# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**021463Orig1s000**

# SUMMARY REVIEW

**Deputy Division Director**
**Summary Review for Regulatory Action**

| | |
|---|---|
| **Date** | **December 29, 2010** |
| **From** | **George S. Benson, MD** |
| **Subject** | **Deputy Division Director Review** |
| **NDA#** | **21-463** |
| **Applicant** | **Endo Pharmaceuticals, Inc.** |
| **Date of Submission** | **June 30, 2010** |
| **PDUFA Goal Date** | **December 30, 2010** |
| **Proprietary Name/ Established name** | **Fortesta**<br>**Testosterone 2% gel** |
| **Dosage forms/Strength** | **Metered dose canister which delivers 0.5 g gel (10 mg testosterone) per complete depression** |
| **Proposed Indication** | **Testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone** |
| **Recommendation** | **Approval** |

| | |
|---|---|
| Medical Officer | Guodong Fang, M.D. |
| CDTL | Mark Hirsch, M.D. |
| Chemistry | Donna Christner, Ph.D.<br>Moo-Jhong Rhee, Ph.D.<br>Jeannie David (PM) |
| Pharmacology/Toxicology | Krishan Raheja, D.V.M., Ph.D.<br>Lynnda Reid, Ph.D. |
| Clinical Pharmacology | Hyunjin Kim, PharmD<br>Myong-Jin Kim, Ph.D. |
| Statistics | Kate Dwyer, Ph.D.<br>Mahboob Sobhan, Ph.D. |
| OSE/DMEPA | Jibril Abdus-Samad, PharmD<br>Todd Bridges,RPh<br>Denise Toyer, PharmD<br>Carol Holquist, RPh<br>Maria Wasilik (PM) |
| Project Management Staff | Jeannie Roule<br>Eufrecina Deguia<br>Jennifer Mercier |
| DDMAC | Janice Maniwang, PharmD, M.B.A.<br>Carrie Newcomer, PharmD |
| Microbiology | Bryan Riley, Ph.D.<br>Peter Cooney, Ph.D. |
| OSE/DRISK | (REMS) Shawna Hutchins, BSN,RN<br>Jodi Duckhorn, MA<br>Claudia Karwoski, PharmD<br><br>(Medguide) Melissa Hulett, MSBA,BSN,RN<br>LaShawn Griffiths, MSHS-PH, BSN,RN<br>Mary Willy,Ph.D. |
| OCS | James Tolliver, Ph.D.<br>Silvia Calderon, Ph.D.<br>Michael Klein, Ph.D.<br>Corrine Moody (PM) |
| DSI | Roy Blay, Ph.D.<br>Carol Rovera-Lopez, Ph.D.<br>Martin Yau, Ph.D.<br>Sean Kassim, Ph.D. |

CDTL: Cross Discipline Team Leader
OSE/DMEPA: Office of Surveillance and Epidemiology/ Divison of Medication Error Prevention and Analysis
DDMAC: Division of Drug Marketing, Advertising and Communications
DRISK: Division of Risk Management
CCS: Controlled Substances Staff
DSI: Division of Scientific Investigations

1. **Introduction**
2. **Background**
3. **CMC**
4. **Nonclinical Pharmacology/Toxicology**
5. **Clinical Pharmacology**
6. **Clinical Microbiology**
7. **Efficacy/Statistics**
8. **Safety**
9. **Advisory Committee Meeting**
10. **Pediatrics**
11. **Other Relevant Regulatory Issues**
12. **Labeling**
13. **Decision/Action/Risk Benefit Assessment**

## 1. Introduction:

This complete response submission for NDA 21-463 [Fortesta (testosterone) Gel 2%] for the indication testosterone "replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone" was submitted on June 30, 2010. This NDA submission is a complete response to a complete response action which was taken on October 16, 2009.

Two deficiencies were noted in the October 16, 2009, "complete response" action letter: "1. The Division of Scientific Investigations (DSI) conducted an audit of the (b) (4) analytical laboratory located in (b) (4). The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from your single phase III clinical study (FOR01C). These deficiencies raise serious questions regarding the validity of the data needed to determine the efficacy and safety of your drug product. In the absence of reliable data upon which an approval decision can be based, this NDA cannot be approved. 2) Sufficient information to adequately assess the known serious risk of secondary transfer of testosterone to children and women from men using this product has not been provided. Therefore, safety data are needed to determine if secondary transfer could occur after washing of the application site."

Testosterone for replacement therapy in men is currently available in a variety of dosage forms and routes of administration including intramuscular injection, testosterone implants, buccal tablets, and transdermal solution, patches and gels. Two testosterone gels, AndroGel and Testim are currently approved.

