CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-633

Administrative/Correspondence Reviews

ITEM 13. PATENT INFORMATION

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Tradename: Femtrace™

Active Ingredient: estradiol acetate

Strengths: 0.45 mg, 0.9 mg and 1.8 mg/tablet

Dosage Form: Tablets

Type of Patent: Drug Product and Method of Use

Approval Date: *Pending*

The patent application has been submitted and is under review. Per the provisions of 21 CFR 314.60, the NDA will be amended with all pertinent patent information after the patent is issued. In accordance with 21 CFR 314.53(d)(1) and 21 CFR 314.53(d)(3), the information will be submitted within 30 days of patent issuance.

EXCLUSIVITY SUMMARY FOR NDA #: **21-633** SUPPL#: **000**

Trade Name: **Femtrace** Generic Name: **estradiol acetate**

Applicant Name: **Warner Chilcott** HFD - **580**

Approval Date: **August 20, 2004**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES / **X** / NO / /

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / **X** / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

c) Did the applicant request exclusivity?

YES / / NO / **X** /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / **X** /

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES / / NO / **X** /

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / **X** / NO / /

If "yes," identify the approved drug product(s) containing the

active moiety, and, if known, the NDA #(s).

NDA# 21-637 Femring®(estradiol acetate)

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical

investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / **X** / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / **X** / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / **X** /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / **X** /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / **X** /

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1 **Study PR 00501**

Investigation #2 **Study PR 01502**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / **X** /

Investigation #2 YES / / NO / **X** /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / **X** /

Investigation #2 YES / / NO / **X** /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study PR 00501 **Study PR 01502**

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # **63,188** YES / **X** / NO / / Explain:

Investigation #2

IND # **63,188** YES / **X** / NO / / Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES / / Explain _____ NO / / Explain _____

Investigation #2

YES / / Explain _____ NO / / Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES / / NO / **X** /

If yes, explain: _____

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

/s/

Daniel A. Shames
8/20/04 11:33:09 AM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-633 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** 000

Stamp Date: October 14, 2003 **Action Date:** August 20, 2004

HFD – 580 **Trade and generic names/dosage form:** Femtrace® (estradiol acetate) Tablets

Applicant: Warner Chilcott Company, Inc. **Therapeutic Class:** S3

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Moderate to severe vasomotor symptoms associated with menopause.

Is there a full waiver for this indication (check one)?

- ■ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ■ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
John Kim, R.Ph., J.D.
Regulatory Project Manager

cc: NDA 21-633
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

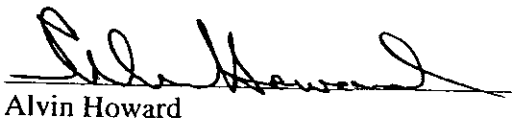
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daniel A. Shames
8/20/04 11:37:00 AM

ITEM 16. CERTIFICATION ABOUT THE USE OF A DEBARRED PERSON

I hereby certify that Galen Limited did not and will not use in any capacity the services of any person debarred under section 306(a) and (b) of the Federal Food, Drug and Cosmetic Act in connection with this New Drug Application for Femtrace™ (estradiol acetate tablets).



10/14/03

Alvin Howard
Vice President Regulatory Affairs
Galen (Chemicals) Limited

Date

Femtrace Division Director's Memorandum

For:	**NDA 21-633** [ ]
From:	**Daniel A. Shames MD** **Director,** **Division of Reproductive and Urologic Drug Products** **CDER/FDA**
NDA Submitted:	**October 14, 2003**
PDUFA Goal Date:	**August 20, 2004**
Date of Memorandum:	**August 19, 2004**
To:	**File**
Drug Name:	
Generic:	**estradiol acetate (EA)**
Trade:	**Femtrace**
Sponsor:	**Warner Chilcott Company Inc.** **Rockaway, New Jersey**
Pharmacologic category:	**Estrogen**
Dosage Form:	**Oral tablet**
Strengths:	**0.45 mg, 0.9mg and 1.8mg all once daily**
Proposed Indications:	**1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. (21-633)** **2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.** [ ]

1.0 Background and Regulatory History

1.1 Regulatory History

Galen (now Warner Chilcott Company, Inc.) opened IND 63,188 with the Phase 3 Protocol PR 00501 on 8/31/01. There were numerous subsequent communications

focusing primarily on the inclusion of the lowest effective dose in the development program and the methodology to be used in establishing efficacy in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy.

As a result of these communications, a second study (PR 01502) to investigate a lowest effective dose was initiated and submitted to the FDA on 4/18/02. The data from phase 3 studies, PR 00501 and PR 01502 provided the bulk of the evidence to support the efficacy of Femtrace.

1.2 Conduct of Studies

Study PR 00501 was a multicenter, double-blind, placebo-controlled, randomized, parallel groups study. This study compared two doses of daily, continuous regimens of EA (0.9 mg and 1.8 mg) against placebo.

Study PR 01502 was a multicenter, double-blind, placebo-controlled, randomized, parallel groups study. This study compared one dose of a daily, continuous regimen of EA (0.45 mg) against placebo.

Study PR 00501 and Study PR 01502 were essentially identical studies which incorporated different dosages of EA. All subjects being considered for enrollment were to discontinue estrogen/hormone therapy prior to the screening period. Both hysterectomized and non-hysterectomized women were eligible for enrollment. Subjects considered for enrollment, pre-screen and screening period requirements, eligibility criteria, and study procedures were identical in both studies. Both studies had the primary objective of determining the effectiveness of continuous administration of EA (either 0.45 mg, 0.9 mg, or 1.8 mg) compared with placebo in decreasing the frequency and severity of hot flushes, and improvement of vulvar and vaginal atrophy, in postmenopausal women over a 12-week period.

The primary efficacy endpoint was the change from baseline in the frequency and severity of hot flushes at weeks 4 and 12. Secondary efficacy endpoints were the weekly, subject-assessed, evaluation of urogenital symptoms [

] In addition, [ ] were done at screening and week 12.

Study PR 00501 was conducted at 44 study sites in the U.S. Three sites were initiated but did not enroll any subjects. The first subject was enrolled on October 3, 2001 and the last subject was completed on November 19, 2002. A total of 44 principal investigators randomized 293 subjects at 41 study sites.

For all target variables an intent-to-treat (ITT) analysis was performed.. A subject was included in the ITT analysis provided she had taken at least one unit of study drug and if at least one observation after dosing was available. Discontinued subjects and missed visits were included in the ITT analysis by carrying forward the last preceding observation for each endpoint (LOCF). The ITT population was used by the sponsor and the division for the primary analysis of the data from study PR00501.

Study PR 01502 was conducted at 40 sites in the U.S. Four sites (Sites 55, 68, 70, and 86) were initiated but did not enroll any subjects. The first subject was enrolled on June 26, 2002 and the last subject was completed on February 26, 2003. A total of 43 principal investigators randomized 259 subjects at 36 study sites.

In the course of monitoring Study PR 01502, it was discovered that subject medication labels were mistakenly unblinded at Site 62 for all 24 subjects randomized at this site. The study protocol was then amended (Amendment 1) to replace the 24 subjects and to exclude them from the primary efficacy analysis, in order to obviate any question of bias in the study results. The statistical analysis plan was revised to define an efficacy analysis subset denoted as ITT*, which excluded all 24 subjects from Site 62. The primary data set for analysis of the efficacy results is the ITT* Population. Both the sponsor and division used the ITT* populations for the primary analyses for study PR 01502

1.3 Standard for Evaluation of Vasomotor Symptoms (VMS) and Vulvar and Vaginal Atrophy (VVA), The January 2003 Draft Guidance (Draft Guidance) for Evaluation of Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms- Recommendations for Clinical Evaluation

1.31 VMS

Vasomotor symptoms in postmenopausal women are commonly known as hot flushes or hot flushes. The severity of vasomotor symptoms in postmenopausal women is defined as follows:

- Mild (sensation of heat without sweating)
- Moderate (sensation of heat with sweating, able to continue activity)
- Severe (sensation of heat with sweating causing cessation of activity)

For products intended to treat moderate to severe vasomotor symptoms, the Division of Reproductive and Urologic Drug Products (DRUDP) recommends conducting one or more randomized, double-blinded, placebo-controlled clinical trials of 12-week duration to support safety and efficacy. The following co-primary endpoints are recommended:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12

The Draft Guidance recommends that the primary efficacy analyses demonstrate a clinically and statistically significant reduction in the frequency and severity of hot flushes in the treated group compared to the control group. This reduction in the frequency and severity of hot flushes should occur within four weeks of initiation of treatment and should be maintained throughout 12 weeks of treatment. Subjective measures (e.g., patient daily diary entries) are used as primary efficacy endpoints.

1.32 VVA

2.0 Efficacy Results

2.1 Frequency of Hot Flushes

2.12 PR00501 (0.9mg, 1.8 mg)

The mean decrease from baseline in the number of moderate to severe hot flushes achieved statistical significance compared to placebo at weeks 4 and 12 for both active treatment groups (for both dosages at both 4 and 12 weeks). See Table 1.

Table 1. Mean Change from Baseline in the Number of Moderate to Severe Vasomotor Symptoms per Week – ITT Population, LOCF

Visit	Placebo (n = 94)	Femtrace 0.9 mg/day (n = 100)	Femtrace 1.8 mg/day (n = 95)
Baseline[1] Mean (SD)	86.1 (40.2)	78.5 (24.9)	82.4 (39.1)
Week 4* Mean (SD)	51.5 (47.2)	24.3 (28.4)	21.9 (25.9)

Mean (SE) Change from Baseline	-30.1 (3.3)	-56.5 (3.2)	-59.3 (3.4)
p value vs. Placebo[2]	-	<0.001	<0.001
Week 12*			
Mean (SD)	46.8 (54.6)	17.5 (28.9)	7.3 (15.2)
Mean (SE) Change from Baseline	-36.3 (3.5)	-63.9 (3.4)	-74.8 (3.6)
p value vs. Placebo[2]	-	<0.001	<0.001

*Primary endpoints

[1] The baseline number of moderate to severe vasomotor symptoms (MSVS) is the weekly average number of MSVS during the two weeks between screening and randomization

[2] p values were based on Wilcoxon rank sum test (van Elteren test)

ITT = intent to treat; LOCF = last observation carried forward; SD = standard deviation; SE = standard error

2.12 PR01502 (0.45mg)

The EA 0.45 mg dosage in the ITT* Population demonstrated a statistically significant reduction in the frequency of moderate to severe hot flushes at the four and twelve week time points. See Table 2.

Table 2: Study PR 01502 mean change from baseline in the number of moderate to severe hot flushes at each study week using LOCF[a] (ITT* Population, ANCOVA)

Study Visit	**Placebo (n=108)**	**EA 0.45 mg (n=113)**	**p-value (95% CI Femtrace – Placebo) [1]**
Baseline Mean (SD)	85.8 (37.8)	86.2 (34.8)	
Week 1 Mean (SE) change	-18.3 (2.8)	-20.5 (2.8)	0.1546 (-10.1, 5.5)
Week 2 Mean change (SE)	-26.0 (3.3)	-29.7 (3.3)	0.1224 (-12.9, 5.4)
Week 3 Mean change (SE)	-30.6 (3.5)	-35.6 (3.4)	**0.0323**** (-15.6, 3.5)
Week 4 Mean change (SE)	-33.8 (3.5)	-41.5 (3.4)	**0.0138**** (-17.3, 1.9)
Week 5 Mean change (SE)	-35.2 (3.5)	-44.1 (3.5)	**0.0069**** (-18.5, 0.9)
Week 6 Mean change (SD)	-36.2 (3.4)	-46.8 (3.4)	**0.0007**** (-20.0, -1.1)
Week 7 Mean change (SE)	-37.4 (3.5)	-46.3 (3.5)	**0.0042**** (-18.5, 0.7)
Week 8 Mean change (SE)	-39.3 (3.4)	-49.5 (3.4)	**0.0007**** (-19.5, -0.7)
Week 9 Mean change (SE)	-39.8 (3.5)	-50.5 (3.4)	**0.0017**** (-20.2, -1.1)
Week 10 Mean change (SE)	-41.4 (3.5)	-51.0 (3.5)	**0.0025**** (-19.2, 0.1)
Week 11 Mean change (SE)	-41.6 (3.5)	-51.0 (3.5)	**0.0056**** (-19.1, 0.3)
Week 12 Mean change (SE)	-41.5 (3.5)	-51.2 (3.5)	**0.0052**** (-19.5, 0.1)

ITT*(with exclusion): exclude 24 subjects inadvertently unblinded at site 62,

[a]LOCF=Last Observation Carried Forward, Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval

**p<0.05 and statistically significant

[1]:p-values were based on Wilcoxon rank sum test (Van Elteren test)

CIs were calculated from an ANCOVA with baseline, treatment, center at weekly

2.2 Severity of Hot Flushes

2.21 PR00501 (0.9mg, 1.8 mg)

The Mean decrease from baseline in the severity of moderate-to-severe hot flushes achieved statistical significance compared to placebo at Weeks 4 and 12 for both the EA 0.9 mg and the EA 1.8 mg treatment groups. See Table 3.

