2012

Comment: The Medical Officer stated that the descriptive statistics above were included in the pharmacokinetic re-analysis submitted on September 8, 2011, but was not recalculated after exclusion of the additional six subjects that were requested by the Division. Recalculation of the above demographic table was not necessary because there were no efficacy concerns raised after evaluation of the demographic data above.

Subject Disposition/Compliance:

On two occasions, subjects received a single topical dose of the testosterone gel. All subjects who completed the study received two doses of the study medication. There was one discontinuation due to an adverse event (hematoma infection) in Subject 23. The clinical reviewer evaluated this subject's narrative and concluded that the subject's withdrawal was unlikely to have been related to the study medication.

The Applicant stated that measurements of treatment compliance were 100% as study medication was applied to the subjects by the study staff.

Efficacy assessment (Study 70343):

The pharmacokinetic parameters evaluated were AUC0-t, Cmax and Tmax for baseline uncorrected and baseline corrected testosterone levels. 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 AUC0-t, and Cmax 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.

On November 3, 2011, the Applicant submitted a re-revised study report for Study 70343 in which the pharmacokinetic and statistical analysis was conducted using reintegrated chromatograms for the baseline corrected testosterone (the primary efficacy data). These data included 72 subjects that were evaluated in the final determination of bioequivalence for this submission. The ratios of the AUC and Cmax between Teva's testosterone gel and AndroGel 1%, and the 90% confidence interval for those ratios (the primary analyses used to support the bioequivalence comparisons) from the recalculated data submitted on November 3, 2011, are shown in the table below:

Table 2: Ratios for AUC and Cmax 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}
Ratio[1]	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: e[Testosterone 5 g packet of 1% topical gel (A) - AndroGel (B)] X l00.
2. 90% Geometric Confidence Interval using In-transformed data.
*Table 2 obtained from Table 6.3 from the Medical Officer's review finalized on January 26, 2012.

Based on the analysis of the pharmacokinetic data presented above, bioequivalence of AUC between Teva's T gel and AndroGel 1% was established. However, bioequivalence of Cmax 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.

Clinical Pharmacology comments regarding the results of Study 70343:

In the review dated January 19, 2012, the Clinical Pharmacology reviewer made the following conclusion regarding the bioequivalence study 70343: "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 Cmax 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."

Statistical review:

In a review dated January 24, 2012, the statistical reviewer stated that, "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."

Comment: I concur that no additional statistical evaluation from the Division of Biometrics of the pharmacokinetic data is required.

Efficacy summary:

The main objective of the Applicant's NDA submission was to demonstrate bioequivalence of their proposed testosterone gel product to the reference listed drug (RLD) AndroGel 1%. The basis for submission of this 505(b)(2) product was summarized by the clinical reviewer in his January 26, 2011, review as follows:

1. "It is understood that a testosterone transdermal gel product in which the formulation uses different inactive ingredients, (b) (4) from those in the reference listed drug (RLD) can not be submitted as an ANDA. (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."

The Clinical Pharmacology and Clinical reviewers each concluded that the results of Study 70343 demonstrated that the Applicant's testosterone product and the approved comparator product (AndroGel) were sufficiently comparable in terms of exposure to allow approval of the proposed testosterone product.

In his review dated, February 10, 2012, the Cross-Discipline team leader concluded that, "This small difference (in Cmax) poses no efficacy nor safety concerns. When assessed using baseline-uncorrected data, the products are bioequivalent for both parameters."

Summary comment: Based on the submitted bioequivalence data, it is reasonable to conclude that the proposed Applicant's product will be efficacious for the stated indication. Therefore, I concur with the recommendations of the primary medical officer reviewer, cross-discipline team leader and clinical pharmacology review teams that there are no outstanding efficacy concerns for this new testosterone gel product.

8. Safety

The safety data for this application are derived from the four clinical studies that were submitted: 1) a comparative BA & bioequivalence study (Study 70343), 2) an irritation and sensitization study (Study 10936025), 3) a comparative hand washing study (Study CRI-00018704), and 4) a comparative BA transfer study (Study M1FX10001). All studies were performed using the to-be-marketed testosterone formulation. The safety database consists of a total of 306 men exposed to at least one dose of the proposed testosterone formulation. An additional 48 men and women were exposed to a single dose of testosterone in the transfer study (M1FX10001).