The transfer of testosterone gel products from patients to others (particularly children) has been recognized as a significant safety concern. An Advisory Committee meeting regarding this issue was held on June 23, 2009. Both AndroGel and Testim currently have Black Box Warnings and Medication Guides relating to the increased awareness of secondary exposure of children to testosterone gels.

## 2. Background

NDA 21-463 was initially submitted on June 3, 2002, and received a "not approvable" action on July 2, 2003. The deficiencies noted in the action letter were:

a) Lack of evidence to support that high supraphysiologic daily $C_{max}$ is safe for chronic administration. This deficiency is evidenced by the observation that 9% of patients had testosterone $1500 \leq C_{max} \leq 1800$, 14% had $1801 \leq C_{max} \leq 2500$, and 6% had $C_{max} > 2500$ ng/dL.
b) Lack of information to support that the dose of this product can be adjusted to consistently preclude achieving these high supraphysiological testosterone levels.

Protocol FOR01C ("An Open Label Phase 3 Study of Fortesta Testosterone Gel") was submitted for Special Protocol Assessment on April 6, 2007. The protocol called for a lower starting dose and a more rigorous dose adjustment strategy. Following modifications, the Division agreed with the design of the trial. The results of study FOR01C formed the basis for the NDA resubmission on April 17, 2009.

A complete response action for this resubmission was taken on October 16, 2009. The two major deficiencies were: "1. The Division of Scientific Investigations (DSI) conducted an audit of the (b) (4) analytical laboratory located in (b) (4). The audit identified several deficiencies in the analytical methods and quality control measures used to analyze specimens from your single phase III clinical study (FOR01C). These deficiencies raise serious questions regarding the validity of the data needed to determine the efficacy and safety of your drug product. In the absence of reliable data upon which an approval decision can be based, this NDA cannot be approved. 2) Sufficient information to adequately assess the known serious risk of secondary transfer of testosterone to children and women from men using this product has not been provided. Therefore, safety data are needed to determine if secondary transfer could occur after washing of the application site."

Subsequent to the October 16, 2009, Complete Response (CR) action, the Division met with the Sponsor in a Type A meeting on December 1, 2009. The meeting included discussion of how to resolve the CR deficiencies, including 1) the Sponsor's plan to re-analyze all available serum samples from Study FOR01C for serum testosterone and compare those to the original analytical results, and 2) a confirmation of the Division's October 1, 2009, agreement that the "wash-off" study could be performed as a post-marketing requirement (PMR).

The Division met again with the Sponsor on June 10, 2010, at a Type C Guidance meeting. At that time, Endo stated that they believed that the deficiencies identified in the DSI audit of the (b) (4) had been adequately addressed and that the data from Study FOR01C should be considered reliable. Further, the sponsor noted that their re-analysis of available samples provided strong support for the conclusions from the original analysis.

In this Complete Response, submitted on June 30, 2010, the Sponsor provided all the requested information needed to address the Clinical and Clinical Pharmacology deficiencies as well as the requested labeling, REMS, and safety update. Fortesta is approved in 22 countries (including 20 in Europe) and is currently marketed in 19 of those countries.

3. **CMC**

The CMC reviewer states that "The Review #3 made a recommendation of "Approval" from the CMC perspective based on the sufficient CMC information submitted to assure the identity, strength, purity, and quality of the drug product: adequate labels/labeling with required information; and "Acceptable" cGMP compliance of all facilities.

For this review cycle, the label and labeling were re-reviewed in the context of a new labeling approach for the testosterone drug products and have been revised satisfactorily, making the previous "Approval" recommendation from the CMC perspective still effective.

As proposed and committed to by the sponsor in the Complete Response submission dated April 17, 2009, it is acceptable to establish a specification for in vitro release within 12 months following product approval."

4. **Nonclinical Pharmacology/Toxicology**

The pharmacology/toxicology reviewer concluded that "although this NDA was issued a not approvable letter on July 3, 2003, and a complete response on October 16, 2009, Pharmacology had recommended approval of the NDA based on extensive preclinical published literature available on the safety of testosterone and clinical experience with testosterone in various formulations for the same indication as for the proposed testosterone gel. From the P/T perspective there are no safety concerns and P/T again recommends approval of the resubmitted NDA."

5. **Clinical Pharmacology**

The clinical pharmacology reviewer concluded that "The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the clinical pharmacology information submitted in NDA 021463 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert."