Table 3. Mean Change from Baseline in the Severity of Moderate to Severe Vasomotor Symptoms per Week – ITT Population, LOCF

Visit	Placebo (n = 94)	Femtrace 0.9 mg/day (n = 100)	Femtrace 1.8 mg/day (n = 95)
Baseline[1]			
Mean (SD)	2.5 (0.2)	2.5 (0.2)	2.5 (0.2)
Week 4*			
Mean (SD)	2.3 (0.6)	1.8 (1.0)	1.9 (1.0)
Mean (SE) Change from Baseline	-0.2 (1.0)	-0.7 (0.1)	-0.7 (0.1)
p value vs. Placebo[2]	-	0.001	0.002
Week 12*			
Mean (SD)	2.2 (0.8)	1.4 (1.2)	1.0 (1.2)
Mean (SE) Change from Baseline	-0.3 (0.1)	-1.1 (0.1)	-1.5 (0.1)
p value vs. Placebo[2]	-	<0.001	<0.001

*Primary endpoints

[1] The baseline severity of moderate to severe vasomotor symptoms (MSVS) is the average severity of MSVS during the two weeks between screening and randomization

[2] p values were based on Wilcoxon rank sum test (van Elteren test)

Note: Hot flush severity was scored using the following scale: 1 = Mild, 2 = Moderate, 3 = Severe

ITT = intent to treat; LOCF = last observation carried forward; SD = standard deviation; SE = standard error

2.22 PR01502 (0.45mg)

In the EA 0.45 mg group, the mean change from baseline in the severity of moderate to severe hot flushes at week 4 was not statistically significant compared to the placebo group. However, at week 7 and week 12 the mean changes from baseline in the severity of moderate to severe hot flushes were statistically significantly greater compared to the placebo group. At weeks 4,5,6,9 and 10 the mean changes from baseline in the severity of moderate to severe hot flushes were numerically but not statistically different from placebo. See Table 4.

Table 4:Study PR 01502 mean change from baseline in the severity of moderate to severe hot flushes at each study week using LOCF[a] (ITT* Population, ANCOVA)

Study Visit	Placebo (n=108)	EA 0.45 mg (n=113)	p-value (95% CI Femtrace – Placebo) [1]
Baseline Mean (SD)	2.6 (0.2)	2.5 (0.2)	
Week 1 Mean (SE) change	0.002 (0.01)	-0.02 (0.01)	0.8975 (-0.05, 0.1)
Week 2 Mean change (SE)	-0.08 (0.04)	-0.1 (0.03)	0.3698 (-0.13, 0.1)

Week 3 Mean change (SE)	-0.1 (0.04)	-0.1 (0.04)	0.2386 (-0.1, 0.08)
Week 4 Mean change (SE)	-0.2(0.06)	-0.3 (0.06)	0.7868 (-0.3, 0.05)
Week 5 Mean change (SE)	-0.1 (0.06)	-0.4 (0.06)	0.2039 (-0.4, -0.05)
Week 6 Mean change (SD)	-0.2 (0.08)	-0.5 (0.08)	0.2228 (-0.5, -0.1)
Week 7 Mean change (SE)	-0.2 (0.08)	-0.5 (0.08)	0.0494** (-0.5, -0.05)
Week 8 Mean change (SE)	-0.2 (0.07)	-0.5 (0.07)	0.0062** (-0.6, -0.1)
Week 9 Mean change (SE)	-0.2 (0.08)	-0.5 (0.08)	0.0627 (-0.5, -0.06)
Week 10 Mean change (SE)	-0.3 (0.08)	-0.6 (0.08)	0.1066 (-0.5, -0.06)
Week 11 Mean change (SE)	-0.2 (0.09)	-0.7 (0.08)	0.0098** (-0.7, -0.3)
Week 12 Mean change (SE)	-0.3 (0.09)	-0.7 (0.09)	0.0164** (-0.7, -0.2)

ITT*(with exclusion): exclude 24 subjects inadvertently unblinded at site 62,
[a]LOCF=Last Observation Carried Forward, Mean=Arithmetic Mean, SD=Standard Deviation,
SE= Standard Error, CI=Confidence Interval
**p<0.05 and statistically significant

[1]:p-values were based on Wilcoxon rank sum test (Van Elteren test)
CIs were calculated from an ANCOVA with baseline, treatment, center at weekly
Change from baseline in the severity defined as SS1 = (2*nr_mod + 3*nr_sev) / nr_ms
where nr_mod and nr_sev were the numbers of moderate and severe hot flushes, and
nr_ms = nr_mod + nr_sev was the total number of moderate to severe hot flushes.

2.3 Vulvar and Vaginal Atrophy

[redacted]

3.0 Conclusions Regarding Efficacy

3.1 Vasomotor Symptoms

3.12 PR00501 (0.9mg, 1.8 mg)

I agree with the primary and secondary reviewer that the data from trial PR00501 provide substantial evidence of effectiveness of the 0.9mg and 1.8 mg doses of Femtrace by the criteria described in the draft guidance.

3.13 PR01502 (0.45mg)

Since the publications of multiple articles related to the WHI studies (beginning July 2002), the Division has been reexamining its approach to regulating hormonal and other products for menopausal symptom therapy (MST). This reevaluation has been taking place in consultation with CDER officials at all levels. The reevaluation continues at the date of publication of this memorandum and includes a intensive internal examination of

Signature of Preparer/
Regulatory Project Manager

___/___/___
Date

Signature of Office/
Division Director

___/___/___
Date

cc:
Archival NDA
HFD-580/Division File
HFD-580/John Kim, RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T. Crescenzi

Form OGD-011347 Revised 05/10/2004

issues discussed in the draft January 2003 Guidance for Industry on Clinical Evaluation of Products for MST (vasomotor symptoms, vulvar and vaginal atrophy)

The Division is evaluating products for MST in various phases of both the IND and NDA process. In addition, the Division is tasked with continuous evaluation of products currently on the market. Although there are many issues to be examined surrounding the safe and efficacious use of products for MST, there is general consensus in medical practice that many adverse events and risks are dose-related. Therefore, postmenopausal women should have availability of the lowest doses that are effective for a particular indication. The Division Director has become concerned that strict adherence to the efficacy endpoints as presented in the January 2003 Draft Guidance may have the unintended consequence of limiting availability of the lower dose of a particular product that may be effective in a meaningful proportion of women.

The data demonstrate that EA 0.45 mg meets the recommended endpoints (as described in the 2003 Draft Clinical Evaluation Guidance) for improvement of efficacy compared to placebo as measured by change from baseline of frequency at weeks 4 and 12 and also for severity at week 12. Femtrace 0.45mg does not improve severity of VMS compared to placebo by week 4, but by week 7. The data from this application met three of the recommended endpoints and the fourth demonstrated drug effect that supports effectiveness. Together, all the data demonstrate the effectiveness of this dose.

There is additional data that indicate that a sizable proportion of women improves on treatment compared to placebo by week 4 (as defined by 75% or more improvement in symptoms) and that this proportion increases through week 12 (see 3.131)

I believe that, post-WHI, the marginally reduced efficacy of 0.45mg EA when measured by traditional standards is relatively inconsequential compared to the unintended consequences of preventing women access to lower doses of drug.

Because of the antecedent arguments, I agree with the primary reviewer and disagree with the secondary reviewer that the data from PR01502 provide substantial evidence of effectiveness of the 0.45 mg dose of Femtrace. I further believe that because of the pattern of efficacy over time as measured in the studied population, 0.45mg can be considered the lowest effective dose.

3.131 Post hoc Responder Analysis of Frequency and Severity

Due to the apparent delayed mean effect of the EA 0.45 mg dose in Study PR 01502 on the improvement in the severity of moderate to severe hot flushes (was not statistically significantly different at week 4), the Division asked the Sponsor to perform a post hoc analysis (Amendment 13) to determine differences in responder rates between the active and the placebo groups with regard to frequency and severity of moderate to severe hot flushes. The purpose was to view the data in a way that might reflect the clinical effect of the 0.45mg dose on the individual patient.

A subject with a 75% or greater decrease in weekly frequency (table 5) or severity (table 6) of moderate to severe hot flushes from baseline was considered a responder and any subject with less than 75% response was considered a non-responder. One must recognize the post hoc nature of these analyses and view them as supportive. They

provide an important descriptive insight into the therapeutic effect of EA at the .45 mg dose.

3.1311 Frequency

Between groups for the ITT* Population, significance was first seen at week 3 and maintained through week 12 with the exception of week 4 where both treatment groups had six additional responders, thus slightly diminishing the proportional difference between groups at week 4 and increasing the p-value to 0.083. See Table 5.

Table 5: Responder Rates for Decrease in Frequency of Moderate to Severe Hot Flushes (ITT* Population), Study PR 01502.

	Placebo	EA 0.45mg	p-value*
Total In Population	n=108	n=113	
Responder Rates			
Week 1	4 (3.7%)	6 (5.3%)	0.749
Week 2	11 (10.2%)	16 (14.2%)	0.415
Week 3	14 (13.0%)	27 (23.9%)	0.039
Week 4	20 (18.5%)	33 (29.2%)	0.083
Week 5	22 (20.4%)	39 (34.5%)	0.024
Week 6	23 (21.3%)	43 (38.1%)	0.008
Week 7	23 (21.3%)	46 (40.7%)	0.002
Week 8	23 (21.3%)	47 (41.6%)	0.001
Week 9	27 (25.0%)	53 (46.9%)	<.001
Week 10	26 (24.1%)	54 (47.8%)	<.001
Week 11	29 (26.9%)	52 (46.0%)	0.003
Week 12	29 (26.9%)	53 (46.9%)	0.002

Note: Responder = 75% or more decrease in the number of hot flushes when compared to baseline
ITT* = Intent-to-Treat but excluding Site 62
[1]p-value is from Fisher's Exact Test.

3.1312 Severity

EA 0.45 mg achieved statistical significance in decreasing the severity of moderate to severe hot flushes by week 6 but did not consistently decrease severity through week 12. See Table 6.

Table 6: Responder Rates for Decrease in Severity of Moderate to Severe Hot Flushes (ITT* Population), Study PR 01502

	Placebo	EA 0.45mg	p-value*
Total In Population	n=108	n=113	
Responder Rates			
Week 1	0 (0.0%)	0 (0.0%)	1.000
Week 2	2 (1.9%)	3 (2.7%)	1.000
Week 3	1 (0.9%)	4 (3.5%)	0.370
Week 4	3 (2.8%)	8 (7.1%)	0.216
Week 5	3 (2.8%)	11 (9.7%)	0.051
Week 6	5 (4.6%)	17 (15.0%)	0.012
Week 7	8 (7.4%)	17 (15.0%)	0.090
Week 8	5 (4.6%)	17 (15.0%)	0.012
Week 9	8 (7.4%)	16 (14.2%)	0.131
Week 10	9 (8.3%)	20 (17.7%)	0.047
Week 11	7 (6.5%)	26 (23.0%)	<.001
Week 12	10 (9.3%)	27 (23.9%)	0.004

Note: Responder = 75% or more decrease in the severity of hot flushes when compared to baseline.
ITT* = Intent-to-Treat but excluding Site 62

*p-value is from Fisher's Exact Test.

3.2 Vulvar and Vaginal Atrophy

I agree with the conclusions of the primary and secondary reviewers, that based upon the findings in studies PR 00501 and PR 01502, Femtrace did not demonstrate efficacy for the treatment of VVA associated with the menopause [redacted]

[redacted]

4.0 Regulatory Recommendations:

I recommend that NDA 21-633 (all three doses) be approved for treatment of moderate to severe vasomotor symptoms associated with the menopause.

I recommend that NDA[redacted] (all three doses) not be approved for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Daniel; A. Shames MD
Director, DRUDP/CDER/FDA

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

/s/

Daniel A. Shames
8/20/04 12:04:50 PM
MEDICAL OFFICER

NDA 21-633
Femtrace
(estradiol acetate)

Demographic Worksheet

Not applicable.

NDA 21-633
Femtrace
(estradiol acetate)

Controlled Substance Staff Review

Review from Control Substance Staff was not requested.

NDA 21-633
Femtrace
(estradiol acetate)

Clinical Inspection Review Summary (DSI)

No Division of Scientific Investigation (DSI) audit was requested.

NDA 21-633
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Risk Management Plan Review

No specific risk management steps are recommended, see the Medical Officer's review in the Clinical Review section, § 1.2, page 6.

NDA 21-633
Femtrace
(estradiol acetate)

Safety Update Review

Please refer to the Medical Officer's review, section 7.8, page 51.

NDA 21-633
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Microbiology Review

Not Applicable.

NDA 21-633
Femtrace
(estradiol acetate)

Federal Register Notices, DESI documents, NAS/NRC reports

This application was not a subject of a Federal Register Notice, DESI document, nor NAS/NRC report.

