# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**203098Orig1s000**

# SUMMARY REVIEW

# Cross-Discipline Team Leader Review
# Response to Complete Response (CR)

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|---|---|
| **Date** | **January 28, 2013** |
| **From** | **Suresh Kaul, MD, MPH** |
| **Subject** | **Cross-Discipline Team Leader Review** |
| **NDA#** | **203,098** |
| **Applicant** | **Perrigo Israel Pharma Ltd.** |
| **Date of Submission** | **September 13, 2012** |
| **PDUFA Goal Date** | **February 1, 2013** |
| | |
| **Proprietary Name / Established (USAN) names** | **Testosterone (b) (4) Gel** |
| **Dosage forms / Strength** | **Gel for Transdermal use** |
| **Proposed Indication(s)** | **Treatment of Male Hypogonadism** |
| **Recommended:** | ***Approval*** |

## 1. Introduction

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, transdermal patch, buccal patch, intramuscular injections and implanted pellets.

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution.

Male hypogonadism results from insufficient secretion of testosterone and is characterized by low serum testosterone. Signs and symptoms associated with male hypogonadism include: erectile dysfunction, decreased sexual desire, fatigue, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has historically been treated with testosterone replacement therapy via oral or parenteral routes to elevate serum testosterone levels into the normal range. Currently available treatment options for hypogonadism include intramuscular injections, subdermal implants, buccal systems, oral formulations, and transdermal patches and gels. The most commonly used formulations are the gels which are applied with the hands to the shoulders and upper arms and/or abdomen.

Testosterone replacement therapy in men is chronic in nature and designed to improve clinical manifestations of low testosterone and also to place circulating levels of this important hormone into the normal physiological range for healthy men (~300 to ~1050ng/dL). These replacement therapies are ideally based on short term titration regimens that result in an optimal dose of product for a particular patient.

**Product Information**

The gel formulation which is the subject of this review contains (b) (4) testosterone dissolved in ethanol. The formulation also contains (b) (4) Carbomer 980, and (b) (4) (b) (4) Isostearic Acid. The product is packaged in two packaging configurations: 2.5g and 5g unit dose aluminum foil packets and bottles with non-aerosol metered-dose pumps. The product is applied by placing the desired dose of gel onto the palm of the hand and then rubbing the gel onto the skin of the shoulder and upper arm.

**Currently approved medications for the treatment of Male Hypogonadism**
Other testosterone replacement therapies include: transdermal systems (Androderm 2.5mg & 5mg), gel formulations (Androgel 1%, Androgel 1.62%, Testim 1%, Axiron, Fortesta, testosterone Gel), implants (Testopel), a buccally applied product (Striant) and testosterone injections.

## 2. Regulatory Background

The Sponsor initially submitted an application to the Agency for Testosterone Gel, (b) (4) in 2.5gm and 5gm packets on June 15, 2007 (b) (4). On September 26, 2007, the Office of Generic Drugs (OGD) sent a Refusal to Receive letter to the Sponsor stating that:

*The inactive ingredient isosteric acid in your proposed formulation for Testosterone Gel (b) (4) has not been previously approved by the Agency in a transdermal product at the specified levels. Therefore, the proposed drug product cannot be received as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain these inactive ingredients in the same concentration range or provide information demonstrating that these inactive ingredients at these concentrations do not affect the safety of the proposed drug product.*

The Sponsor resubmitted the ANDA, with the requested information, on November 19, 2007. On January 23, 2008, the Office of Generic Drugs (OGD) sent a Refusal to Receive letter to the Sponsor stating that:

*Your proposed drug product contains inactive ingredients that are significantly different than those contained in the RLD Androgel. The Agency has concluded that additional information will be needed to demonstrate that your proposed product does not have the potential to cause greater skin irritation or sensitization than the RLD. Cumulative skin irritation and sensitization studies may provide sufficient information to address this issue.*

The Sponsor performed the requested studies and on November 27, 2008 resubmitted (b) (4) . At that time they also submitted (b) (4) for Testosterone Gel (b) (4) in a multi

dose pump configuration. These applications were accepted for review by OGD on May 13, 2009 and May 20, 2009 respectively.