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, and both occurred in the contact irritation/sensitization study. One subject was hospitalized for an arm fracture during the washout period between active treatments. The other subject 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 and had a buttock hematoma which eventually became infected and which led to his withdrawal from the study.

Comment: The clinical reviewer and cross-discipline team leader concurred with the assessments of the SAEs and withdrawal as not related to the proposed product. I concur with their assessments.

Adverse Events

Bioequivalence study (70343): A total of 208 treatment-emergent adverse events (TEAE) were reported by a total of 80 subjects. Fifty-nine (59) of 93 subjects (63%) reported a TEAE during the Applicant's product treatment period, and 61 of 90 subjects (68%) reported a TEAE during the RLD Androgel treatment period.

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 Applicant's and AndroGel groups, respectively, and "Application site pruritus" reported by 9.7% and 7.8% of subjects in the Applicant's and AndroGel 1% groups, respectively. None of these application site TEAEs were significant and only one led to an abnormality on physical examination (one subject with superficial erythema and a pimple at the application site). The table below displays the overall adverse events that were reported in the bioequivalence study.

Table 3: Treatment Emergent Adverse Events (TEAEs) 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 (l.1%)
Abdominal distension		1 (l.1%)
Diarrhoea		1 (l.1%)
Dyspepsia	1 (1.1%)	
Nausea		1 (1%)
Toothache	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.%)	
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 (l.1%)
Heart rate increased	1 (l.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 (l.1%)	
Muscle spasms		1 (1.1%)
Musculoskeletal pain	1 (l.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 (l.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%)
Pharngolaryngeal 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%)**

*Table 3 obtained from Table 6.3 from the Medical Officer's review finalized on January 26, 2012.

Laboratory Findings

Bioequivalence study (70343): All final results were within normal limits or were judged to be not clinically significant by a Medical Sub-Investigator, with the following exception(s) in the table below, judged to be clinically significant:

Table 4: Abnormal Clinical Laboratory Evaluations in Study 70343*

Subject No.	Test Name (Normal Range)	Initial Result	Repeat Result
16	GGT (8-61 U/L)	173	189*
35	PSA (0.00 - 4.00 µg/L)	6.85	4.42**
58	Red blood cells in urine (Negative/HPF)	5-10	5-10**

*Table 4 obtained from the Clinical review finalized on January 26, 2012
**Subject referred to family physician for follow-up.

Comment: The Clinical Reviewer did not identify any new safety signals from the laboratory data for the proposed product from these results.

Irritation and Sensitization Study – Study 10936025

Study 10936205 was a multiple site, multiple-application, randomized, double-blind (subject and irritation assessor), two-phase study that enrolled 265 healthy adult male subjects. The two primary objectives of this study included:

- To compare the cumulative irritation potential of TEVA's two test formulations of testosterone 1% topical gel with an Orange Book Listed Reference products AndroGel® (testosterone gel), CIII, when applied over a continuous 21 day period.
- To evaluate the incidence of potential sensitization observed with the two test formulations compared to the reference formulations of testosterone topical gel (AndroGel). This trial was performed at a single U.S. site. Inclusion criteria for the showering study included an off-treatment testosterone level of <300 ng/dL.

Irritation Assessment: During the irritation/induction period, 0.1 ml of gel (or 0.025 ml gel per cm^2, which is equivalent to 0.25 mg/cm^2 of testosterone) was applied to an area of 2 cm x 2 cm and replaced once daily to the same application site for a total of 21 days. On Day 22, the Day 21 applications were removed and no new product applied. Signs and symptoms of irritation were evaluated by trained, blinded evaluators daily during the irritation/induction period. Standardized rating scales were utilized. To ensure the integrity of the study blinding, a member of the clinic staff who was not involved in any of the skin irritation grading assessments applied the formulations to each subject according to the randomization schedule. The study subject and staff members performing the irritation assessments were blinded to the treatment allocation.