NDA 21-633
Femtrace
(estradiol acetate)

Advisory Committee Meeting

This application was not a subject of an Advisory Committee meeting.

NDA 21-633
Femtrace
(estradiol acetate)

Post-marketing commitments

Not applicable for this application.

NDA 21-633
Femtrace
(estradiol acetate)

Press Office Information

Not applicable for this application.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-633	Efficacy Supplement Type SE- N/A	Supplement Number 000
Drug: **Femtrace® (estradiol acetate) 0.45, 0.9, 1.8 mg Tablets**		Applicant: **Warner Chilcott Company, Inc.**
RPM: **John Kim**	HFD- **580**	Phone # **301-827-3003**

Application Type: **(X)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **(X)** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): **N/A**

❖ Application Classifications:	
• Review priority	**(X)** Standard **( )** Priority
• Chem class (NDAs only)	**3**
• Other (e.g., orphan, OTC)	**N/A**
User Fee Goal Dates	**20-Aug-04**
❖ Special programs (indicate all that apply)	**(X)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(X)** Paid UF ID number **# 4518**
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify)
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify)
Application Integrity Policy (AIP)	
• Applicant is on the AIP	**( )** Yes **(X)** No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	(X) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary	**20-Aug-04**
• Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	**N/A**
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	**28-Apr-04**

❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	18-Aug-04
• Most recent applicant-proposed labeling	17-Mar-04
• Original applicant-proposed labeling	14-Oct-03
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	27-May-04 (DDMAC) 08-Jul-04 (DMETS) 29-Apr-04 (DSRCS)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	11-Feb-04
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	05-Aug-04 17-Mar-04 14-Oct-03
• Reviews	8-Jul-04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	28-Jul-04 20-Jul-04 11-Feb-04 18-Dec-03 10-Dec-03 03-Dec-03 27-Oct-03
❖ Memoranda and Telecons	18-Aug-04 12-Aug-04 01-Jul-04 27-Apr-04 05-Mar-04 03-Dec-03 02-Dec-03
Minutes of Meetings	
• EOP2 meeting (indicate date)	20-Nov-01
• Pre-NDA meeting (indicate date)	25-Sep-03

• Pre-Approval Safety Conference (indicate date; approvals only)	**N/A**
• Other	**N/A**
Advisory Committee Meeting	
• Date of Meeting	**N/A**
• 48-hour alert	**N/A**
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	**N/A**
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**20-Aug-04** (Division Director) **20-Aug-04** (Medical Team Leader)
❖ Clinical review(s) *(indicate date for each review)*	**13-Aug-04** **06-Apr-04**
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**N/A**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**Clinical Review § 7.8, page 52**
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	**Not recommended** **See Clinical Review § 1.2, page 6**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**20-Aug-04**
❖ Demographic Worksheet *(NME approvals only)*	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**17-Aug-04** **06-Aug-04**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**30- Jul-04**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
Clinical Inspection Review Summary (DSI)	
• Clinical studies	**N/A**
• Bioequivalence studies	**N/A**
❖ CMC review(s) *(indicate date for each review)*	**18-Aug-04** **11-Aug-04**
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**11-Aug-04 (see Chemistry Review, page 44)**
• Review & FONSI *(indicate date of review)*	**N/A**
• Review & Environmental Impact Statement *(indicate date of each review)*	**N/A**
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**N/A**
❖ Facilities inspection (provide EER report)	Date completed: **12-Nov-03** **(X)** Acceptable **( )** Withhold recommendation
❖ Methods validation	**(X)** Completed **( )** Requested **( )** Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**28-Jun-04** **02-Dec-03** **20-Feb-03**
❖ Nonclinical inspection review summary	**N/A**

❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**N/A**
❖ CAC/ECAC report	**N/A**

Appendix A to NDA/Efficacy Supplement Action Package Checklist

ɿ application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

ᵔᶜ you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with ; Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appears This Way
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS
Galen (Chemicals) Limited
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

2. TELEPHONE NUMBER *(Include Area Code)*
(973) 442-3233

3. PRODUCT NAME
Femtrace (estradiol acetate tablets)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER
NDA 21-633

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER
4518

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?
☐ YES ☒ NO
(See item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
[signature]	Vice President, Regulatory Affairs	10/14/03

FORM FDA 3397 (1/03)

PSC Media Arts (301) 443-1090 EF

NDA 21-633
Femtrace
(estradiol acetate)

Application Integrity Policy (AIP)

Not applicable for this application.

MEMORANDUM OF TELECON

DATE: August 18, 2004

APPLICATION NUMBER: NDA 21-633, FEMTRACE™ (estradiol acetate) Tablets

BETWEEN:

Name: Ileanna Brown, Manager, Regulatory Affairs
Phone: 973-442-3229
Representing: Warner Chilcott Company, Inc.

AND

Name: John C. Kim, Regulatory Health Project Manager
Brenda Gierhart, M.D., Medical Team Leader
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Comments to Sponsor regarding final labeling

CLINICAL PHARMACOLOGY

- Addition of "AUC" and "$t_{1/2}$" columns to Table 1 are acceptable with the Division.

CHEMISTRY

- In the **HOW SUPPLIED** section of the PI, the addition of Warner Chilcott logo and movement of the description, "Marketed by: Warner Chilcott...." line to now follow the "Manufactured by: Pharmaceutics...." line are acceptable with the Division.
- The addition of a blank line in the PPI between the question "What are the ingredients in Femtrace?" and the answer to the questions listing all the ingredients are also acceptable.

BIOMETRICS

- Deleting all the Week 8 data in Tables (2a, 2b, 3a, and 3b), changing the name from "Van Elteren's test" to "van Elteren test," and changing "ITT* (with exclusion)[a]" to "ITT (modified)[1]" are acceptable with the Division.

CLINICAL

- The Division accepted the following changes proposed by the Sponsor:
    1) Omitting a comma between the second to the last item in a list and the word, "and."
    2) Changing "In-vitro" to "In vitro" and "in-vivo" to "in vivo" in the first sentence of the Pharmacokinetics subsection.
    3) Changing the word "plasma" to "serum" in the ***Effect of Food*** subsection.
    4) In the ***Effects on vasomotor symptoms*** subsection, changing the words in "compared to placebo" to "compared with placebo" on page 5.
    5) Changing "nonfatal" to "non-fatal."

6) Removing the spacing between sentences under "Who should not use Femtrace?" section in the PPI on page 2.
7) Changing the date from "August 4, 2004" to "August 20, 2004" on page 1 of the PPI.

- The Sponsor agreed to the following changes proposed by the Division:
  1) To place the period inside the parentheses when the labeling refers to another section of the label as in, "(See **CLINICAL PHARMACOLOGY, Clinical Studies.**)" instead of outside the parentheses.
  2) To eliminate the hyphen in the words, "sulfate-conjugated," to "sulfate conjugated" in the second paragraph of the **CLINICAL PHARMACOLOGY** section.
  3) To eliminate the hyphen to "follicle-stimulating" to make it "follicle stimulating" hormone (FSH) in the fourth paragraph of the **CLINICAL PHARMACOLOGY** section.
  4) To change "vs." to "vs" throughout the body of the text but to keep "vs." in the tables.
  5) To remove the hyphen in "sex hormone-binding globulin" in the **PRECAUTIONS** section, **D. Drug/Laboratory Test Interactions** subsection to "sex hormone binding globulin."
  6) To add the word, "of" in the clause, "Among women who reported prior use [of] hormone therapy," on page 13 in the **WARNINGS** section in the *b.* ***Breast cancer*** subsection.
  7) To combine the sentences, "Femtrace therapy is indicated in the: [space & indent] Treatment of moderate to severe vasomotor symptoms associated with the menopause," into one sentence on page 11 of the **INDICATIONS AND USAGE** section.
  8) To add visible vertical and horizontal lines to Table 4, as recommended on page 7 in the Draft "Guidance for Industry: Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Prescribing Information for Health Care Providers and Patient Labeling" dated February 2004.

/S/

Brenda Gierhart, M.D.
Medical Team Leader

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/s/

John C. Kim
8/18/04 03:49:07 PM
CSO

Brenda Gierhart
8/18/04 04:31:11 PM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: August 12, 2004

APPLICATION NUMBER: NDA 21-633, FEMTRACE™ (estradiol acetate) Tablets

BETWEEN:

Name: Alvin Howard, Vice President, Regulatory Affairs
Ileanna Brown, Manager, Regulatory Affairs
Phone: 973-442-3229
Representing: Warner Chilcott Company, Inc.

AND

Name: John C. Kim, Regulatory Health Project Manager
Brenda Gierhart, M.D., Medical Team Leader
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Comments to Sponsor regarding Division's revisions to proposed labeling

- [

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[

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Sponsor was informed that the review team will verify whether the July 28, 2004 submission was reviewed. (Post telecon information: The July 28, 2004 submission had been reviewed and this information was conveyed to the Sponsor by the Project Manager.)

- Sponsor was also informed that there was a scientific disagreement as to whether the 0.45 mg strength supported an indication for vasomotor symptoms (VMS). However, based on a re-analysis of the data using the rank sum test rather than ANOVA, efficacy was statistically significant for the 0.45 mg strength at Weeks 4 and 12 for frequency. This re-analysis of the data explains the revisions to the tables in the labeling. The re-analysis was performed due to the assumptions in ANOVA being violated, particularly regarding a parametric distribution and normality. Because the Statistical Analysis Plan had not

prespecified an alternative analysis if the assumptions in ANOVA were violated, the Division statistician used the rank sum test.

- The Division cited an error to page 5, under the CLINICAL STUDIES section of the revised labeling. The number "6" in the last sentence on page 5, "*...a reduction in the severity of moderate to severe vasomotor symptoms at weeks 6 and 12*," should be the number "7." The Sponsor will review this with their clinical team.

- It will be the Sponsor's option whether they wish to delete the severity tables from the CLINICAL STUDIES section and whether they wish to delete the Week 8 data from the frequency and severity tables, consistent with labeling of similar products.

- The Division explained that the p values for week 8 were deleted from the labeling because they did not relate to the primary efficacy endpoints, and that this deletion was consistent with other approved products.

/S/

Brenda Gierhart, M.D.
Medical Team Leader

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/s/

John C. Kim
8/13/04 11:34:28 AM
CSO

Brenda Gierhart
8/13/04 11:39:03 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-633

7/28/04

Warner Chilcott Company, Inc.
Attention: Ileana Brown, Director
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

Dear Ms. Brown:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for estradiol acetate tablets.

We also refer to the teleconference held on July 16, 2004, between your Staff and the Division wherein you were informed that the use of the tradename, "FEMTRACE®," is not recommended.

We have reviewed your tradename proposal in consultation with the Division of Medication Errors and Technical Support (DMETS). We have the following comments:

1. The use of the proprietary name Femtrace is not recommended. The primary concerns are related to look-alike and/or sound-alike confusion with Estrace®, Premphase®, FemHRT® and Femtrol™.

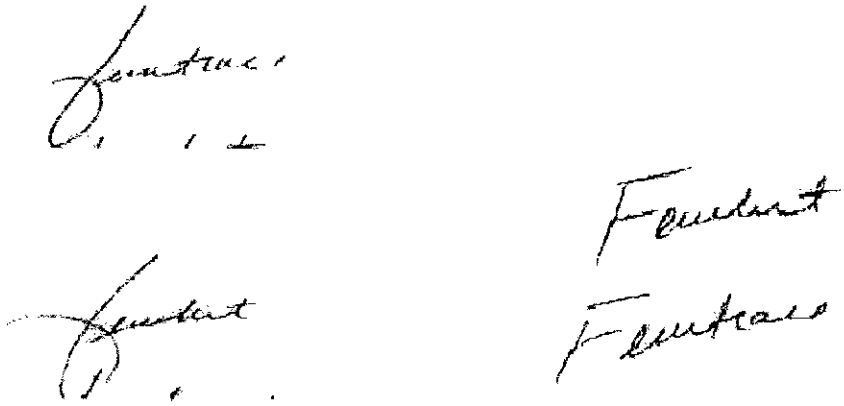
   a. Estrace may look and sound similar to Femtrace. Estrace contains micronized estradiol and is indicated for the treatment of menopausal symptoms, osteoporosis prevention, breast cancer and prostate carcinoma. The usual dose is 0.5 mg to 2 mg daily. The primary visual similarity results from the shared concluding phoneme of "trace." In addition, a printed and scripted capital E can resemble an F, which can compound the visual association. The leading "f" and "e" of Femtrace can extend over each other to give the appearance of a singular "e" as well. Furthermore, a scripted "s" can look like an "m."