The Clinical Pharmacology review team noted that in the current submission, the sponsor submitted a new dataset to address the deficiencies in the bioanalytical assays after analyzing the back-up serum samples. In addition, the sponsor submitted a timeline to conduct the hand and application site washing trial as a PMR. The following important findings from this review were stated:

- "…the DSI reviewer recommended that the dataset provided by the sponsor was valid, therefore, acceptable to review."
- When using the new dataset generated by the valid back-up samples (n=129), "Trial FOR1C met the primary and secondary endpoints…."

The Clinical Pharmacology review team constructed the following table (Table 1) of efficacy results from the analysis of back-up samples (n=129). They note that, in the current submission, 93.5% (129/138) of the patients' back-up serum samples were available for re-analysis compared to the original MITT analysis.

**Table 1**: **Efficacy Results (Back-up Sample Dataset)**

| **$C_{avg}$ of total T on Day 90** | |
|---|---|
| Mean (SD) | 440.3 (163.4) ng/dL |
| % Patients with Values ≥300 and ≤1140 ng/dL, n/n[a] | 77.5%, 100/129 |
| 95% CI* for % Patients with Values ≥300 and ≤1140 ng/dL | 70.3 – 84.7% |
| % Patients with Values <300 ng/dL, n/n | 22.5%, 29/129 |
| % Patients with Values >1140 ng/dL, n/n | 0%, 0/129 |
| **$C_{max}$ of total T on Day 90** | |
| Mean (SD) | 827.6 (356.5) ng/dL |
| % Patients with Values ≤1500 ng/dL, n/n[b] | 94.5%, 122/129 |
| % Patients with Values ≥1800 and <2500 ng/dL, n/n[b] | 1.5%, 2/129 |
| % Patients with Values ≥2500 ng/dL, n/n[b] | 0%, 0/129 |

a: primary endpoint; b: secondary endpoint
CI: confidence interval

Clinical Pharmacology also reiterated the Clinical Pharmacology findings from the original review of the male to female transfer study (T-01-02-02). The conclusion was that, generally, a 1.5-2 fold increase in serum T concentration was observed in female partners at each time point (when 15 minutes of skin-to-skin rubbing contact was made); however, the potential for transfer "may be abolished by wearing occlusive clothing to cover the application site."

Clinical Pharmacology also reiterated the Clinical Pharmacology findings from the original review of the showering study (T-00-02-03). The conclusion was that no trend was detected to indicate that showering 2 hours post gel administration leads to a detectable difference in daily serum total T profiles.

A Clinical Pharmacology Addendum was completed on December 28, 2010. The addendum notes that "agreement on the language in the package insert labeling between the sponsor and the Division was reached on December 27, 2010." "The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the NDA 021463 acceptable."

**6. Clinical Microbiology:**

The microbiology review was performed during the original submission and the microbiology reviewer recommended approval of the application from a microbiology perspective. No new microbiology data were submitted nor were they requested for the current Complete Response NDA submission.

**7. Efficacy/Statistics**

The primary source of efficacy data for this NDA is the original and re-analysis data from phase 3 Study FOR1C. The NDA also contains supportive evidence from Phase 2 studies as well as a Phase 3 study (TSX/01/C) conducted in Europe.

FOR1C was a multicenter, 90 day open-label, non-comparative trial of 149 men conducted in the United States (32 clinical sites).

Inclusion criteria included:

- BMI (body mass index) >22 kg/m2 and <35 kg/m2
- Screening serum total testosterone of < 250 ng/dL or two consecutive serum total testosterone levels of < 300 ng/dL

Patients were Caucasian (80.5%), Black (10.1%), Hispanic (7.4%), and other (2.0%).

Fortesta was applied once each morning to the thighs at a starting dose of 2.0 g gel (40 mg testosterone) per day. The dose was adjusted between a minimum of 10 mg and a maximum of 70 mg testosterone on the basis of total serum testosterone concentration obtained two hours post drug application on Days 14, 35, and 60 (+/- 3 days) according to parameters described in Table 2.

**Table 2. Dose Adjustment Criteria for Study FOR01C**

| **Total serum Testosterone Concentration (C2)** | Dose Titration |
|---|---|
| **C2 ≥ 2500 ng/dL** | Decrease daily dose by 20 mg T (1 g gel) |
| **1250 ≤ C2 < 2500 ng/dL** | Decrease daily dose by 10 mg T (0.5 g gel) |
| **500 ≤ C2 < 1250 ng/dL** | No change continue on current dose |
| **C2 < 500 ng/dL** | Increase daily dose by 10 mg T (0.5 g gel) |

If a patient had a C2 total serum T value > 2500 ng/dL at 2 successive visits, then the patient was withdrawn from the study.

KEY: T = testosterone Source: Module 5.3.5.1 FOR01C Main Report.