On August 28 and 29, 2009 the Sponsor received deficiency letters for both (b) (4) . The deficiencies were explained as follows:

*CDER is concerned with the safety of transdermal testosterone gel products because of reports of significant adverse events resulting from unintentional transfer of testosterone from patients to young children and to female partners. Therefore, we are unable to approve your abbreviated new drug application (ANDA). You have failed to provide data to show that your use of different inactive ingredients, including but not limited to the different penetration enhancers, from those found in the reference listed drug (RLD) do not affect the safety or effectiveness of your proposed drug product. See 21 CFR 314.94 (a) (9) (ii) and (a) (9) (v). We have determined that investigations such as clinical trials should be conducted to demonstrate that your inactive ingredients do not affect the safety and efficacy of your proposed drug product. Because these types of studies cannot be submitted in an ANDA, your ANDA cannot be approved. If you wish to pursue approval of your product, you are encouraged to contact the Division of Reproductive and Urologic Products in the Office of New Drugs.*

The Sponsor then submitted IND 107,130 to the Division of Reproductive and Urologic Products and met with the Division on May 19, 2010 to discuss the design of the necessary transfer and washing studies and also to discuss their plans for an NDA submission. The Sponsor subsequently performed the requested studies and NDA 203098 was submitted to DRUP on July 4, 2011.

The Sponsor initially submitted NDA 203,098 on July 4, 2011. On May 3, 2012 the Agency issued a Complete Response letter to the Sponsor which stated that they were unable to approve the application because of the following issues.

*Your Bioequivalence (BE) study between the proposed product (testosterone gel) and the reference listed drug (RLD; AndroGel® 1%) cannot be adequately evaluated. As outlined in Form 483s (dated March 1 and 30, 2012), there are unresolved clinical and bioanalytical site inspection deficiencies. Specifically, a major deficiency of missing dosing records for study period 3 was reported in FDA Form 483. As a result, data from study period 3 were excluded from statistical evaluation. The resultant small sample size makes it unfeasible to do any meaningful statistical analysis for the BE evaluation.*

*In addition, as reported in Form 483 from the bioanalytical site inspection, the measured concentrations of plasma testosterone are not adjusted for the endogenous testosterone in blank plasma used to prepare calibrators and quality control samples. To date, you have not adequately addressed these deficiencies.*

***CTDL Comment:***
***The Sponsor subsequently located the missing dosing records after receiving the Complete Response letter from the Division. In addition, the Sponsor adjusted blank plasma samples for endogenous testosterone using methodology as recommended by OSI and Clinical Pharmacology in the Complete Response. The missing dosing records for period 3 and adjusted testosterone values were submitted with the Sponsor's Complete Response and are the basis of the bioequivalence study evaluated in this review.***

***From this point in my review, I will refer to the Sponsor's testosterone product as Testosterone Gel to distinguish it from other testosterone gel formulations.***

***PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY***
*The primary reviewer, Donald McNellis, MD, stated in his final review, dated January 15, 2013*:

*"Recommendation on Regulatory Action:*

*From a clinical perspective, Testosterone Gel for transdermal use should be approved for the indication of "hypogonadism" in adult males.*

*This recommendation is based on the demonstration of substantial evidence of bioequivalence to an approved testosterone gel, Androgel, and on an acceptable safety profile demonstrated in safety studies carried out by the Sponsor of Testosterone Gel.*

*The Clinical Review Team and other disciplines through their reviews believe that the results from sensitization study, hand washing study, and transfer study included in this 505(b)(2) NDA submission are acceptable. The results of these studies demonstrate that Perrigo's* (b) (4) *testosterone gel product is safe for the replacement of testosterone in hypogonadal men.*

***CDTL Comment***
***This NDA submission provided substantial evidence from an adequate study that the Sponsor's Testosterone Gel product is bioequivalent to an approved testosterone gel, Androgel 1%. This demonstration of bioequivalence allows the reasonable conclusion that Testosterone Gel will have the effect claimed in labeling. Therefore, the clinical team determined that this gel will be an effective treatment for men with hypogonadism.***