   The similarities in speech result from the identical final phoneme of "trace." The names have audible leading letter combinations of "es" in comparison to "fem", which should help to make the names distinctive in speech. The drug products

have overlapping dosing regimens (one tablet daily), indications of use (menopausal symptoms), and dosage forms (tablets). The prescriber or patient populations will also overlap. The names also share similar available strengths (Estrace 0.5 mg, 1 mg and 2 mg compared with Femtrace 0.45 mg, 0.9 mg and 1.8 mg). Thus, the products share similar names, the same prescribing population, and possible confusion with available strengths. Post-marketing reports demonstrate that cognitive errors occur with drug products that have similar names and overlapping characteristics. However, if an error occurred, the patient harm would probably be minimal as the products are of the same drug class, for the same indication and vary little in strength.

b. Premphase may sound similar to Femtrace. The auditory similarities result from the shared phoneme of "em," which has the same location in both names. In addition, "P" and "F" and "ase" and "ace" of Premphase and Femtrace, respectively, may sound analogous in speech, particularly if one considers various dialects and speech patterns. In addition to sounding alike, Femtrace and Premphase have similarities in indication of use (menopausal symptoms), dosing regimens (once a day), dosage forms (tablets), and prescriber and patient population. But unlike Femtrace, which only contains a form of estrogen, Premphase contains a combination of both estrogen and progestin.

c. FemHRT may look similar to Femtrace. The primary visual similarity results from the shared leading phoneme of "Fem." In addition, the "h" of FemHRT may look like "tr" when scripted, and the "rt" of FemHRT and "ace" may look similar when the letters trail off (see below).



These drug products share overlapping dosing regimens (one tablet daily), indications of use (treatment of menopausal symptoms), dosage forms (tablets), and prescriber/patient populations.

d. Femtrol may look and sound similar to Femtrace. The visual and auditory similarities result from the shared leading letters of "Femtr." Although these products differ in dosing regimens, dosing form and prescription status (over-the-

counter herbal vs. prescription), Femtrace and Femtrol have overlapping indications and prescriber/patient populations.

2. Additionally, we reviewed the container and sample labels, and insert labeling from a safety perspective. We have identified the following areas of possible improvement, which might minimize potential user error.

   a. GENERAL COMMENTS

      1) The current presentation is confusing as it lists two strengths on the container label and sample carton. The strength should be based on the amount of estradiol acetate and should be expressed in the following format:

         tradename
         (estradiol acetate tablets)
         XX mg

         This convention should be followed for all container/carton labels. Accordingly, the mentions of estradiol amounts should be removed from all container/carton labels.

   b. CONTAINER LABEL (100 tablets) & SAMPLE CARTON

      1) The colors used to differentiate the 0.9 mg and 1.8 mg strengths are similar in appearance [redacted]. A more contrasting color should be utilized to differentiate these strengths.

      2) The prominence of the strength on the principal display label should be increased.

      3) When the proprietary name appears on the container label or sample carton, the name of the drug product should be displayed in a single font and with a consistent prominence.

      4) On the sample carton, colors used to differentiate the 0.45 mg, 0.9 mg and 1.8 mg should be consistent for the respective container labels.

If you have any questions, please call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
7/28/04 10:28:48 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-633

INFORMATION REQUEST LETTER

Warner Chilcott Company, Inc.
Attention: Ileana Brown, Director
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

7/20/04

Dear Ms. Brown:

Please refer to your October 14, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for estradiol acetate tablets.

We also refer to your submission dated July 9, 2004.

We are reviewing the Statistical sections of your submissions and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1) In addition to the above submission dated July 9, 2004, which contains the Responder Analysis for moderated to severe hot flushes at Weeks 1 to 12 using the ITT population in study PR 01502, provide a table with Responder defined as a subject having a 75% or more decrease in the severity of hot flushes when compared to baseline.

2) Provide the age (in years) variable in datasets PR501VMS.xpt and PR502VMS.xpt submitted on December 16, 2003.

3) For treatment of moderate to severe vasomotor symptoms, provide the analysis data sets for study PR 01502, including those 24 subjects that were inadvertently unblinded. The analysis data sets should contain the following:

a) Change from baseline in frequency of moderate-to-severe vasomotor symptoms at weekly intervals.

b) Change from baseline in the severity score (SS1) at weekly intervals, with the (daily) severity score (SS2) defined as follows:
- SS1 = (2*nr_mod + 3*nr_sev) / nr_ms
- where nr_ms = nr_mod + nr_sev is the total number of moderate to severe hot flushes.

4) [ ]

a) [redacted]

b) [redacted]

For statistical analysis, use the following modeling methods for the above calculations:

Apply an analysis of covariance model where the observation variable is a change from baseline; and where the independent variables include treatment, center, treatment by center interaction, and baseline as covariate. Treatment by center interaction may be dropped if not significant. Apply a Shapiro-Wilkes or comparable test to evaluate the residuals for the normality assumptions. If the normality assumptions are not valid, reanalyze using a stratified Wilcoxon rank sum test with center as the stratification variable. (This test is also referred to as the van Elteren test, see for example, http://ftp.sas.com/techsup/download/stat/vanelter.html for references and example of source code).

If you have any questions, call John C. Kim, R.Ph., J.D., Regulatory Health Project Manager, at (301) 827-3003.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
7/20/04 05:47:27 PM
Chief, Project Management Staff

7/8/04

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: March 11, 2004	**DESIRED COMPLETION DATE:** May 11, 2004 **PDUFA DATE:** August 20, 2004	**ODS CONSULT #:** 04-0090

TO: Daniel Shames, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Dale Cutright
Project Manager
HFD-580

PRODUCT NAME: **Femtrace®** (Estradiol Acetate Tablets) 0.45 mg, 0.9 mg, and 1.8 mg **NDA#:** 21-633	**NDA SPONSOR:** Galen Limited

SAFETY EVALUATOR: Kimberly Culley, RPh

RECOMMENDATIONS:

DMETS does not recommend the use of the proprietary name Femtrace.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review, in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Femtrace acceptable from a promotional perspective.

Carol Holquist, RPh
Director, Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242
Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 15, 2004

NDA# 21-633

NAME OF DRUG: Femtrace® (Estradiol Acetate Tablets)
0.45 mg, 0.9 mg, and 1.8 mg

NDA HOLDER: Galen Limited

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for an assessment of the proprietary name, Femtrace, in regard to potential name confusion with other proprietary or established drug names. Container labels and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Femtrace contains estradiol acetate, which is indicated for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. Femtrace is available as a tablet formulation in three strengths, which include the following: 0.45 mg (equivalent to 0.39 of 17-β estradiol), 0.9 mg (equivalent to 0.78 mg of 17-β estradiol) and 1.8 mg (equivalent to 1.56 mg of 17-β estradiol). It is recommended that patients start on the lowest dose, to be taken daily and adjusted as necessary. In addition, the patient with a uterus should also take a progestin concurrently to reduce the risk of endometrial cancer. A patient without a uterus does not need progestin. Estrogen should be used at the lowest effective dose for the shortest duration of time possible to adhere to treatment goals and avoid risks. Femtrace will be supplied in bulk bottles containing 100 tablets. The various tablet strengths will be differentiated by color, which are represented as follows: 0.45 mg tablets are cream, 0.9 mg tablets are white and 1.8 mg tablets are yellow.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Femtrace to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Femtrace. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Error Prevention Staff with representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Femtrace acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Femtrace. These products with the available dosage forms and usual dosage are listed in table 1 (see below).

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Proprietary Name	Established name, Dosage Form(s) and Strength(s)	Usual dose/dose range	Other
Estrace®	Micronized Estradiol Tablets 0.5 mg, 1 mg and 2 mg	1 to 2 mg daily.	LA/SA
Premphase®	Premarin® Tablets(Conjugated Estrogens 0.625 mg) and a combination tablet containing Conjugated Estrogens 0.625 mg and Medroxyprogesterone 5 mg	One 0.625 mg conjugated estrogens tablet daily for days 1 through 14 and one 0.625 mg conjugated estrogen/5 mg medroxyprogesterone tablet daily on days 15 through 28.	SA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA identified FemHRT which was considered to have significant phonetic or orthographic similarities to Femtrace. The available dosage forms and usual dosage is listed in table 2 (see below).

Table 2: Potential Sound-Alike/Look-Alike Names Identified by POCA

			Other**
FemHRT®	Each Tablet Contains Ethinyl Estradiol 5 mcg and Norethindrone Acetate 1 mg	One tablet daily. Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary	SA/LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Femtrace with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Femtrace (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail and sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

[illegible]	[illegible]
Outpatient RX: Femtrace 1.8 mg Tpo qd #30	Femtrace 1.8 mg Take one every day Dispense number 30
Inpatient RX: Femtrace 1.8 mg po qd #30	

2. Results:

One respondent from the inpatient prescription study interpreted the proposed name as FemHRT, which is a currently marketed U.S. product. A second respondent from the inpatient prescription study interpreted the proposed name as Femtrol™. Femtrol is a dietary supplement composed of herbs, vitamin C and bioflavonoids to support female glandular function. The third respondent from the verbal prescription study interpreted the proposed name as stem trace, which is a tool used for RNA structure analysis. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

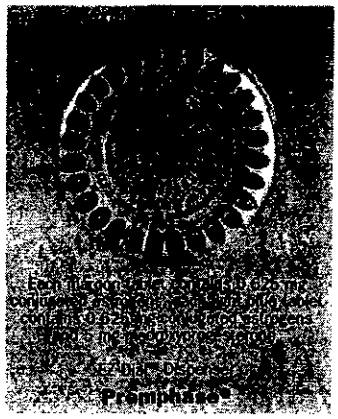
In reviewing the proprietary name Femtrace, the primary concerns related to look-alike and sound-alike confusion with Estrace, Premphase, Femtrol and FemHRT.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Femtrace could be confused with FemHRT. One respondent from the inpatient study misinterpreted the proposed name for this already marketed drug product. Another inpatient study respondent interpreted the proposed name as Femtrol. Femtrol is a dietary supplement composed of herbs, vitamin C and bioflavonoids to support female glandular function. Although there are limitations to the predictive value of these studies that are primarily due to sample size, we have safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. In the verbal prescription study, another participant identified Stem Trace for the proposed name. Stem Trace is a tool used for RNA structure analysis. Given the context of use, a misinterpretation of Stem Trace instead of Femtrace should not contribute to any medication errors. The majority of remaining misinterpretations were misspelled/phonetic variations of the proposed name, Femtrace.

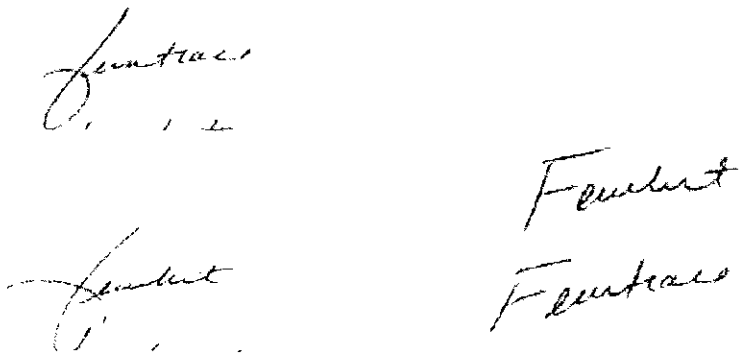
1. Estrace may look and sound similar to Femtrace. Estrace contains micronized estradiol and is indicated for the treatment of menopausal symptoms, osteoporosis prevention, breast cancer and prostate carcinoma. The usual dose is 0.5 mg to 2 mg daily. The primary visual similarity results from the shared concluding phoneme of "trace." In addition, a printed and scripted capital E can resemble an F, which can compound the visual association. The leading "f" and "e" of Femtrace can extend over each other to give the appearance of a singular "e" as well. Furthermore, a scripted "s" can look like an "m."

The similarities in speech result from the identical final phoneme of "trace." The names have audible leading letter combinations of "es" in comparison to "fem", which should help to make the names distinctive in speech. The drug products have overlapping dosing regimens (one tablet daily), indications of use (menopausal symptoms), and dosage forms (tablets). The prescriber or patient populations will also overlap. The names also share similar available strengths (Estrace 0.5 mg, 1 mg and 2 mg compared with Femtrace 0.45 mg, 0.9 mg and 1.8 mg). As the products share similar names, same prescribing population, and possible confusion with available strengths, DMETS believes the potential for medication error does exist. Furthermore, post-marketing reports demonstrate that cognitive errors occur with drug products that have similar names and overlapping characteristics. However, if an error occurred, the patient harm would probably be minimal as the products are of the same drug class, for the same indication and vary little in strength.

2. Premphase may sound similar to Femtrace. Premphase is packaged in an EZ dial dispenser which contains two different tablets that are indicated for the treatment of menopausal symptoms. The first fourteen tablets contain conjugated estrogens (Premarin 0.625 mg) and the second fourteen tablets contain a combination of 0.625 mg of conjugated estrogens and 5 mg of medroxyprogesterone. Dosing is a tablet daily for twenty-eight days. The auditory similarities result from the shared phoneme of "em", which has the same location in both names. In addition, "P" and "F" and "ase" and "ace", of Premphase and Femtrace respectively may sound analogous in speech. Especially if one considers various dialects and speech patterns. The drug products have overlapping dosing regimens (one tablet daily), indications of use (menopausal symptoms), dosage forms (tablets), and prescriber and patient populations. Although the names may sound similar, they differ in available strengths (one product package including 0.625 and 0.625/5mg strengths compared with 0.45 mg, 0.9 mg and 1.8 mg, and product packaging (EZ dial with product name written centrally (see below) compared with typical pharmacy labeled bottle) which may contribute to decreased confusion and errors.