The primary efficacy endpoint for trial FOR01C was serum total testosterone $C_{avg}$ within physiological range in ≥ 75% of patients with the lower bound of 95% CI at 65% on Day 90.

The Sponsor worked with the [redacted] (b) (4) to respond to the DSI audit deficiencies outlined in the FDA Form 483. The Sponsor believes and DSI has concurred that all of the FDA 483 observations have been successfully resolved. The reanalysis data generated at [redacted] (b) (4) support concordance with the original data; therefore, the data from the original NDA are considered reliable and accurate. After the Type C Meeting with the Division on June 10, 2010, the Sponsor provided a detailed description of the re-analysis and individual patient narratives associated with the pivotal Phase III study FOR01C.

The results for the primary and secondary endpoints from the original data analysis and from the re-assay data analysis are shown in Table 3.

**Table 3. Analysis of the Original and Re-assayed Results of Total Serum Testosterone $C_{avg}$ and $C_{max}$ at Day 90 for All Modified ITT (MITT) Subjects**

| Assay | N (number of samples) | % Subjects (95% CI) Who Met the Criterion: $C_{avg}$ Within [300, 1140 ng/dL] | % Subjects Who Met the Criteria | | |
|---|---|---|---|---|---|
| | | | $C_{max} \leq$ 1500 ng/dL | $C_{max}$ Within [1800, 2500 ng/dL] | $C_{max} >$ 2500 ng/dL |
| Original | 138 (1374) | 76.1 (69.0-83.2) | 91.3 | 4.3 | 0 |
| Re-assay | 129 (1247) | 77.5 (70.3-84.7) | 94.6 | 1.6 | 0 |
| Re-assay imputing with valid original values[a] | 138 (1368) | 76.8(69.8-83.9) | 92.8 | 2.9 | 0 |

Of the 138 subjects in the original mITT population, 129 subjects' re-assayed total serum testosterone values were available for the re-analysis (the re-analysis population). The 9 subjects with no backup samples came from 5 different sites. The Sponsor provided two reasons why backup samples were unavailable for re-assay for these 9 subjects: 4 of the subjects had their backup samples used during the original assay, and 5 had their backup sample stored at the investigative site rather than shipped to the laboratory. This error was uncovered only recently, so the samples have been in long term storage at the involved sites for approximately 2 years, where the storage conditions have not been adequately monitored to ensure sample integrity.

The reliability and accuracy of the original data are supported by the similarity of the results. The analysis of the original data and the re-assayed data both met the criteria for the primary and all of the secondary endpoints at Day 90.

**Statistical review:**

According to their final review dated November 19, 2010, the statistical review team believes that based on the re-assayed percentage of successful responders and the concordance between the original results and the re-assayed results, the re-assayed data appears acceptable. Results from re-assayed values and sensitivity analysis all met the study acceptance criteria. Biometrics concluded that the results from phase 3 study FOR01C with original and re-assayed values support the efficacy of Fortesta for testosterone replacement in male hypogonadism. The study confirmed that with the right starting dose of Fortesta, sampling time points and the titration schedules, testosterone levels were achieved within the physiologic range for the majority of the patients. Fortesta also minimized supraphysiologic concentrations of testosterone levels. From a statistical perspective, the Statistical Review Team recommended approval of the current Complete Response/NDA.

Efficacy summary:

Both the original data analysis (n=138) and the re-assay data analysis (n=129) show that the primary endpoint was met. In addition, at Day 90 none of the patients had a $C_{max}$ of >2500 ng/dL and <5% had a $C_{max}$ between 1800 and 2500 ng/dL. Therefore, efficacy by currently accepted criteria was demonstrated.

## 8. Safety

In addition to evaluating the primary trial (FOR1C) for safety, three additional phase 3 trials (2 with safety extensions) were also reviewed by the primary medical officer in his review of the April 16, 2009, Fortesta submission (Table 4).

**Table 4. Summary of studies included in the ISS**

| Study | Study design | No. of Subjects Enrolled/Safety | Subjects | Length of Study |
|---|---|---|---|---|
| **Phase III Studies** | | | | |
| FOR01C | Open-label, non-vehicle controlled | 149/149 | Hypogonadal men | 3 months |
| T 00-03-01 | Open-label, non-vehicle controlled | 204/204 | Hypogonadal men | 6 months |
| T 00-03E 01 Extension | Open-label, non-vehicle controlled 12-mo. (to 24-mo.) extension study | 83/83 (11/11) | Hypogonadal men | 12-24 months |
| T 02-03-01 | Open-label, non-vehicle controlled | 68/68 | Hypogonadal men | 8 weeks |
| T 02-03E-01 Extension | Open-label, non-vehicle controlled l2-mo. extension study | 55/55 | Hypogonadal men | 12 months |
| TSX/01/C | Double-blind placebo-controlled, randomized, Phase IIIb/IV study | 108/108 | Hypogonadal men of metabolic synd. or type 2 diabetes | 2 years |

Source: Module 5.3.5.3: Integrated Summary of Safety.