***The information submitted by the Sponsor was adequate to allow the reasonable conclusion that Testosterone Gel is an effective and safe treatment for men with hypogonadism. The data also provide an adequate basis for labeling the product so that it can be used in a safe and effective manner.***

**3. CMC/Device**

**T- gel Clinical versus To-Be-Marketed (TBM) formulations**:
The clinical formulation (T06P033) used in all clinical studies was manufactured with Carbomer 940, NF. For commercial formulation, the Sponsor plans to use Carbopol 980 instead of Carbomer 940 to be consistent with the RLD formulation. According to the Chemistry, Manufacturing and Controls (CMC) review by Rajiv Agarwal dated March 6,

2012, this change is classified as a Level 2 excipient change, requiring updated stability data and comparative *in vitro* release data, and not a BE study. The results of the in vitro studies demonstrated no significant differences in the release of Testosterone Gel from the preparation with Carbopol 980 (refer to CMC review on April 11, 2012 in DARRTS).

The Chemistry review team concluded that the Sponsor has provided sufficient information on drug substance controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug product. The Sponsor has also provided sufficient stability information on the drug product to assure strength, purity and quality of the drug product during the expiration dating period.

**4. Nonclinical Pharmacology/Toxicology**

The toxicology reviewer's opinion is that the nonclinical data support approval of Testosterone Gel for testosterone replacement in hypogonadal men as a topically applied product.

**5. Clinical Pharmacology/Biopharmaceutics**

An analysis of the results of the bioequivalence study was done based upon the adjusted data submitted by the Sponsor in their Complete Response on September 13, 2012. Based on this analysis of the adjusted data, it was the opinion of clinical pharmacology reviewer that it is reasonable to conclude that the Sponsor's testosterone gel product is bioequivalent to the reference listed drug Androgel 1%. (See review dated 1.25.2013)

**Summary of Clinical Pharmacology and Biopharmaceutics Findings BE Assessment**

During the original review cycle, the Office of Scientific Investigations (OSI) conducted an inspection of clinical and bioanalytical sites of the pivotal BE study (Study 03-0415-0010). Two major deficiencies identified by OSI included:

1) Clinical site: drug administration records for Period 3 did not indicate the date and time at which the drug was administered. The proper dosing of subjects during Period 3 can not be assured. Therefore, OSI recommended that the data from Period 3 should be excluded from statistical evaluation.

2) Bioanalytical site: the measured concentrations of plasma testosterone (T) were not adjusted for the endogenous T in blank plasma used to prepare calibrators and quality control (QC) samples.

Details of these OSI inspection findings are included in Dr. Gopa Biswas's OSI consult review and addendum dated April 2, 2012 and April 20, 2012, respectively.. Based on the findings of OSI inspection, data from study period 3 of the pivotal bioequivalence (BE) study were excluded from the BE assessment during the first review cycle. As a result, the number of study subjects eligible for BE analysis was reduced from 24 to 8. The remaining small sample size (N=8) of the BE study was unfeasible to do any meaningful statistical analysis for BE evaluation *(refer to the Clinical Pharmacology review of the original NDA 203098 by Dr. Li Li dated on May 1, 2012 in DARRTS).*

In the current resubmission, the Sponsor submitted the missing drug administration records for the study period 3 of the pivotal BE study. In addition, the Sponsor submitted a new full data set for concentration of plasma T adjusted for the endogenous T. Based on the review of the new data set and the drug administration records from study period 3 of the pivotal BE study, this application is recommended for approval from the Clinical Pharmacology and OSI perspectives.