Sensitization Assessment: Following Day 22 removal and assessments, 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 applications were removed on Day 38 after at least 48 hours of application and the sites of application monitored over the next 72 hours (30 minutes, 24, 48, and 72 hours after removal) 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 the Applicant's testosterone gel and 2.1% for AndroGel. The adjusted mean cumulative total irritation score are shown in the table below:

Table 5: 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

*Adapted from Table 7.1.2 of the Clinical review dated January 26, 2012.
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 safety analyses were conducted by the Applicant and they concluded that their product was statistically non-inferior to AndroGel for cumulative total irritation.

The Applicant also evaluated other adverse events in this study. 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 were described previously in the section above regarding Serious Adverse Events (SAEs).

After review of Study 10936025, the clinical reviewer concluded that, "The results of irritation and sensitization study showed neither a cumulative irritation effect nor

sensitization reactions occurring in any study subjects." (See clinical review dated January 26, 2012.

The cross-discipline team leader further stated in his review dated February 10, 2012 that, "The irritation/sensitization study demonstrated little, if any, evidence of cumulative irritation potential and no hypersensitivity reactions were observed. "

Comment: I concur with the clinical conclusions of the clinical reviewer and CDTL that this study was sufficient to demonstrate that the Applicant's product does not result in cumulative irritation or sensitization of clinical significance.

Hand Washing Study - Study CRI-00018704:

Study CRI-00018704 was an open-label, two-period crossover study in healthy adult male subjects comparing the amount of residual drug remaining on the hands after a hand washing procedure between the Applicant's test product (testosterone gel) and an approved testosterone product (AndroGel 1%). A total of 39 subjects applied a dose of each product to their arm and shoulder. At five minutes after dosing, the subjects washed their hands as described in the protocol and then the subject's hands were wiped with three ethanol damped gauze pads use as samples for assessment. The Applicant's results of the hand-washing study are outlined in the table below:

Table 6* **Residual T (µg) from Hand Washing Study (N=39)**

	Test Product (A) (Batch # X145)	AndroGel (B) (batch # 31848)
Mean	**285**	**287**
Max	**593**	**547**
Min	**62**	**99**

*Table 6 obtained from Table 7.2.8 from the Medical Officer's review dated January 26, 2012

The study results, (based on a total of 48 subjects), demonstrated that a total of 285 µg and 287 µg (<0.3 mg) of testosterone remained on the hands following application of Applicant's testosterone gel and AndroGel, respectively. The Applicant's testosterone gel was found to be statistically non-inferior to AndroGel. The Applicant concluded that the study results demonstrated that their proposed testosterone gel product was non-inferior to the reference testosterone product for the amount of testosterone remaining on the hands after hand-washing.

Comment: The clinical and clinical pharmacology review teams agreed that minimal testosterone remained on the hands following application of the Applicant's testosterone gel. The clinical reviewer concluded that, "The results of this study show that a very, very small amount of testosterone remains on the hands after application and these results are clinically acceptable."

However, the clinical and clinical pharmacology review teams also noted that this hand-washing study did not measure residual testosterone on the subject's application site after applying the proposed drug product to the application site and washing. Both review teams expressed concern that the residual testosterone on the skin at the

application site could potentially be transferred to a partner if skin-to-skin contact occurred. Therefore, the clinical reviewer concurred with the clinical pharmacology review team that an application site washing study was reasonable and appropriate to assess the washoff potential from the application site.

On January 4, 2012, the Applicant was contacted via Email about the necessity of conducting an application site washing study as a postmarketing requirement (See Regulatory Project Manager memo under NDA 202-763 dated January 13, 2012). On February 6, 2012, the Applicant acknowledged the Email from the Division and agreed to specific milestones (see Regulatory Project Manager's memo to file under NDA 202-763 dated February 6, 2012)

Transfer Study:

Study M1FX10001 was an open-label, open-label, single-dose, randomized, 4-period, 4-treatment crossover study that assessed the relative bioavailability of the new testosterone gel product compared to that of an approved testosterone gel product (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 (2 x 5 g of gel for a total of 100 mg testosterone). Potential for transfer was assessed from males to females with a male wearing a T-shirt and not wearing a T-shirt. Product was applied to the arms and shoulders only.