Phase 1/2 studies included in the ISS (April, 2009, submission) are shown in Table 5.

**Table 5. Summary of studies included in the ISS (Cont.)**

| Study | Study design | No. of Subjects Enrolled/Safety | Subjects | Length of Study |
|---|---|---|---|---|
| **Phase I/II Studies** | | | | |
| T 98-03-01 | Open-label, non-vehicle-controlled, randomized, 7 treat-ment regimen, 3-way, 3-period, matrix-type crossover (Treatment G added by amendment) | 18/18 | Hypogonadal men | 21 days (28 days) |
| T 00-03-03 | Open-label, non-vehicle-controlled, randomized, 2-treatment, 2-period crossover | 7/7 | Hypogonadal men | 14 days |
| T 00-03-07 | Open-label, non-vehicle-controlled, randomized, 3-treatment, 3-period crossover | 12/12 | Hypogonadal men | 24 days |
| T 00-03-08 | Open-label, non-vehicle-controlled, randomized, 3-treatment, 3-period crossover | 15/15 | Hypogonadal men | 24 days |
| T 00-03-09[a] | Open-label, randomized, 3-treatment, parallel groups | 72/72 | Healthy volunteers | 56 days |
| T 01-03-02[b] | Open-label, vehicle-controlled, randomized, 3-period crossover | 8/8 males | Healthy volunteers | 3 months[C] |

Source: Module 5.3.5.3: Integrated Summary of Safety.

Deaths: One death occurred in the Phase 3 trials (including the primary phase 3 study FOR01C) and Phase 1/2 studies listed above. The death was secondary to a myocardial infarction in a man assigned to placebo.

Serious adverse events (SAE's):

In the Phase 3 studies, 32 (6.1%) of 526 subjects experienced a total of 47 treatment-emergent serious adverse events (TEAE's). Five of the treatment-emergent serious adverse events were considered by the investigator to be at least possibly related to study drug. These five TEAE's were congestive heart failure, polycythemia in 3 subjects, and deep vein thrombosis. The subject who experienced congestive cardiac failure had a medical history significant for rheumatic fever. In the primary phase 3 study FOR01C, 5 SAE's were reported. The medical officer reviewed the narratives from these 5 patients and concluded that none of these SAE's was likely related to study medication.

There were no SAEs reported in the Phase 1 or 2 studies.

The lack of a placebo control group in these trials complicates the analyses of adverse events. Polycythemia and deep vein thrombosis are well recognized complications of testosterone replacement therapy and can be adequately labeled.

Common adverse events:

In primary phase 3 trial FOR01C, the most common TEAE's were skin reaction (16.8%), upper respiratory infection (6.7%), sinusitis (4%), and hypertension (2.7%).

Those adverse events judged at least possibly related to study drug and reported in >1% of patients in Trial FOR01C (N=149) were skin reaction 24 (16.1%), PSA increased 2 (1.3%), and abnormal dreams 2 (1.3%).

Adverse events leading to study discontinuation:

Subjects with adverse events leading to study discontinuation in Trial FOR01C are shown in Table 6.

**Table 6. Patients with Adverse Events Leading to Discontinuation of Study Medication**

| Patient Number | Preferred Term | Severity | Relationship |
|---|---|---|---|
| 006-004 | Dermatitis contact | Moderate | Probably related |
| 014-058 | Dyspnea | Severe | Unrelated |
| 027-004 | Skin reaction | Moderate | Probably related |
| 032-024 | Contusion | Moderate | Unrelated |
| 032-052 | Gastric Hypomotility | Moderate | Possibly related |

Source: Module 5.3.5.1 FOR01C: Main Report.

Application site reactions:

The results of dermatologic assessment in Trial FOR01C are shown in Table 7.