3. FemHRT may look similar to Femtrace. FemHRT contains 5 mcg ethinyl estradiol and 1 mg norethindrone acetate and is indicated for the treatment of menopausal symptoms. The usual dose is one tablet daily. The primary visual similarity results from the shared leading phoneme of "Fem." In addition, the "h" of FemHRT may look like "tr" when scripted (see page 7).



However, the concluding "rt" of FemHRT and contrasting "ace" of Femtrace should provide distinguishing written characteristics except when the letters trail off. The drug products share overlapping dosing regimens (one tablet daily), indications of use (treatment of menopausal symptoms), dosage forms (tablets), and prescriber/patient populations. In addition, the leading identical "Fem" may result in similar placement or close proximity on pharmacy shelves, which increases the potential for error. Although the names may look similar upon scripting, the differences in available strengths (combination product of 5 mcg ethinyl estradiol and 1 mg norethindrone acetate compared with 0.45 mg, 0.9 mg, and 1.8 mg) should help to diminish medication errors and confusion.

4. Femtrol may look and sound similar to Femtrace. Femtrol is a dietary supplement for which each capsule contains vitamin C (50 mg), Don Quai extract (125 mg) , Hesperiden Complex Standardized (50% bioflavonoids), Licorice root extract (25 mg), Chaste Tree Berry extract (25 mg), Black Cohosh (25 mg), False Unicorn root extract (25 mg), and fennel seed extract (12.5 mg). This supplement is indicated to support female glandular function and dosed at one to two capsules three times daily. The primary visual and auditory similarities result from the shared leading letters of "Femtr."

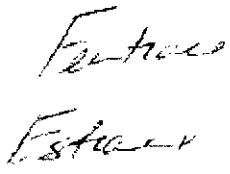
FEMTROL
FEMTRACE

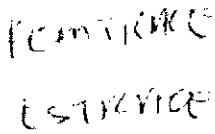
However, the concluding "ol" of Femtrol and contrasting "ace" of Femtrace should provide distinguishing written and verbal characteristics. The drug products have overlapping indications, and prescriber and patient populations, but differ in dosing regimen, dosage form and prescription status. Femtrol is an over-the-counter herbal supplement that is only available from specialty stores and online. This status will help to diminish drug name confusion since Femtrace will require a phone or written prescription in opposition to Femtrol.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name Femtrace. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Estrace.

Estrace may look and sound similar to Femtrace. Estrace contains micronized estradiol and is indicated for the treatment of menopausal symptoms, osteoporosis prevention, breast cancer and prostate carcinoma. The usual dose is 0.5 mg to 2 mg daily. The primary visual similarity results from the shared concluding phoneme of "trace." In addition, a printed and scripted capital E can resemble an F, which can compound the visual association. The leading "f" and "e" of Femtrace can extend over each other to give the appearance of a singular "e" as well. Furthermore, a scripted "s" can look like an "m."





The similarities in speech result from the identical final phoneme of "trace." The names have audible leading letter combinations of "es" in comparison to "fem", which should help to make the names distinctive in speech. The drug products have overlapping dosing regimens (one tablet daily), indications of use (menopausal symptoms), and dosage forms (tablets). The prescriber or patient populations will also overlap. The names also share similar available strengths (Estrace 0.5 mg, 1 mg and 2 mg compared with Femtrace 0.45 mg, 0.9 mg and 1.8 mg). As the products share similar names, same prescribing population, and possible confusion with available strengths, DMETS believes the potential for medication error does exist. Furthermore, post-marketing reports demonstrate that cognitive errors occur with drug products that have similar names and overlapping characteristics. However, if an error occurred, the patient harm would probably be minimal as the products are of the same drug class, for the same indication and vary little in strength.

Additionally, DMETS reviewed the container labels and insert labeling from a safety perspective. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. GENERAL COMMENTS

From the insert provided, it is unclear if the drug product is dosage is based on the salt or the active moiety. The current presentation is confusing as it lists two strengths on the label. This format has led to confusion with the dosing of other similar products (e.g. Ogen®). If it is based on the salt, the equivalency statement should be deleted from the principal display panel. If based on the active moiety, the strength should be expressed in one the following formats:

a. femtrace
(estradiol tablets)
XX mg

b. femtrace
(estradiol acetate tablets)
XX mg*

*Each tablet contains estradiol acetate equivalent to XX mg of 17-β estradiol.

c. femtrace
(estradiol acetate tablets)
equivalent to XX mg 17-β estradiol

Of note, DMETS prefers the first example ("a") since this nomenclature is consistent with USP recommendations on the "labeling of salts of drugs." Additionally, the Dosage and Administration section should be revised to clarify the dosing as well.

2. CONTAINER LABEL (100 tablets)

a. The colors used to differentiate the 0.9 mg and 1.8 mg strengths are similar in appearance [ ] A more contrasting color should be utilized to differentiate these strengths.

b. Increase the prominence of the strength on the principle display label.

c. We note the font of "fem" portion of the name appears in a bolder font than the remaining portion of the name. DMETS recommends name of the drug product be displayed in the same font and with the same prominence.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name Femtrace.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary name Femtrace acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

/S/

Kim Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur: /S/

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A: DMETS Prescription Study Results

Inpatient	Outpatient	Voice
Femtrace	Femtrace	Femtrace
Femhrt	Femtrace	Femtrate
Femtrace	Femtace	Tentrace
Feintrace	Femtrace	Centrate
Femtrace	Femtrace	Stem Trace
Femtrace	Femtrace	Bentrace
Femtrace	Femtrace	Zemtrain
Femtruse	Femtace	Zemtrate
Femtrane	Femtace	Femtrace
Femtrace	Temtace	Feltrate
Femtrace	Femtray	Femtrace
Feintrace	Femtrace	
Femtrace	Femtrace	
Ferntrace	Femtrace	
Femtrol	Femtrace	
Femtreve	Femtrace	
Femtrace	Femtrace	
Femtrase	Femtrace	
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	Femtrace	

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/s/

Kimberly Culley
7/8/04 10:27:52 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
7/8/04 11:09:19 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM OF TELECON

DATE: July 1, 2004

APPLICATION NUMBER: NDA 21-633, Femtrace™ (estradiol acetate) tablets

BETWEEN:

Name: Olu Aloba, Ph.D., Director of Pharmaceutics
Alvin Howard, Vice President, Regulatory Affairs
Ileana Brown, Director, Regulatory Affairs
Phone: 973-442-3229
Representing: Galen (Chemicals) Limited

AND

Name: John C. Kim, R.Ph., J.D., Regulatory Health Project Manager
Sarah Pope, Ph.D., Chemist, Division of New Drug Chemistry II
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Justification for the acceptance criteria for Related Substances.

DISCUSSION:

- Dr. Pope proposed the following acceptance criteria to the Sponsor for consideration, as indicated in parentheses below:

	0.45 mg	0.9 mg	1.8 mg
Related Substances			
	NMT	NMT	NMT
	NMT	NMT	NMT
	NMT	NMT	NMT
	NMT	NMT	NMT
	NMT	NMT	NMT
Highest unknown related substance	NMT	NMT	NMT
Total Related Substances	NMT	NMT	NMT

- The Sponsor indicated that the specification was not based on the actual product but rather on estradiol, USP's specification and believed that the initially proposed values were well below ICH guidelines.

- The Sponsor was asked to provide a detailed justification for the Sponsor's initially-proposed acceptance criteria for Related Substances, Highest Unknown Related Substance, and Total Related Substances.

ACTION ITEMS:

- PM will fax copy of memorandum of teleconference with the proposed acceptance criteria.
- Sponsor will submit provide a detailed provide a justification for the firm's initially-proposed acceptance criteria for Related Substances, Highest Unknown Related Substance, and Total Related Substances next week.

{See appended electronic signature page}

Sarah Pope, Ph.D.
Chemist

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/s/

John C. Kim
7/1/04 03:40:21 PM
CSO

Sarah Pope
7/1/04 04:22:55 PM
CHEMIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 29, 2004

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: Dale Cutright, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Femtrace (estradiol acetate tablets), NDA 21-633

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Femtrace (estradiol acetate tablets), NDA 21-633. We have made it consistent with the February 10, 2004 revised *Draft Guidance: Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Prescribing Information for Health Care Providers and Patient Labeling*, based on the WHI study. These revisions are based on revised draft labeling submitted by the sponsor on March 17, 2004.

We also have the following recommendation:
Do not use all upper case letters (the tradename is an exception) to emphasize words or statements. Mix upper and lower case letters and bold or increase the font size for emphasis. All upper case letters are difficult to read.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please call us if you have any questions.

5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Jeanine Best
4/29/04 02:09:24 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
4/29/04 02:11:36 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

4/28/04

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA # 21-633 Supplement # _____ SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Femtrace (oral tablet)
Generic Name: estradiol acetate
Strengths: 0.45, 0.9, and 1.8 mg

Applicant: Galen Holdings

Date of Application: October 14, 2003
Date of Receipt: October 20, 2003 (due to late user fee payment)
Date of Filing Meeting: December 2, 2003
Filing Date: December 19, 2003

Indication(s) requested: Treatment of moderate to severe vasomotor symptoms, vulvar and vaginal strophy associated with menopause

Type of Application: Original (b)(1) NDA X Original (b)(2) NDA _____
(b)(1) Supplement _____ (b)(2) Supplement _____
[If the Original NDA was a (b)(2), all supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or a (b)(2).]

If the application is a 505(b)(2) application, complete the 505(b)(2) section at the end of this summary.

Therapeutic Classification: S X P _____
Resubmission after a withdrawal _____ or refuse to file _____
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) _____

Has orphan drug exclusivity been granted to another drug for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

Is the application affected by the application integrity policy (AIP)? YES NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

User Fee Status: Paid Yes Waived (e.g., small business, public health) _____
Exempt (orphan, government) _____
Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # 4518
Clinical data? YES x NO _____, Referenced to NDA # _____

Date clock started after UN: October 20, 2003

User Fee Goal Date: August 20, 2004

- Does the submission contain an accurate comprehensive index? YES NO

- Was form 356h included with an authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

- If in Common Technical Document format, does it follow the guidance? N/A YES NO

- Is it an electronic CTD? N/A YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

- Patent information included with authorized signature? YES NO

- Exclusivity requested? YES, _____years NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure information included with authorized signature? YES NO
  (Forms 3454 and/or 3455 must be used and must be signed by the APPLICANT.)

- Has the applicant submitted pediatric waiver request for all ages and indications?

  YES NO

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers:

- End-of-Phase 2 Meeting? Date _____ NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) February 12, 2003
  NO
  If yes, distribute minutes before filing meeting.

Project Management

- Package insert consulted to DDMAC? YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/Div. of Medication Errors and Technical Support? YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/Div. of Surveillance, Research and Communication Support?
  YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/ Div. of Surveillance, Research and Communication Support?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 2, 2003

TIME: 10:30 a.m.

LOCATION: 17B-43

APPLICATION: NDA 21-633/Femtrace (estradiol acetate)

TYPE OF MEETING: 60-day filing

MEETING CHAIR: Theresa van der Vlugt, MD

MEETING RECORDER: Dale Cutright, PM

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Theresa van der Vlugt, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products
Ron Orleans, M.D., Medical Officer, DRUDP
Moo-Jhong Rhee, Ph. D., Chemistry Team Leader, DNDC II
Sarah Pope, Ph. D., Chemist, DNDC II
Lynda Reid, Ph. D., Pharmacologist, DRUDP
Ameeta Parekh, Ph. D., Clinical Pharmacology Team Leader, OCPB
DJ Chatterjee, Ph. D., Clinical Pharmacology Reviewer, OCPB
Moh-Jee Ng, M.S. – Statistician, DBII
Dale Cutright, Regulatory Project Manager, DRUDP

BACKGROUND: Femtrace (estradiol acetate), submitted by Galen (Chemicals) Limited, located in NJ, has proposed dosages of 0.45mg, 0.9 and 1.8 mg once daily oral tablet indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. This NDA was received on October 14, and the user fee was paid on October 20, 2003, making the PDUFA goal date August 20, 2004. The tablets are manufactured by Pharmaceutics International, Inc. in Hunt Valley, Maryland.

Estradiol acetate (EA) is a 3-acetate ester prodrug of estradiol. In vitro, estradiol acetate is very rapidly hydrolyzed to estradiol; the hydrolysis half-life is 28 seconds. In vivo, following oral administration of a 1.8 mg estradiol acetate tablet to healthy postmenopausal women, estradiol acetate was not detected in serum samples. Therefore, systemic exposure to estradiol acetate is not considered to be significant.