The key comparison in this study was testosterone systemic exposure in women who had physical contact with men using the Applicant's testosterone gel without a T-shirt (Treatment Period A) compared to men using Applicant'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 Applicant's testosterone gel and AndroGel 1%. The results of the transfer study for the Applicant's product are outlined in the table below:

Table 7* % Difference of Testosterone C_{max} and AUC_{0-t} Post-Transfer vs. Pre-Transfer With / Without T-Shirt

Parameter (Mean±SD)	Without T-Shirt (N = 47)			With T-Shirt (N = 45)		
	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

*Table 7 adapted from Table 7.3.5 from the Medical Officer's review dated January 26, 2012

The results of this study demonstrated that in men without T-shirts, both products did "transfer" to females (n=47 couples). For the Applicant's testosterone gel without a T-shirt barrier, AUC increased almost 200%, and Cmax increased by 272%.

Based on the data from Study M1FX1001, the Applicant concluded that data from periods with a T-shirt covering the application site showed that transfer was minimal.

The clinical reviewer concluded in his January 26, 2012, review that, "It was determined through this study that transfer of testosterone to women and children can be effectively mitigated by a t-shirt for both test and reference products."

Comment: I concur with the assessment of the clinical reviewer and CDTL that no new safety signals related to transfer to others were identified for this product and that clothing over the application site appears to mitigate the risk of transfer.

Safety summary:

The safety data, although limited, support that there is no evidence to suggest that the safety profile of this product would be substantially different from other topically applied testosterone gel products currently marketed. In addition, there is a history of use of these topical testosterone gel products. The known safety profile of these testosterone products can be adequately labeled. Finally, the concerns of interpersonal testosterone transfer in a gel formulation will be addressed through a Medication Guide-only Risk Evaluation and Mitigation Strategy (REMS). The REMS for this product will be similar to those for other topically applied testosterone products.

The clinical reviewer concluded the following in his review dated January 26, 2012, "The results of these studies demonstrate that Teva 1% testosterone gel is effective and safe for the replacement of testosterone in hypogonadal men"

The cross-discipline team leader (CDTL) concurred with the primary medical officer's recommendation in his CDTL review (dated February 10, 2012) and stated, "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."

Comment: I concur with the recommendations of the primary clinical reviewer and cross-discipline team leader that there are no outstanding safety issues for this submission other than the requirement for an application site washing study. This study can be conducted as a postmarketing requirement. The PMR was conveyed to the sponsor and the sponsor has acknowledged the need for this study.

9. Advisory Committee Meeting

Transdermal testosterone patch systems have been used since 1995 and other formulations of testosterone have been used for many years prior to that time. The safety issues associated with testosterone therapy are well known and can be adequately labeled. No Advisory Committee was convened.

10. Pediatrics

The Pediatric Research Equity Act (PREA) does not apply to this application as this NDA does not seek a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration.

11. Other Relevant Regulatory Issues

Controlled Substance Staff:

The Controlled Substance Staff made labeling recommendations in their review dated September 16, 2011, regarding sections 9.1, 9.2, and 9.3 of labeling. These recommendations were followed and included information concerning the fact that Testosterone Gel 1% is in Schedule III under the Controlled Substances Act.

Division of Medical Policy Programs (DMPP):

DMPP reviewed the Medication Guide on January 20, 2012, and found it to be acceptable with several recommended changes. The recommendations were implemented.

Division of Risk Management (DRIS)

DRISK reviewed the Risk Evaluation and Mitigation Strategy (REMS) document and supporting document and completed their review on January 31, 2012. Their recommendations were implemented.

Office of Prescription Drug Promotion (OPDP):

OPDP reviewed the Prescribing Information, the PPI, and the Dear Healthcare Provider Letter and completed their review on January 20, 2012. Their recommendations implemented.

Office of Scientific Investigations (OSI):

OSI conducted a (b) (4) inspection of (b) (4) the contract research organization that conducted bioanalysis of study samples for the pivotal bioequivalence study 70343. The Office of Scientific Investigation (OSI) identified deficiencies in the bioanalysis and issued a Form 483 letter dated June 21, 2011, with the following deficiencies:

1) (b) (4) failed to properly train a laboratory technician who was responsible for sample processing; specifically, repeated long-term freezer stability studies for testosterone failed during the partial validation-6 (5 of 6 runs containing long-term freezer stability data was failed). An investigation of the failures concluded that the technician who processed samples in the failed runs made an error during sample handling. Further, training records ('spiking check' conducted after the investigation) indicated that technician who handled the failed runs could not handle the pipettes properly. A total of 11 validation runs (run # 01SVT, 02SVT,

06SVT, 07SVT, 08SVT, 09SVT, 10SVT, 01FTY, 02FTY, 03FTY and 04FTY), and 4 production runs (run # 58PQM, 67PQM, 71PQM and 74PQM) were affected by this technician's practice.