**Bioanalytical Method:**
Study samples from the BE study were analyzed for total T concentrations using the following methods:

- BE study: Gas Chromatography/Mass Spectrometry (GC/MS)
- Inter-personal transfer study: Liquid Chromatography with Tandem Mass Spectrometry (LCMS/MS)
- Hand and application sites washing study: High performance liquid chromatography with ultraviolet detector (HPLC-UV)

Overall, the bioanalytical method was determined to be acceptable and satisfied the requirements of Bioanalytical Method Validation (Guidance for industry – Bioanalytical method validation, FDA, 2001) as determined by OSI in their review dated 12.28.2012.

**Transfer Potential Assessment**
Study results determined that covering the application site with clothing barrier such as a t-shirt significantly reduced testosterone transfer to others *(refer to the Clinical Pharmacology review of the original NDA 203098 by Dr. Li Li dated on May 1, 2012 in DARRTS).*

**Hand and Application Site Washing Study**
Study results determined that hand washing removed 95.3% of recoverable testosterone and showering procedure (2 hours after dose application) removed 79.5% of recoverable testosterone from the arm/shoulder dosing area, indicating that washing hands with soap and water and a shower can sufficiently remove Testosterone Gel from hands and application sites *(refer to the Clinical Pharmacology review of the original NDA 203098 by Dr. Li Li dated on May 1, 2012 in DARRTS).*

**T gel versus the RLD**
The Sponsor's formulation was determined to be similar to AndroGel 1%. However,isostearic acid is included in the formulation (b) (4) whereas isopropyl myristate is used in the RLD AndroGel product. Because of the difference (b) (4), this testosterone gel product could not be a generic product because of the need for additional transfer studies.

**Drug-Drug Interactions (DDI):**
No new DDI studies were conducted with Testosterone Gel. The Sponsor proposed to use publically available information from the RLD for their product.

***The Clinical Pharmacology reviewer concluded in their review dated 1.25.2013 that the information supplied with the Sponsor's Complete Response now adequately supports the***

***bioequivalence of testosterone gel and AndroGel 1%. The Clinical Pharmacology team (DCP3) recommends that the product (NDA 203098) be approved and I concur with their recommendation.***

### 6. Clinical Microbiology

Microbiology consult was not requested for this NDA during this resubmission cycle.

### 7. Efficacy/Review of Bioequivalence

The efficacy of the Sponsor's Testosterone Gel was not evaluated in a clinical study. Rather, the efficacy of the Gel was established by a study showing that it is bioequivalent to the reference listed drug, AndroGel. The Agency previously concluded that AndroGel 1% was shown to be an effective treatment for hypogonadal males . The basis of support for the efficacy of this Testosterone Gel product is a bioequivalence study that demonstrated that there were equivalent blood levels of testosterone from both products.

***CDTL comment***
***I believe that demonstration of equivalent blood levels of total testosterone between the two products provides adequate support for that the Sponsor's Testosterone Gel is also an effective treatment for this indication.***

During the original review cycle, the Office of Scientific Investigations (OSI) conducted an inspection of clinical and bioanalytical sites of the pivotal BE study (Study 03-0415-0010). Two major deficiencies identified by the OSI dated April 2012 were as follows:

> 1) Clinical site: drug administration records for Period 3 did not indicate the date and time at which the drug was administered. The proper dosing of subjects during Period 3 can not be assured. Therefore, OSI recommended that the data from Period 3 should be excluded from statistical evaluation.
>
> 2) Bioanalytical site: the measured concentrations of plasma Testosterone were not adjusted for the endogenous Testosterone in blank plasma used to prepare calibrators and quality control (QC) samples. Details of these OSI inspection findings can be found in Dr. Gopa Biswas's OSI consult review and addendum dated April 2, 2012 and April 20, 2012, respectively, in DARRTS.

***CDTL Comment***
***As discussed above, the two specific deficiencies as pointed out by OSI have been adequately addressed. In my opinion, the Sponsor therefore has provided sufficient information to demonstrate that there product is bioequivalence to RLD, AndroGel 1% and therefore, will have equivalent efficacy in clinical use.***

### 8. Safety

Sponsor's formulation of Testosterone Gel differs (b) (4) from the formulation of the RLD, AndroGel. Because of the difference (b) (4), the Sponsor was asked to perform clinical studies evaluating safety that could possibly be affected by this formulation difference. These studies included: 1)An evaluation of the potential to transfer Testosterone Gel from the

skin of a patient to another individual by direct skin to skin contact, 2) An evaluation of the ability of washing to remove the Testosterone Gel from the hands and application site after the drug is applied, and 3) An evaluation of the potential for irritation and sensitization of the skin by Testosterone Gel.