Estradiol-3-acetate is synthesized [ ]. The principle impurity is [ ] [ ] manufactures estradiol-3-acetate, the active ingredient. Pharmaceutics International, Inc. in Hunt Valley, MD will manufacture the 0.45 mg E3A and placebo tablets.

MEETING OBJECTIVES:

45-day filing meeting: to make a determination if there is sufficient material to be reviewed, adequate information to perform the review, in correct order, legible, etc.

Chemistry

- The application has all the necessary sections to review.
- Drug substance manufacture is referenced to DMF [ ]

- The drug product manufacturing sites all returned as acceptable from the Office of Compliance.
- Limited Stability data has been submitted for this NDA. Additional stability data should be provided when available.
- Justification of the exclusion of [ ] specifications [ ] for all three dosages strength tablets should be provided.
- NDA is fileable.

Pharmacology/Toxicology

- Based on evidence of rapid hydrolysis of estradiol acetate to estradiol, resulting in no detectable systemic levels of estradiol acetate, the use of previous nonclinical studies and clinical experience with estradiol to support the safety of Femtrace is acceptable.
- NDA is fileable.

Clinical Pharmacology/Biopharmaceutics

- There are 3 studies presented in this NDA to support information on pharmacokinetics.
- The to-be marketed product is similar in formulation to the product in Phase 3 studies. Note that the minor difference [ ] with the 0.45 mg dose between the Phase 3 and the to-be-marketed formulation is a review issue and will be addressed following review of the relevant dissolution data.
- NDA is fileable.

Clinical

- The Phase 3 Study 00501 and Study 00502 to investigate a lowest effective dose were consistent with the recommendations in the Agency's 2003 draft clinical evaluation guidance document.
- Study 00501 was a 41 center, 12-week, double-blind, and placebo-controlled randomized study, with a total of 293 subjects randomized to EA 0.9 mg treatment group, 1.8 mg treatment group, or placbo. 263 subjects completed the study (89%).
- Study 00502 was a 36 center, 12-week, double-blind, and placebo-controlled randomized study with 259 subjects randomized to EA 0.45 mg treatment group or the placebo-treatment group. 218 subjects complted the study (84.2%).
- The first 50 subjects enrolled in Study 00501 were not asked to record their most bothersome urogenital symptom at baseline.
-
- In Study 00502, subject medication labels were mistakenly unblinded at site 62 for all 24 subjects randomized at that site. The statistical analysis plan was revised (Amendment 1) to define an efficacy analysis subset which excluded all 24 subjects at site 62.
- NDA is fileable.

Statistical

- Information needed from Sponsor is the efficacy analysis data sets, data definition files in SAS transport format, and also include SAS source code used for the analyses above and any supporting output.
- NDA is fileable.

Action Items

- Team members will e-mail to PM and a copy to team leader any comments (cut and paste format) to be forward to sponsor in 74-day filing letter, (July 11).

- Team members will also e-mail to PM any their notes of meeting minutes.
- The PM will telephone the sponsor and request:
  - The number of subjects enrolled by study site for each study.
  - The number of subjects discontinued by study site for each study
  - The number of protocol violations by study site for each study
  - The efficacy analysis data sets, data definition files in SAS transport format, and also include SAS source code used for the analyses above and any supporting output.
- The PM will forward the package insert to DDMAC and DMETS for review.
- The PM will forward the request for clinical inspections.

Cc:
HFD-580/Division Files
HFD-580/Original NDA 21-633
HFD-580/Cutright/van der Vlugt 12/10/03, Orleans, Pope 12/8/03, Rhee 12/8/03, Reid 12/8/03, Thornton, Chatterjee 12/8/03, Parekh, Ng 12/5/03

Created by: Dale Cutright, 12.2.03
Revised by: DCutright

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/s/

Dale Cutright
4/28/04 03:08:01 PM
CSO

MEMORANDUM OF TELECON

DATE: April 27, 2004

APPL NUMBER: NDA 21-633– Femtrace (estradiol acetate) Tablets

BETWEEN:

Name: Galen Limited
Ileana Brown, Director, Regulatory Affairs
Tina deVries, Ph.D., Vice President, Pharmaceutics
Olu Aloba, Ph.D., Director of Pharmaceutics

Phone: 973-442-3229

AND

Name: Sarah Pope, Ph.D., Reviewing Chemist
Dale Cutright, Regulatory Project Manager, DRUDP

SUBJECT: Clarification on April 8, 2004 chemistry submission

The sponsor was telephoned with issues on the April 8, 2004, submission and general NDA clarification/questions:

Issue 1
On page 371 of Table 1.3, a table is presented for all in-process controls. A footnote states that [ ] testing is performed [ ] The Sponsor clarified that [ ] testing is performed [ ] Once this is established, [ ] testing is [ ] of the entire batch. In contrast, [ ] testing [ ] of the entire batch. The Sponsor reasoned that [ ] testing would [ ]

The in-process [ ] data for all batches in is in the index.

Issue 2
It was noted that a — overage is utilized for the 0.45 mg dosage, but only — overage is used for the two higher doses. The Sponsor clarified that the overages are due to [ ] during manufacture. The Sponsor also confirmed that [ ]

A specific description will be made in writing as a formal submission.

Issue 3
The Sponsor was asked to confirm the locations for the certificates of analysis (COA) for the drug product and drug substance, including the batches described on page 278, sec 4.2.

The Sponsor will find and clarify the location of this documentation.

/S/

Dale Cutright
Project Manager

/S/

Sarah Pope, Ph.D.
Reviewing Chemist

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/s/

Dale Cutright
4/29/04 06:56:28 AM
CSO

Sarah Pope
4/29/04 03:00:35 PM
CHEMIST

MEMORANDUM OF TELECON

DATE: March 5, 2004

APPL NUMBER: NDA 21-633– Femtrace (estradiol acetate tablets)

BETWEEN:

Name: Galen Chemicals, Ltd.
Ileana Brown, Director, Regulatory Affairs

Phone: 973-442-3229

AND

Name: Dale Cutright, Regulatory Project Manager, DRUDP
Sarah Pope, Ph.D., Chemist, DNDCII, DRUDP

SUBJECT: Request for additional stability data and justification for specifications

The sponsor was contacted with two additional chemistry information requests:

- Limited stability data has been submitted for this NDA. Please provide additional stability data when available.
- Justify the exclusion of [ ] specifications for [ ] for all three dosage strength tablets.

The sponsor agreed to submit as an amendment the above requested information within the next two weeks.

/S/

Dale Cutright
Regulatory Project Manager

/S/

Sarah Pope, Ph.D.
Reviewing Chemist

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/s/

Dale Cutright
3/23/04 11:35:47 AM
CSO

Sarah Pope
4/6/04 09:53:52 AM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-633

2/11/04

Galen (Chemicals) Limited
Attention: Alvin Howard
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, New Jersey 07866

Dear Mr. Howard:

Please refer to your new drug application (NDA) for Femtrace™ (estradiol acetate tablets).

The Division of Reproductive and Urologic Drug Products (DRUDP) is continuing to encourage manufacturers of estrogen- and progestin-containing products indicated for use by postmenopausal women to update the labeling for their products. Information from the Women's Health Initiative (WHI) trial about estrogens and progestins continues to have significant public health implications for postmenopausal women. As the series of new study results from the WHI become available, we strongly recommend that sponsors update their labels for estrogen- and progestin-containing drug products for postmenopausal women to include new information from these studies. In addition, in the absence of data to show whether risks that may be associated with use of estrogen- and progestin-containing drug products are dose-related, it is important for labeling to specify whether the lowest effective dose has been determined.

Access to the most current information available is important to health care providers and postmenopausal women who are prescribed estrogen- and progestin-containing products. This information will allow individuals to understand the risks of these products and whether the lowest effective dose has been determined or is available. Appropriate health care decisions can then be made.

Results of the WHI study:

On May 31, 2002, the WHI study of PREMPRO (conjugated estrogens 0.625 mg/day, plus medroxyprogesterone acetate 2.5 mg/day) in postmenopausal women was stopped after a mean of 5.2 years of follow-up because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. Data on the major clinical outcomes through April 30, 2002, regarding increased risks for invasive breast cancer, heart attacks, strokes, and venous thromboembolism rates, including pulmonary embolism, became available July 17, 2002. These data were updated March 17, 2003.

The Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, recently concluded that women treated in the study with conjugated estrogens (CE 0.625mg) combined with medroxyprogesterone acetate (MPA 2.5mg) have a greater risk of developing probable dementia than those on placebo. Detailed information about WHIMS is available at www.nih.gov/PHTindex.htm.

Labeling changes related to risk:

We are recommending labeling revisions to address the above risks. The recommended labeling revisions are described generally in the revised draft guidance located on FDA's web site at www.fda.gov/cder/guidance/index.htm. (The revised draft guidance also includes labeling revisions recommended in the draft guidance of the same title issued January 2003.) In addition, for your convenience, we have included more specific language relevant to your specific product in an attachment to this letter. Although we are seeking public comment on the draft guidance, we are encouraging sponsors to update the labeling for their products as soon as possible to make this information available to health care practitioners and patients.

Sponsors who plan to update the labeling for their products but believe that the recommended revised labeling does not accurately reflect the risk of their product should submit controlled clinical data to demonstrate the difference in risk profile, compared to the drug product used in the WHI, in support of their proposed labeling changes.

Labeling changes related to lowest effective dose:

To provide adequate information for health care practitioners and women prescribed estrogen- and progestin-containing drug products for their postmenopausal symptoms, we recommend revised labeling to delineate whether the lowest effective dose has been determined and is available for the product. The recommended labeling revisions that address this issue are described in the draft guidance and product-specific attachment. The guidance and attachment may be revised after public comments are received, but at this time the recommended language reflects the Agency's current thinking on what the labeling should say about the WHI findings.

Sponsors who plan to update the labeling for their products and have controlled clinical data demonstrating that the lowest effective dose for their product has been determined should submit the data or, if previously submitted, identify the submission that contains the data.

Procedures to submit revised labeling:

We encourage sponsors to submit without delay the recommended revised labeling to address the risk and lowest effective dose issues described above.

a. Sponsors who hold approved NDAs for estrogen- and progestin-containing products are encouraged to submit revised draft labeling as a prior approval supplemental application to their application(s). If your draft labeling proposes different risk statements or if you have demonstrated determination of lowest effective dose for your product(s), include these data to support the proposed statements. You can incorporate in this supplement

any changes proposed in previously submitted supplements that are under review by the Agency. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the proposed changes.

b. Sponsors of pending NDAs for estrogen- and progestin-containing products can submit revised draft labeling.

c. Sponsors developing estrogen- and progestin-containing products for treatment of postmenopausal symptoms who believe that the recommended revised labeling will not accurately reflect the risk of their product should include in their drug development plan controlled clinical trials to demonstrate the difference in risk profile. In addition, we recommend that the drug development plan include controlled clinical trials designed to determine the lowest effective dose for the product. We encourage you to discuss with us any protocols concerning risk assessment and determination of lowest effective dose prior to conduct of these studies.

The Agency has received requests from the public to provide updated product information for estrogen- and progestin-containing drug products used for treating postmenopausal symptoms. We are establishing a web page that lists products with approved updated labeling that includes the important information from the WHI, WHIMS and any other related studies. We encourage you to respond promptly to this letter as the requested labeling changes provide important information to health care practitioners and women prescribed estrogen- and progestin-containing products.

If you have any questions, call Margaret Kober, Chief, Project Management Staff, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
2/11/04 11:58:08 AM
signed for Dr. Shames

52 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-633

12/18/03

Galen (Chemicals) Limited
Attention: Alvin Howard
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

Dear Mr. Howard:

We refer to your October 20, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Femtrace™ (estradiol acetate tablets).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on December 19, 2003 in accordance with 21 CFR 314.101(a).

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have any questions, please call Dale Cutright, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
(HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
12/18/03 12:24:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-633

12/10/03

Galen (Chemicals) Limited
Attention: Alvin Howard
Vice President Regulatory Affairs
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

Dear Mr. Howard:

Please refer to your October 14, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Femtrace™ (estradiol acetate tablets).

We are currently reviewing your submission and have the following requests:

- The proposed acceptance criterion for "Highest Unknown Related Impurity" is [ ] for the two higher dosage strength tablets (0.9 mg and 1.8 mg), while the same acceptance criterion for the 0.45 mg tablet is proposed as NMT [ ] Provide a rationale for these criteria, and explain the difference in this criteria for the lower (0.45 mg) and higher (0.9, 1.8 mg) dosage strengths.

- Provide rationales for the proposed acceptance criterion for each of the "Related Substances," as well as for the proposed criterion for "Total Related Substances."

- The included "Note to Reviewer" (Vol. 3) refers to [ ] used in manufacture. However, this [ ] is not mentioned in the Manufacturing section. The [ ] should be explicitly detailed in the manufacturing process.