2) (b) (4) failed to provide adequate security for electronic source records, specifically, (a) A common access procedure is used to access the computer workstation and the 'Analyst' software used for analytical data integration. (b) Technical writers who do not work in the bioanalytical laboratory were given inappropriate permission to edit chromatograms in 'Analyst' software.

3) Integration parameters from most chromatographic runs in the validation and production were modified and were different from the method SOP. These changed integration parameters were not applied to all samples in the respective runs.

4) (b) (4) failed to use appropriate informed consent forms (ICF) during study # 70343. Specifically, Testosterone ICF dated June 12, 2008 was used in place of ICF dated December 6, 2008 for subjects # 1, 3, 5, 6, 19, 28, 41, 71 and 73.

Based the concerns that were raised in this FDA-483 Form, the Division issued a letter to Applicant on July 29, 2011, requesting the following:

- To submit a revised study report for Study 70343, to include new bioequivalence (BE) analysis results using data generated from re-integrated chromatograms, but excluding data generated from the 6 subjects in question (Subjects 60, 61, 62, 92, 93, and 94);
- To submit supporting documentation to explain how the chromatograms were re-integrated consistently (e.g., using a standard operating procedure [SOP]).

The Applicant and the Division subsequently initiated discussions and further communication regarding the pharmacokinetic and chromatogram data. On September 14, 2011, the Applicant submitted a revised study report for study 70343, in which a revised pharmacokinetic and statistical analysis was again conducted using the reintegrated chromatograms for the testosterone baseline corrected data. The submission containing revised data was considered a major amendment, and the user fee goal date was extended to February 14, 2012.

Additional communications between the Division and the Sponsor were held regarding presentation of concentration-time profiles and justification for subject exclusion in Study 70343. A revised study report for Study 70343 was received on November 3, 2011. The Clinical and Clinical Pharmacology evaluations of the revised pharmacokinetic data from that November 3, 2011, submission are presented in Section 7 of this review.

Division of Medication Error Prevention and Analysis (DMEPA):

The DMEPA review team reviewed the carton and container labels, labeling. In their review dated November 4, 2011, the DMEPA review team made recommendations to the

FPI and carton/container labeling. In their November 4, 2011, review, the DMEPA reviewer raised the following concerns, "The proposed labels and labeling introduce vulnerability that can lead to medication errors because the strength presentation and lack of statement concerning noninterchangeability increases the likelihood of inappropriate product substitution. Additionally, the presentation of other information on the labels and labeling requires improvement." The DMEPA reviewer supported their concerns with reports of medication errors retrieved from the Adverse Event Reporting System (AERS).

Several meetings were subsequently held that included the Clinical review team, Clinical Pharmacology review team, the DMEPA review team and representatives from other groups including OGD to further discuss these concerns. At the final group meeting to discuss the lack of interchangeability of the products on January 19, 2012, the group agreed to adopt DMEPAs general recommendations and also to come to consensus on the specific text that would be necessary for labeling after the meeting. The specific labeling recommendations that were conveyed to the Applicant included:

- The (b) (4) (b) (4) was deleted and replaced with milligrams of testosterone per packet for all labeling, 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 will state: "Testosterone gel should be used only in the prescribed doses and application instructions."
- The Medication Guide will state: "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."

The final labeling recommendations were discussed with the DMEPA, Clinical Pharmacology and sent to the Applicant and subsequently implemented.

Financial Disclosure**:**

The clinical review team did not identify any issues related to financial disclosures for these studies (See Cross-Discipline Team Leader review dated February 10, 2012).

Study Endpoints and Labeling Development Team (SEALD)**:**

The SEALD review team concluded in a review finalized on February 10, 2012, that the final labeling is acceptable.

12. Labeling

Labeling negotiations are complete. Labeling for testosterone gel is now consistent with previously approved topically applied testosterone products with respect to transfer potential. Labeling was also evaluated by the following groups:

- Division of Risk Management (DRISK) found the Medication Guide to be acceptable.