**Table 7. Findings of Dermato1ogic Exam of Thigh Application Sites by Visit (Safety Population)**

| | Day 14 | Day 35 | Day 60 | Day 90 |
|---|---|---|---|---|
| Number of patients with an assessment | 147 | 143 | 140 | 146 |
| **Dermal Response** | | **n (%)** | | |
| 0= No evidence of irritation | 146 (99.3%) | 139 (97.2%) | 134 (95.7%) | 138 (94.5%) |
| 1 = Minimal erythema, barely perceptible | 1 (0.7%) | 4 (2.8%) | 3(2.1%) | 4 (2.7%) |
| 2 = Definite erythema. readily visible, minimal edema or minimal popular response | 0 | 0 | 3(2.1%) | 3 (2.1 %) |
| 3 = Erythema and papules | 0 | 0 | 0 | 1 (0.7%) |
| 4 = Definite edema | 0 | 0 | 0 | 0 |
| 5 = Erythema, edema and papules | 0 | 0 | 0 | 0 |
| 6 = Vesicular eruption | 0 | 0 | 0 | 0 |
| 7 = Strong reaction spreading beyond the test site | 0 | 0 | 0 | 0 |
| **Other Dermal Effects** | | **n (%)** | | |
| A = No other dermal effects | 144 (98.0%) | 138 (96.5%) | 132 (94.3%) | 140 (95.9%) |
| B = Slight glazed appearance | 3 (2.0%) | 4 (2.8%) | 4 (2.9%) | 3 (2.1 %) |
| C = Marked glazing | 0 | 1 (0.7%) | 1 (0.7%) | 1 (0.7%) |
| D = Glazing with peeling and cracking | 0 | 0 | 3 (2.1%) | 2 (1.4%) |
| E = Glazing with fissures | 0 | 0 | 0 | 0 |
| F = Film of dried serous exudates covering all or Part of the application site | 0 | 0 | 0 | 0 |
| G = Small petechial erosions and/or scabs | 0 | 0 | 0 | 0 |

Source: Module 5.3.5.1 FOR01C: Main Report.

The dermatologic adverse event profile is acceptable. Only 2 of the 149 subjects in Trial FOR01C discontinued because of dermatologic adverse events (both judged as “moderate.”)

Laboratory assessment:

Hematology:

There were 4 patients in study FORO1C in whom the hematocrit went from normal at baseline to high at Day 90. In one patient the hematocrit was high at baseline and continued to be high at Day 90 (Table 8).

**Table 8. Patients with high Hematocrit on Day 90 (Study FOR01C)**

| Patient I.D. | Baseline Hematocrit | | Day 90 Hematocrit | |
|---|---|---|---|---|
| | Baseline HCT (%) | Normal or High | Day 90 HCT (%) | Normal or High |
| 003-006 | 42.4 | Normal | 53.1 | High |
| 005-001 | 44.3 | Normal | 51.0 | High |
| 012-021 | 47.0 | Normal | 51.2 | High |
| 018-008 | 50.0 | Normal | 50.1 | High |
| 032-004 | 53.5 | High | 55.7 | High |

Source: Division's Clinical Analysis.

PSA:

Two (1.3%) of the 149 subjects in trial FOR01C had increases in PSA over baseline in this 90 day study.

The PSA elevations are difficult to evaluate in the absence of a control group.

Post-marketing experience:

FORTESTA has marketing authorizations in 20 member states of European Union (EU) and 2 other countries. It is marketed in 19 countries. Since first launch in 2005, 56 case reports of AE cases have been received by the Marketing Authorization Holder (MAH) possibly related to the use of the product, including 9 SAE's and 47 non-serious. The Sponsor submitted a Periodic Safety Update Report (PSUR) covering the 12 month period April 1, 2009 to March 31, 2010. For that time period, the estimated packs of testosterone 2% gel distributed to market during this period were 92,225, and the estimated patient exposure (excluding patients treated in clinical trials) during the 12 month period covered by the PSUR is 5,053 patient-years. Overall, the adverse reactions reported are consistent with the expected safety profile for topical testosterone products. Review of these data reveal no new safety concerns.

Testosterone transfer from patients to partners:

An open-label, vehicle controlled, pharmacokinetic study in healthy couples evaluated whether Fortesta could be transferred from a male patient to a female partner following skin contact and whether any transfer could be prevented by covering the application site in the male with clothing. Two hours after Fortesta application, the female partner engaged in vigorous skin to skin contact with the application site for 15 minutes. Mean $C_{avg}$ and $C_{max}$ values for testosterone were higher (approximately two-fold) in the female partners. Despite this increase, mean testosterone values remained within the physiologic range for women of reproductive age. Transfer of testosterone to the female was prevented by covering the male application site with clothing.

Effect of showering on testosterone pharmacokinetics:

An open-label, randomized, two-treatment, two-period crossover study evaluated the effects of showering on the PK of testosterone following application of Fortesta. Based on the analysis of

$C_{avg}$, $C_{max}$, and $C_{min}$, showering 2 hours after the application of Fortesta has no meaningful effect on the PK of testosterone.