**Testosterone Transfer – Study M1IU09001**

This study assessed the relative transfer of testosterone from a male, who had been treated with a single topical dose of Testosterone Gel to a female partner. Transfer was evaluated both when the subject was wearing a T-shirt and without a T-shirt. The relative amounts of testosterone transfer from males to females for each condition (with a T-shirt and without a T-shirt) using a comparator product was also assessed in this study. For detailed review of study design, see MO reviewdated 1.30.2013..

***CDTL Comment: The objective of this transfer study was to evaluate the ability of a clothing barrier to prevent testosterone transfer from a patient treated with the Sponsor's Testosterone Gel product to another individual with whom he has direct contact. The study showed that, with a clothing barrier, the mean maximal increase from baseline testosterone level at any time during the 24 hours following contact is 0.043 ng/ml (4.3 ng/dl). This compares to a mean maximal increase from baseline of 0.313 ng/ml (31.3 ng/dl) when contact occurs without the clothing barrier.***

***In summary, the Medical Officer concurs with me that there is a clinically meaningful reduction in the transfer of testosterone from person to person, when a clothing barrier is present. Based on the data from this study, the risk of transfer appears to be comparable to other approved products and therefore, acceptable. The data from this study will be included in labeling.***

**Residual Testosterone after Washing – Study PRG-806**

This study evaluated the residual amount of topically delivered Testosterone Gel present on normal skin of the hand, arm, and shoulder in healthy adult male subjects following washing procedures.

To quantify and compare the amount of residual testosterone remaining on the hands and arm/shoulder before and after the hand and application site washing that followed a single topical dose (10 g of gel for a total of 100 mg testosterone) of Testosterone Gel. A comparator product was assessed in this study, but results from the comparator were not considered for labeling claims.

***CDTL Comment***

***In my opinion, this study demonstrated that the proposed testosterone drug product can be acceptably washed from the hands and from the application site. The data from this study will be included in labeling. For a detailed review of this study, see the MO and CP reviews.***

**Skin Sensitization Study (DS102308)**

This study evaluated the potential of the Sponsor's Testosterone Gel product to cause sensitization or irritation of normal skin. The study focused on the potential for sensitization and irritation after repeated topical application under controlled conditions.

***CDTL Comment***

***From a clinical perspective, no skin reactions to either the investigational product or the comparator product indicative of a possible sensitization response were reported. In addition, no reactions were noted that required a rechallenge.***

***Therefore, study DS102308 provided sufficient evidence that there is no significant sensitization or irritation of the skin by the proposed Testosterone Gel product. It also supports the clinical conclusion that the proposed Testosterone Gel does not have a significant likelihood of irritating the skin with chronic use. Results of this study will be included in labeling.***

**Skin Irritation Study (DS310208)**

This study was a 21-day, randomized, controlled study to evaluate the irritation potential of Testosterone Gel on normal skin of healthy volunteers using cumulative irritant patch test design. The design of this study was consistent with other studies that evaluated skin irritation and also included a comparator product.

***CDTL Comment***

***The proposed Testosterone Gel, AndroGel 1%, Vehicle, and Saline when applied to skin showed no evidence of significant irritation. All products were statistically significantly less irritating than the SLS 0.2% positive control group (P<.001), which had a mean cumulative irritation score of 2.824. This supports the clinical conclusion that the product is unlikely to cause significant skin irritation. For a detailed review of the study, see MO Review dated 1.30.2013..***

**Adverse Events**

There were a total of 21 adverse events reported in 15 subjects who were treated in the bioequivalence study. Ten subjects discontinued medication because of an adverse event.