- Controlled Substance Staff (CSS) recommended changes to the Drug Abuse and Dependency portion (Section 9) of the label. These recommendations were incorporated into the testosterone gel (b) (4) labeling.
- Office of Medical Policy Programs (DMPP) reviewed the label and the Medication Guide and their recommendations were considered during labeling negotiations with the sponsor.
- Office of Prescription Drug Promotion (OPDP) reviewed the label and Medication Guide and their recommendations were considered during labeling negotiations with the sponsor.

Labeling was also acceptable to the Study Endpoints and Label Development (SEALD) Team.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the cross-discipline team leader, primary medical officer, and the clinical pharmacology, pharmacology/toxicology, CMC, and statistical reviewers that this testosterone gel application can receive an Approval action.

Risk Benefit Assessment:

The primary endpoint for the pivotal phase 1 bioequivalence study (Study 70343) was determined by the Clinical Pharmacology and Clinical teams to be acceptable. The pharmacokinetic data that was submitted along with the other safety studies are acceptable "bridging data" to support the approval of this proposed testosterone gel product from an efficacy standpoint. After review of the pharmacokinetic data, the CDTL, primary medical officer, and the clinical pharmacology and statistical reviewers believe that these data support Approval and I agree.

From an efficacy perspective, the data submitted in this NDA was sufficient to demonstrate that the product will provide similar testosterone exposure to an approved product when used as directed. I agree with the clinical pharmacology, primary medical officer and the CDTL that the finding from the bioequivalence study (70343) that the upper limit of the Cmax exceeding 125% alone should not preclude approval. It can also be concluded that the pharmacokinetic results show that exposure to this proposed testosterone gel product will be comparable to other approved testosterone products.

It also is reasonable to conclude, based on data showing equivalence to an approved product from the submitted study and no identified safety signals in the supportive studies, that the proposed product will be safe. In addition, based on comparable exposure of the Applicant's product to a reference list testosterone gel product (AndroGel), the extensive safety experience with the approved product (AndroGel) is relevant and provides robust support for safety.

In summary, based on the data presented in this NDA submission as well as previous data and experience with other approved testosterone gel products, I believe that the proposed testosterone product will be effective and safe for the indication of testosterone replacement therapy for adult men with either primary or secondary hypogonadism.

Labeling, including the package insert, the Medication Guide and container/carton labeling has been completed. The proposed Medication Guide REMS, which pertains to the potential risk of secondary exposure to children and women has been deemed acceptable by all review teams.

The benefit/risk evaluation favors approval of the Applicant's testosterone gel.

Post-Marketing Requirement/Commitment and Risk Evaluation and Mitigation Strategies (REMS):

- A REMS to include a Medication Guide and assessment plan will be required when this product is approved. This is consistent with all currently marketed testosterone gels to mitigate the potential for drug transfer, primarily to children and women. The final REMS document from the Applicant was submitted on February 3, 2012.
- The Applicant has committed to conduct a postmarketing requirement (PMR) study. There was no application site washing study conducted in this application. The Clinical and Clinical Pharmacology review teams have both concurred that this study is necessary to demonstrate that application site washing is effective in removing residual testosterone, similar to results observed for handwashing. The Applicant was originally informed of this PMR via Email on January 4, 2012 (See Regulatory Project Manager dated January 13, 2012 under NDA 202-763). The Applicant acknowledged the commitment and agreed to proposed milestones (See memo to file under NDA 202-763) as outlined in a Regulatory Project Manager memo dated February 6, 2012.

Comments on REMS and PMR requirements for this proposed testosterone gel product:

- *I concur with the decision that this product should have a class REMS containing a Medication Guide because of the known risk of secondary exposure with use of topical testosterone products.*
- *I also concur with the Clinical and Clinical Pharmacology review teams that the postmarketing requirement (PMR) of an application site washing study is needed to demonstrate that application site washing is effective in removing residual testosterone, similar to results observed for handwashing. This PMR was conveyed to the Applicant, and the Applicant has proposed acceptable milestones (See Regulatory Project Manager memo to file for NDA 202-763 dated February 6, 2012).*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN
02/14/2012