If you have any questions, please call Dale Cutright, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
Division of Reproductive and Urologic Drug Products
(HFD-580)
DNDC II, Office New Drug Chemistry
Center for Drug Evaluation and Research

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/s/

Moo-Jhong Rhee
12/10/03 03:41:08 PM

MEMORANDUM OF TELECON

DATE: December 3, 2003

APPL NUMBER: NDA 21-633– Femtrace (estradiol acetate tablets)

BETWEEN:

Name: Galen Limited
Ileana Brown, Director, Regulatory Affairs

Phone: 973-442-329

AND

Name: Dale Cutright, Regulatory Project Manager, DRUDP

SUBJECT: Information requested from Medical Reviewer, Dr. Ron Orleans

The sponsor was telephoned upon the request of the medical reviewer and the following was conveyed:

- The number of subjects enrolled by study site for each study.
- The number of subjects discontinued by study site for each study
- The number of protocol violations by study site for each study
- The efficacy analysis data sets, data definition files in SAS transport format, and also include SAS source code used for the analyses above and any supporting output.

/S/

Dale Cutright

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/s/

Dale Cutright
12/17/03 01:59:17 PM

NDA FILEABILITY CHECKLIST

NDA Number: 21-633 **Applicant:** Galen Chemicals, Ltd. **Stamp Date:** 14-OCT-2003

Drug Name: Femtrace (estradiol acetate tablets)
0.45, 0.9, and 1.8 mg

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	*Yes*	*No*	*Comment*
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		Drug substance manufacture is referenced to DMFs [ ] (estradiol acetate) and DMF [ ] (estradiol).
5	Is a statement provided that all facilities are ready for GMP inspection?	√		All sites have been recommended as Acceptable, by the Office of Compliance (12-NOV-2003).
6	Has an environmental assessment report or categorical exclusion been provided?	√		Reference to CFR 25.31(a) and (b) – the Sponsor has filed a claim for categorical exclusion (Vol. 5, page 1127).
7	Does the section contain controls for the drug substance?	√		See DMF [ ]
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Additional data should be submitted when available – see filing comments.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has an investigational formulations section been provided?	√		
14	Is there a Methods Validation package?	√		Vol. 4-5.
15	Is a separate microbiological section included?		√	Not necessary, since this is an solid oral dosage form (tablet).

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

Review Chemist: Sarah C. Pope, Ph.D. Date: 03-DEC-2003

Team Leader: David T. Lin, Ph.D. Date: 03-DEC-2003

Original NDA 21-633

HFD-580/Division File
HFD-580/D. Lin/S. Pope
HFD-580/D. Cutright

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: December 3, 2003

To: Ms. Ileana Brown, Manager	**From:** Dale Cutright, Project Manager
Company: Galen (Chemicals) Limited	
Fax number: 973-442-3280	**Fax number:** 301-594-0747
Phone number: 973-442-3229	**Phone number:** 301-827-4260

Subject: NDA 21-633 Femtrace – Request from Statistician

Total no. of pages including cover: 3

Comments:

Document to be mailed: • YES ☑ NO

NDA 21-633 - Femtrace™

Please provide the analysis data sets and data definition files in SAS transport format for studies PR 00501 and PR 00502, include your source code used for the analyses listed below and any supporting output.

- **treatment of moderate to severe vasomotor symptoms**

(1) change from baseline in frequency of moderate-to-severe vasomotor symptoms at weeks 4, 8 and 12

(2) change from baseline in the severity score at weeks 4, 8 and 12,

with the (daily) severity score (SS1) is defined as follows:

SS1 = (nr_mild + 2*nr_mod + 3*nr_sev) / nr_total
where nr_mild, nr_mod and nr_sev are the numbers of mild, moderate and severe hot flushes, respectively, and nr_total is the total number of all hot flushes.

(3) change from baseline in the severity score (SS2) at weeks 4, 8 and 12,

with the (daily) severity score (SS2) is defined as follows:
SS2 = (2*nr_mod + 3*nr_sev) / nr_ms
Where nr_ms = nr_mod + nr_sev is the total number of moderate to severe hot flushes.

Please use the following statistical modeling methods:

Apply an analysis of covariance model where the observation variable is change from baseline; independent variables include treatment, center, treatment by center interaction, and baseline as covariate. Treatment by center interaction may be dropped if not significant. Apply a Shipiro-Wilkes or comparable test to evaluate the residuals for the normality assumptions. If the normality assumptions are not valid, re-analyze using a stratified Wilcoxon rank sum test with center as the stratification variable. (This test is also referred to as the van Elteren test, see for example,
http://ftp.sas.com/techsup/download/stat/vanelter.html for references and example of source code).

Perform the above analyses for the ITT population with last observation carried forward.
Also perform the analyses with only completers (no imputation).

Present tables of analysis results in terms of average change from baseline per 24 hours.

For protocol 00502, those 24 subjects inadvertently unblined should be indicated in the datasets.
For protocol 00501, those 50 subjects did not record their most bothersome urogenital symptoms at baseline should be indicated in the datasets.

- **treatment of vulvar and vaginal atrophy**

1. [
2.
3.
4.]

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/s/

Dale Cutright
12/8/03 07:49:21 AM
CSO

Dale Cutright
12/8/03 07:50:56 AM
CSO

Filing Memorandum
Division of Reproductive and Urologic Drug Products

NDA 21-633/S-000

Trade Name:	**Femtrace**
Generic Name:	**Estradiol Acetate**
Sponsor:	**Galen Holdings PLC** **Rockaway 80 Corporate Center** **100 Enterprise Drive, Suite 280** **Rockaway, New Jersey 07866**
Submission Date:	**October 14, 2003**
Date Received:	**October 14, 2003**
Indication:	**Treatment of moderate to severe vasomotor symptoms associated with the menopause.** **Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause**
Dose form:	**Tablet**
Dosage Schedule:	**0.45 mg once daily oral tablet** **0.9 mg once daily oral tablet** **1.8 mg once daily oral tablet**
Related Submission:	**IND 63,188**
User Fee Goal Dates:	**August 20, 2004**
Division Goal Date:	**July 23, 2004**
Filing Meeting Date:	**December 2, 2003**
Medical Reviewer:	**Ronald J. Orleans, MD**

Submission Resume

Galen submitted IND 63,188 to the Division of Reproductive and Urologic Drug Products on August 31, 2001. Numerous communications focused primarily on 2 issues:

- Inclusion of lowest effective dose in the development program.
- Methodology to be used in establishing efficacy in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

As a result of these communications a second study to investigate a lowest effective dose was initiated on April 18, 2002. The design of Phase 3 Study 00501 and Study 00502 were consistent with the recommendations in the Agency's 2003 draft clinical evaluation guidance document.

Estradiol acetate (EA) is a 3-acetate ester prodrug of estradiol. In vitro, estradiol acetate is very rapidly hydrolyzed to estradiol; the hydrolysis half-life is 28 seconds. In vivo, following oral administration of a 1.8 mg estradiol acetate tablet to healthy postmenopausal women, estradiol acetate was not detected in serum samples. Therefore, systemic exposure to estradiol acetate is not considered to be significant.

Study PR 00501 was a 41center, 12-week, double-blind, and placebo-controlled randomized study. A total of 293 subjects were randomized to EA 0.9 mg treatment group, 1.8 mg treatment group, or placebo. A total of 263 subjects completed the study (89%). The primary efficacy endpoint was the change from baseline in the frequency and severity of hot flushes at weeks 4 and 12. Weekly subject-assessed urogenital symptoms ,

. The most commonly reported adverse events for this study were vaginal bleeding, headaches, and breast tenderness.

Study PR 01502 was a 36 center, 12-week, double-blind, and placebo-controlled randomized study. A total of 259 subjects were randomized to EA 0.45 mg treatment group or the placebo-treatment group. A total of 218 subjects completed the study (84.2%). The primary and secondary efficacy endpoints were the same as Study 00501. Per the submission, the study drug product did not produce a statistically significant mean change from baseline in the number of moderate to severe hot flushes at week 4 (p-value= 0.113). However the mean change at week 12 was statistically significant (p-value=0.049). The EA 0.45 mg group first achieved statistical significance compared to placebo at week 6 (p-value=0.042). The mean reduction in the severity of hot flushes was statistically significant starting at week 5. The EA 0.45 mg dose achieved variable statistically significant results for VVA. The most commonly reported adverse events for this study were headaches, nasopharyngitis, and nausea.

Fileability of NDA 21-633/S-000

NDA 21-633/S-000 is fileable.

Review Issues

The first 50 subjects enrolled in Study PR 00501 were not asked to record their most bothersome urogenital symptom at baseline.

In Study PR 01502, subject medication labels were mistakenly unblinded at site 62 for all 24 subjects randomized at that site. The statistical analysis plan was revised (Amendment 1) to define an efficacy analysis subset which excluded all 24 subjects at site 62.

Recommendations for a Division of Scientific Investigations site inspections

The following sites have been identified for inspection:

PR 00501: Site 10 with 24 subjects
PR 01502: Site 87 with 15 subjects

We request that the above inspections be performed by June 30, 2004.

NDA: 21-371

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		
5) Are the requisite number of adequate and well controlled studies submitted in the application?	X		
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?	X		
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?	NA		
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division?	X		
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	X		
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?	NA		
14) Has draft labeling been submitted?	X		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	X		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		

17) Reasons for refusal to file:

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/s/

Ronald Orleans
4/26/04 03:12:14 PM
MEDICAL OFFICER

Brenda Gierhart
4/27/04 07:30:44 AM
MEDICAL OFFICER
I concur with the Medical Officer's comments and recommendations.

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 2, 2003

TIME: 10:30 a.m.

LOCATION: 17B-43

APPLICATION: NDA 21-633/Femtrace (estradiol acetate)

TYPE OF MEETING: 60-day filing

MEETING CHAIR: Theresa van der Vlugt, MD

MEETING RECORDER: Dale Cutright, PM

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Theresa van der Vlugt, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products
Ron Orleans, M.D., Medical Officer, DRUDP
Moo-Jhong Rhee, Ph. D., Chemistry Team Leader, DNDC II
Sarah Pope, Ph. D., Chemist, DNDC II
Lynda Reid, Ph. D., Pharmacologist, DRUDP
Ameeta Parekh, Ph. D., Clinical Pharmacology Team Leader, OCPB
DJ Chatterjee, Ph. D., Clinical Pharmacology Reviewer, OCPB
Moh-Jee Ng, M.S. – Statistician, DBII
Dale Cutright, Regulatory Project Manager, DRUDP

BACKGROUND: Femtrace (estradiol acetate), submitted by Galen (Chemicals) Limited, located in NJ, has proposed dosages of 0.45mg, 0.9 and 1.8 mg once daily oral tablet indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. This NDA was received on October 14, and the user fee was paid on October 20, 2003, making the PDUFA goal date August 20, 2004. The tablets are manufactured by Pharmaceutics International, Inc. in Hunt Valley, Maryland.

Estradiol acetate (EA) is a 3-acetate ester prodrug of estradiol. In vitro, estradiol acetate is very rapidly hydrolyzed to estradiol; the hydrolysis half-life is 28 seconds. In vivo, following oral administration of a 1.8 mg estradiol acetate tablet to healthy postmenopausal women, estradiol acetate was not detected in serum samples. Therefore, systemic exposure to estradiol acetate is not considered to be significant.

Estradiol-3-acetate is synthesized [redacted]. The principle impurity is [redacted]

[ ] , manufactures estradiol-3-acetate, the active ingredient. Pharmaceutics International, Inc. in Hunt Valley, MD will manufacture the 0.45 mg E3A and placebo tablets.

MEETING OBJECTIVES:

45-day filing meeting: to make a determination if there is sufficient material to be reviewed, adequate information to perform the review, in correct order, legible, etc.

Chemistry

- The application has all the necessary sections to review.
- Drug substance manufacture is referenced to DMF [ ]
- The drug product manufacturing sites all returned as acceptable from the Office of Compliance.
- Limited Stability data has been submitted for this NDA. Additional stability data should be provided when available.
- Justification of the exclusion [ ] specifications for [ ] for all three dosages strength tablets should be provided.
- NDA is fileable.

Pharmacology/Toxicology

- Based on evidence of rapid hydrolysis of estradiol acetate to estradiol, resulting in no detectable systemic levels of estradiol acetate, the use of previous nonclinical studies and clinical experience with estradiol to support the safety of Femtrace is acceptable.
- NDA is fileable.

Clinical Pharmacology/Biopharmaceutics

- There are 3 studies presented in this NDA to support information on pharmacokinetics.
- The to-be marketed product is similar in formulation to the product in Phase 3 studies. Note that the minor difference [ ] with the 0.45 mg dose between the Phase 3 and the to-be-marketed formulation is a review issue and will be addressed following review of the relevant dissolution data.
- NDA is fileable.