Safety summary:

FORTESTA (testosterone gel 2%) was well-tolerated in the Phase 3 study FOR01C with a starting dose of 40 mg of testosterone, and dose adjustment on days 14, 35 and 60, and doses ranging from 10 mg of testosterone to 70 mg of testosterone. The dose adjustment was in gradations of 10 mg or 20 mg of testosterone. The incidence of treatment emergent adverse events (TEAE's) in Study FOR01C was low and was consistent with the adverse event profile for already approved topical testosterone products. The incidence of skin reactions is also in line with already approved products in this class. The majority of these reactions were mild and none were severe. Several patients showed increases from baseline in hematocrit and increases in serum PSA. These are known adverse reactions to testosterone. These abnormalities were not excessive in study FOR01C and the label advises prescribers to monitor these clinical laboratory values. The overall incidences of serious adverse events and adverse events that led to premature study discontinuation were low.

The Sponsor has shown that covering the application sites with clothing is an effective barrier to transfer. The Sponsor has agreed to conduct a hand and application site "wash-off" study as a post-marketing requirement. As discussed above, a REMS to include a Medication Guide and a Timetable for Assessments will be required.

**9. Advisory Committee Meeting**

No advisory committee was convened to discuss the approval of this drug. There are multiple approved testosterone preparations and Fortesta would be the third testosterone gel to be approved. An Advisory Committee meeting was held on June 23, 2009, to discuss the transfer potential of testosterone gels from patients to others, including children. The Advisory Committee agreed with the Division's plans to require labeling revisions (including a Black Box Warning) and a Medication Guide for Androgel and Testim. The same labeling and a Medication Guide dealing with the potential transfer of testosterone to others will be applied to Fortesta.

**10. Pediatrics**

Fortesta was granted a full pediatric waiver by the Pediatric Review Committee (PeRC) on August 20, 2009, because "PREA does not apply."

**11. Other Relevant Regulatory Issues:**

**a. Division of Scientific Investigations (DSI):**

In the final reviews dated October 6, 2010, and November 18, 2010, for the June 30, 2010, submission, DSI provided comments and conclusions regarding how (b) (4) and the Sponsor resolved the DSI concerns from the original audit.

DSI conducted a follow-up inspection of the [redacted] (b) (4) on August 9-17, 2010. Based on the follow-up inspection and the Sponsor's responses to the follow-up Form 483, DSI had the following comments:

1. In a document sent to the review Division on August 9, 2010, (and noted again in DSI's final review dated November 18, 2010), DSI stated that the laboratory's incurred sample reproducibility (of the LC/MS/MS method for total testosterone) appeared sufficient. These ISR data were reviewed at the 2010 inspection and the results were considered "acceptable".

2. The process that generated data to support the long-term frozen stability for SHBG was clarified during the August, 2010, audit, and DSI concluded that the SHBG frozen stability was established to 168 days.

3. The laboratory provided additional long-term stability data for estradiol, free T and DHT. The DSI report states that both the estradiol and DHT studies had greater than 66% of the samples within 15% or 20% of expected values, respectively, for estradiol and DHT. DSI stated that the DHT and estradiol long-term stability had been demonstrated up to 960 and 1025 days. Therefore, DSI concluded that the re-assay for the DHT and estradiol samples is acceptable.

4. DSI stated that the average bias or decrease in free T samples was less than 15% indicating that degradation was not significant.

Thus, DSI believes that the "back-up" samples can be used in the re-analysis of total testosterone, DHT, and estradiol.

**b. Compliance:**

Compliance determined that the inspections of the drug substance and drug product manufacturing and testing operations are acceptable.

**c. Office of Surveillance and Epidemiology (OSE):**

- **Division of Pharmacovigilance (DPV):**

  The DPV agreed with the Division that a REMS (including a Medication Guide) and labeling to include a Black Box Warning should be required upon approval of Fortesta. As previously discussed, transfer of testosterone from patients using testosterone gel products to others (including children) was the subject of a June 23, 2009, Advisory Committee Meeting. A Medication Guide and a Black Box Warning have been instituted for the two currently approved testosterone gel products.

- **Division of Medication Error Prevention and Analysis (DMEPA):**

  DMEPA conducted a "re-assessment" of the proprietary name Fortesta and found it to be acceptable.

DMEPA reviewed the container, carton and package insert labeling and found that the Sponsor had implemented all DMEPA's previous recommendations. The DMEPA review concluded: "The revised labels and labeling submitted by the Applicant adequately addresses our concerns from a medication error perspective. We do not have any additional comments at this time."

- **Division of Risk Management (DRISK):**

  DRISK reviewed the Prescribing Information, REMS, and the Medication Guide.