**Adverse Events Reported in Study DS102308**

| Event | Number | Drug Related |
|---|---|---|
| Headache | 12 | Possible |
| Phlebitis | 1 | Unrelated |
| Diarrhea | 1 | Possible |
| Flea Bites | 1 | Unlikely |
| Chest Pain | 1 | Unlikely |
| Priapism | 1 | Possible |
| Dyspnea | 1 | Possible |
| Insomnia | 1 | Possible |
| Discolored penis | 1 | Possible |
| Breast tenderness | 1 | Probable |

***CDTL Comment:***
***The adverse events reported from the bioequivalence study above do not show a signal or trend that would indicate that the safety profile of this product will be significantly different from other approved testosterone gel products.***

**Overall Assessment of Safety Findings**

*Based on the results of the interpersonal transferability study, the hand washing study, skin sensitization study, and the skin irritation study, Perrigo's testosterone gel demonstrated acceptable safety.*

**9. Advisory Committee Meeting**

No advisory committee meeting was held to discuss this product as there were no outstanding issues that required outside input.

**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 acceptable and consistent with guidance that the Division has received previously from PeRC for other testosterone gel products.

**11. Other Relevant Regulatory Issues**

As discussed in this review, the response to the complete response (CR) during this submission has met the requirement and the drug product is deemed to be bioequivalent to the RLD AndroGel by both the clinical and the clinical pharmacology reviewers. Therefore, Testosterone Gel is recommended for approval.

## 12. Labeling

This was a 505(b)2 application and approvability determination required that the proposed testosterone gel product be demonstrated bioequivalent to the reference related drug (RLD), AndroGel 1%. The clinical reviewer, Donald McNellis, MD recommended that the label be similar to the current AndroGel labeling, but that the Sponsor needed to include a clinical section of the label with the BE study data and also update the safety section with the Transfer, Hand and Application site washing data and Skin Sensitization and Irritation data respectively. These and other recommended changes were incorporated into a completed and finalized agreed upon label.

## 13. Recommendations/Risk Benefit Assessment

**Recommendation**

***From a clinical perspective, I recommend that Testosterone Gel for transdermal use should receive an approval action for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.***

***This recommendation is based on the current submission which included the missing dosing records for Period 3 of bioequivalence (BE) study and also included properly adjusted testosterone levels in the Sponsor's Complete Response.***

**Risk Benefit Assessment**

The concerns of bioequivalence to the RLD product, AndroGel, 1% were resolved with the data in the Complete Response. The demonstration of bioequivalence is sufficient to demonstrate the efficacy of the Sponsor's testosterone product.

From a safety perspective, the proposed Testosterone Gel product was shown in the safety studies (Transfer, Washing of Hands and Application site and Skin sensitization and irritation) to be reasonably safe for its intended use from a clinical perspective. The general pattern of adverse events for this Testosterone Gel product were reasonable and were likely to be similar to other drugs in the class. The most common adverse events (seen in >2% of subjects) for drugs in this class are: application site erythema and irritation, nasopharyngitis, increase in hematocrit, headache, diarrhea and vomiting, which is similar in profile to other approved testosterone products.

As to the safety studies:
1. The potential for transferring testosterone to another individual by direct contact was evaluated in a clinical study by the Sponsor. This evaluation showed that skin-to-skin contact resulted in transfer of testosterone to the female partner. However, a clothing barrier was shown to be effective in preventing clinically significant transfer.

2. The ability to wash the product from the skin was also evaluated in a clinical study. This study showed that approximately 5% of the applied testosterone remained on the skin of the hands following washing the hands with soap and water. Following showering, approximately 20% of the applied testosterone remained at the application site. This finding is similar to that for other testosterone products, and is therefore acceptable.

3. The skin irritation and sensitization studies showed that there was no evidence of skin adverse reactions with repeated administration.

***In summary, I conclude that the information submitted by the Sponsor is adequate to allow the reasonable conclusion that the proposed Testosterone Gel product would be effective and safe for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.***

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/s/

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SURESH KAUL
01/31/2013

AUDREY L GASSMAN
01/31/2013