Clinical

- The Phase 3 Study 00501 and Study 00502 to investigate a lowest effective dose were consistent with the recommendations in the Agency's 2003 draft clinical evaluation guidance document.
- Study 00501 was a 41 center, 12-week, double-blind, and placebo-controlled randomized study, with a total of 293 subjects randomized to EA 0.9 mg treatment group, 1.8 mg treatment

group, or placbo. 263 subjects completed the study (89%).

- Study 00502 was a 36 center, 12-week, double-blind, and placebo-controlled randomized study with 259 subjects randomized to EA 0.45 mg treatment group or the placebo-treatment group. 218 subjects complted the study (84.2%).
- The first 50 subjects enrolled in Study 00501 were not asked to record their most bothersome urogenital symptom at baseline.
-
- In Study 00502, subject medication labels were mistakenly unblinded at site 62 for all 24 subjects randomized at that site. The statistical analysis plan was revised (Amendment 1) to define an efficacy analysis subset which excluded all 24 subjects at site 62.
- NDA is fileable.

Statistical

- Information needed from Sponsor is the efficacy analysis data sets, data definition files in SAS transport format, and also include SAS source code used for the analyses above and any supporting output.
- NDA is fileable.

Action Items

- Team members will e-mail to PM and a copy to team leader any comments (cut and paste format) to be forward to sponsor in 74-day filing letter, (July 11).
- Team members will also e-mail to PM any their notes of meeting minutes.
- The PM will telephone the sponsor and request:
  - The number of subjects enrolled by study site for each study.
  - The number of subjects discontinued by study site for each study
  - The number of protocol violations by study site for each study
  - The efficacy analysis data sets, data definition files in SAS transport format, and also include SAS source code used for the analyses above and any supporting output.
- The PM will forward the package insert to DDMAC and DMETS for review.
- The PM will forward the request for clinical inspections.

Cc:
HFD-580/Division Files
HFD-580/Original NDA 21-633
HFD-580/Cutright/van der Vlugt 12/10/03, Orleans, Pope 12/8/03, Rhee 12/8/03, Reid 12/8/03, Thornton, Chatterjee 12/8/03, Parekh, Ng 12/5/03

Created by: Dale Cutright, 12.2.03
Revised by: DCutright
Concurrence:

NDA 21-633

Finalized: DFS
Filename:C:Data/MyDocuments/aNDA/N21633/Filing Mtg min.doc

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/s/

Theresa Van Der Vlugt
12/15/03 01:38:18 PM
I concur wiht the filing meeting minutes.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

10/27/03

NDA 21-633

Galen (Chemicals) Limited
Attention: Alvin Howard
Vice President Regulatory Affairs
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, NJ 07866

Dear Mr. Howard:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Femtrace (estradiol acetate tablets)
Date of Application:	October 14, 2003
Receipt Date of User Fees:	October 20, 2003
Our Reference Number:	NDA 21-633

This application was considered incomplete and was not accepted for filing because all fees owed for this application, products, establishments, or previous applications were not paid. Subsequently, we received on October 20, 2003, all fees due. The receipt date for fees due is considered the new receipt date for this application.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 19, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 20, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call Dale Cutright, Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
10/27/03 04:41:43 PM
Chief, Project Management Staff

MEMORANDUM OF TELECON

MEETING DATE:	February 12, 2003
TIME:	10. 00 AM- 11. 00 AM
LOCATION:	Pkln. 17B-43
APPLICATION NUMBER:	IND 63-188 (estradiol acetate tablets)tablets
SPONSOR:	Galen Holdings
TYPE OF MEETING:	Teleconference Ph. # 1-888-827-8686 ID. 1292897
Meeting Recorder:	George Lyght, R.Ph., Regulatory Project Manager

FDA Participants
Shelley R. Slaughter, M.D. Ph.D. Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Moh-Jee Ng, M.S. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Alexander Jordan, Ph.D. - Pharmacology Team Leader, DRUDP (HFD-580)
Lynnda Reid, Ph.D., Pharmacologist, DRUDP (HFD-580)
Margie Kober, R.Ph. - Chief, Project Management Staff, DRUDP (HFD-580)
George Lyght, R.Ph. - Regulatory Project Manager, DRUDP (HFD-580)

Participants: For Galen Holdings:
Herman Ellman, M.D., Senior Vice President, Clinical Development
Olu Aloba, Ph.D. Director, Pharmaceutics
Tina deVries, Ph.D., Vice President, Pharmaceutics
Alvin Howard, Vice President , Regulatory Affairs
Ileana Brown, Manager, Regulatory Affairs

BACKGROUND:
Galen Holdings requested a Pre NDA meeting to seek guidance for the NDA it plans to file. The indication of the planned submission is for the treatment of moderate to severe vasomotor symptoms associated with menopause and the treatment of vulvar and vaginal atrophy.

Meeting Objective:
Galen Holdings hopes to reach consensus on the proposed content and structure of the planned NDA

Discussion:

Clinical:
Item 8.

- We recommend that the sponsor review the Agency's 2003 Draft Clinical Evaluation Guidance Document (Federal Register, Volume 68, Number 21, 1/31/03 Notice), including the following regarding primary endpoints:

1) For the treatment of moderate to severe vasomotor symptoms, we recommend the following co-primary endpoints:

- mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4 and week 12
- mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4 and week 12. Data for week 8 may be submitted but would not be included in efficacy analyses

2) [

]

The outline proposed for Item 8 is acceptable. Data from two independent, parallel phase 3 studies will be presented in NDA: Study 00501 for the 0.9 mg and 1.8 mg estradiol acetate tablets, and Study 01502 for the 0.45 mg tablet. We recommend that the analyses of study results should be presented separately. Since neither study assessed the most bothersome self-reported VVA symptom at baseline, we recommend that both studies should data for the subset of subjects who reported at least one moderate to severe symptom of vulvar and vaginal atrophy at baseline.

Item 11. Case Report Tabulations

- Individual patient data by parameter may be submitted in Item 8.

Item 12. Case Report Forms

- Case report forms may be submitted as part of the final study reports in Item 8.

Electronic Components of the NDA

- Please submit readable tables in draft labeling in MS Word.

Statistics

- The Division concurs with the content and outline proposed.

- For protocol 1502 , those 24 subjects inadvertently un-blinded should be included in the Intent-to-treat population (provide with and without those 24 subjects in the statistical analyses).
- [
  ]
- All tables should include baseline visit, sample sizes, mean, standard deviation, change from baseline, p-values based on raw data, and 95% confidence intervals. Non-parametric p-values include if it is not normally distribution.

Clinical Pharmacology and BioPharmaceutics

- Describe in the NDA submission the formulation similarity between the proposed marketed products and the — formulation used in the relative bioavailability study where comparison is made to the micronized estradiol tablet; clarify that the estradiol tablet is the marketed product
- In the multiple dose study, please address whether steady state is reached for SHBG as well as estradiol
- Provide data to support the rapid hydrolysis of estradiol acetate to estradiol; this can be supported with the currently existing in-vitro test that shows rapid hydrolysis as well as analysis of some bio-study plasma samples previously collected (e.g. food effect study samples).
- Justification must be provided for in-vitro dissolution methodology. Dissolution specifications will be decided after review of the NDA data;
- Submit individual and mean (SD) in-vitro release data and profiles for all formulations and lots for the purpose of setting specifications
- SUPAC IR Guidance provides f2 assessments for profile comparisons, if needed

Pharmtox

- On item 5, Questions 2 and 3, DRUDP concurs provided the rapid hydrolysis of estradiol acetate to estradiol has been substantiated in clinical studies
- Question 9 proposal is acceptable

  Requests Pharmtox information in Word or PDF

  Requests readable hard copies of the literature

Chemistry

Question 1

FDA response

- It is preferred that the sponsor submits the drug substance information in the proposed NDA and not cross-reference, NDA 21-367
- Include a section on Container Closure system for the drug substance
- Include a section on Justification of specifications
- Provide information on [
  ]
- Adopt specifications for [ ] the drug product, unless justified.

•

Question 1A

FDA Response

- The number of stability lots is adequate but the shelf life would depend on the stability data from tablets manufactured using both the processes.
- The processes should be bridged by generating dissolution profiles. The dissolution study is preferred to be conducted based on the recommendation above and the results are recommended to be compared using the similarity factor.

Minutes Preparer:

George Lyght, R.Ph.
Regulatory Project Manager

Chair Concurrence:

Shelley R. Slaughter, M.D., Ph.D. .
Team Leader, DRUDP

Meeting Package

cc: Original
HFD-580/Div. Files

Drafted by: gl/08.06.03+
Initialed
by:A.Mitra/09.11.03/T.Vlugt/09.11.03/M.Ng/09.11.03/L.Reid/09.16.03/A.AlHabet/
09.16.03/
final: gl/09.16.03

MEETING MINUTES

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

/s/

Theresa Van Der Vlugt
9/25/03 09:43:59 AM

TELECONFERENCE MINUTES

Date: October 24, 2001 **Time:** 11:00-11:30 p.m. **Location:** Parklawn; 17B-43

IND 63,188 **Drug:** estradiol acetate

Indication: relief of vasomotor symptoms **Sponsor:** Warner-Chilcott

Type of Meeting: Guidance

Meeting Chair: Shelley Slaughter, M.D., Ph.D.

External Lead: Alvin Howard, M.D.

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H., Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Dornette Spell-LeSane, NP-C, MHA, Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Alvin Howard, Vice President, Regulatory Affairs
Grexan Wulfs, Manager, Clinical Operations
Ileana Brown, Regulatory Affairs

Meeting Objectives:
To discuss the correspondence dated October 11, 2001, in which, the sponsor provided the rationale to support the lowest effective dose of estradiol acetate for their clinical trials.

Background:
IND 63,188 was opened September 2001, the sponsor requested a teleconference to discuss clinical protocol comments provided during the IND review. The sponsor reported that they had begun enrolling patients and plan to begin randomization within the week.

Discussion:
Question 1
Does the division concur that tablets of 0.9 and 1.8mg estradiol acetate would be approvable for this indication if shown to be statistically better than placebo, and that there is no need to show no effect for still a lower dose of estradiol acetate?

- Dr. Howard from Warner Chilcott, explained the rationale for the selection of 0.9 mg estradiol acetate as the lowest effective dose for their studies; Dr. Howard explained that after review of the [redacted] application in which the [redacted] mg estradiol dose used in their study was demonstrated to be not effective, the sponsor determined that a 0.45 mg dose would not be effective and chose 0.9 mg as their lowest effective dose; further, based on extrapolation of results from the pilot bioavailability study, 0.9mg and 1.8 mg are approximately equivalent to 90% of the 1.0 mg and 2.0mg and therefore are

likely to be effective; a lower dose of 0.45 mg/day of estradiol acetate would be equivalent to approximately 90% of — g dose of estradiol and would therefore be ineffective

Response

- DRUDP explained that the rationale for dose selection was not acceptable for the following reasons: (1) [ ] is a combination product, and therefore cannot be used to make the same assumptions for their product, estradiol acetate a single product; (2) the decision for approval based on demonstration of the lowest effective dose will be determined by reviewing the sponsor's own clinical trial data not referenced data
- Per the 1995 HRT guidance, clinical trial data should demonstrate the lowest effective dose; this applies to all products (estrogen alone or combination products) seeking approval for the treatment of vasomotor symptoms and vulvar and vaginal atrophy
- DRUDP cannot confirm for the sponsor that 0.9 mg is the lowest effective dose for this product
- DRUDP recommends the sponsor include a dose that would demonstrate a no effect or low effective dose
- the sponsor questioned the ability to obtain the indications associated with HRT products [ ] DRUDP explained that in the past, sponsors were extended additional indications for HRT products under the Drug Efficacy Study Implementation rule (DESI); however, this is no longer the practice and clinical data is required to demonstrate the safety and efficacy of those indications to support labeling

Question 2

Decisions Reached:

1. A lowest effective dose must be identified as part of the clinical development program for this product.
2. The sponsor may submit for review and comment a randomization plan that would support the addition of a lower dose strength of estradiol acetate to the current program.

Action:

1. The Sponsor will submit a revised protocol to the IND.
2. Meeting minutes will be provided to the sponsor within 30days.

/S/

Minutes Preparer:

/S/

Meeting Chair

Addendum:

- the sponsor submitted a randomization plan October 26, 2001, in support of the addition of a lower strength of estradiol acetate arm to the current program
- DRUDP statistician has reviewed the plan and has the following comments:
  - the plan is acceptable
  - the sample size is acceptable

Note to Sponsor:
These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original IND 63, 188
HFD-580/Div. Files
HFD-580/

Drafted by: Spell-LeSane, 11.2.01
Concurrence: Rumble, 11.6.01/Parekh, van der Vlugt, 11.8.01, Slaughter, 11.19.01
final: Spell-LeSane, 11.20.01

MEETING MINUTES

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

/s/

Dornette Spell-LeSane
11/20/01 02:17:31 PM
CSO

Shelley Slaughter
11/20/01 02:25:50 PM
MEDICAL OFFICER
I concur.