  DRISK concurred with the proposed REMS and Medication Guide.

**d. Division of Drug Marketing, Advertising and Communications (DDMAC):**

DDMAC reviewed the proposed product labeling (PI), carton labeling, and container labeling for Fortesta. The DDMAC recommendations were considered during labeling negotiations with the sponsor.

**e. Controlled Substance Staff (CSS):**

The Controlled Substance Staff recommended revised labeling under Section 9 in the label ("Drug Abuse and Dependence"). The recommended changes (specifically dealing with abuse, addiction, and dependence) were incorporated into the label.

**f. Financial Disclosure:**

The primary medical officer reviewed the financial disclosure information which was submitted for all required studies submitted to the NDA during the previous review cycle and stated that "there is no evidence to suggest that a financial relationship had any impact on the study results."

**12. Labeling:**

Labeling negotiations are completed.

The "Indications and Usage" statement was changed to more accurately reflect the indication and to be consistent with the labeling of other testosterone products.

The "Dosage and Administration" section of the label will include the statement that "The dose should be titrated based on the serum testosterone concentration from a single blood draw 2 hours after applying Fortesta and at approximately 14 days and 35 days after starting treatment or following dose adjustment. In addition, serum testosterone concentration should be assessed periodically thereafter." Requiring serum testosterone concentrations at both days 14 and 35 is based on data which show that two patients had normal serum testosterone levels at day 14, but had levels >2500 ng/dL at day 35. Although a third dose adjustment was performed in Trial

FOR01C, it does not appear that a third titration step significantly increases the overall efficacy or safety of Fortesta.

The Black Box Warning, Contraindications, and Warnings are now consistent with the two previously approved testosterone gel products. The potential for secondary exposure of children is adequately presented in labeling.

The Drug Abuse and Dependency (Section 9) of the label was updated following consultation with the Controlled Substance Staff.

Table 5 in the Clinical Studies section (Section 14) will not include (b) (4)

The Patient Counseling Information (Section 17) is consistent with other testosterone gel labeling, the Medication Guide, and the labeling for the other two approved testosterone gels.

SEALD has reviewed the final labeling and found it to be acceptable.

**13. Decision/Action/Risk Benefit Assessment:**

Decision/Action:

I agree with the cross discipline team leader, primary medical officer, and the clinical pharmacology, pharmacology/toxicology, chemistry, and statistical reviewers that NDA 21-463 (Fortesta) should be approved for the indication "testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone."

Risk Benefit Assessment:

The Sponsor conducted one primary phase 3 clinical trial (FOR01C) evaluating the efficacy of Fortesta (2% testosterone gel) in producing serum testosterone levels within the normal range (24 hour $C_{avg}$ levels) when the gel is used in men with low testosterone levels. This trial was adequately designed and evaluated accepted endpoints which are currently used for the evaluation of testosterone products. The pre-specified endpoints were met. DSI concluded that the data set containing the "back up" samples was acceptable for review. The NDA contains supportive evidence from Phase 2 studies as well as a Phase 3 study (TSX/01/C) conducted in Europe.

A "showering" study and a male to female transfer study were also performed. Based on the analysis of $C_{avg}$, $C_{max}$, and $C_{min}$, showering 2 hours after the application of Fortesta has no meaningful effect on the PK of testosterone. Transfer of testosterone to others is prevented by covering the male application site with clothing. No study to evaluate the effect of washing the hands or application site on removing Fortesta was performed; this study will be a post-marketing requirement.

No new safety concerns with testosterone replacement therapy with Fortesta arose during the drug development program. The product can be adequately dose titrated to achieve testosterone levels ($C_{avg}$) within the normal range. The known adverse reactions which can occur with testosterone administration can be adequately labeled. Because of the potential for transfer to others (including children), the label will contain a Black Box Warning and a REMS including a Medication Guide and Timetable for Assessment will be required.

Recommendations for Risk Evaluation and Mitigation Strategies (REMS)/Post Marketing Requirement (PMR):

Transfer of testosterone from patients using testosterone gel products to others (including children) was the subject of a June 23, 2009, Advisory Committee Meeting. A Medication Guide and a Black Box Warning have been instituted for the two currently approved testosterone gel products. Because of similar potential for drug transfer with Fortesta, a REMS to include a Medication Guide and a Timetable for Assessment will be required.

The sponsor has agreed to perform a hand and application site drug "wash-off" study as a Post-Marketing Requirement. The sponsor's proposed timeline is:

Final Protocol Submission: February, 2011
Study/Trial Completion: September, 2011
Final Report Submission: April, 2012

---

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

---

/s/

---

GEORGE S BENSON
12/29/2010