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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-633

Medical Review(s)

MEMORANDUM

To: NDA 21-633: Original NDA
C J

Through: Daniel Shames, MD
Director, HFD-580

From: Brenda S. Gierhart, MD
Medical Team Leader, HFD-580

Date: August 19, 2004

Re: NDAs 21-633 and C J Femtrace (estradiol acetate)
Tablets
Warner Chilcott Company, Inc
Submitted: October 14, 2003
Received: October 14, 2003
PDUFA date: August 20, 2004

[*Note: On August 17, 2004, NDA 21-633 was administratively split into NDA 21-633 for vasomotor symptoms indication and C J for the vulvar and vaginal atrophy indication.]

I. RECOMMENDATIONS

Recommendations on Approvability

This reviewer recommends approval of the 0.9 and 1.8 mg doses and non-approval of the 0.45 mg dose of Femtrace™ (estradiol acetate) for the treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause. This recommendation is based upon an analysis of the efficacy and safety data from the two Phase 3, placebo-controlled clinical trials (Study PR 00501 evaluated Femtrace 0.9 and 1.8 mg; Study PR 01502 evaluated Femtrace 0.45 mg) submitted in the Original NDA 21-633. Femtrace 0.45 mg did not achieve statistical significance for the treatment of moderate to severe vasomotor symptoms by Week 4 and through Week 12 for all four of the following co-primary efficacy endpoints:

- 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 specific co-primary endpoints that did or did not achieve statistical significance for Femtrace 0.45 mg varied depending upon the study population (i.e., ITT or modified ITT) and the method of analysis [i.e., the Statistical Analysis Plan prespecified ANOVA model with p-values based on Fisher's least significant differences, a CDER proposed ANCOVA model with p-values based on the Wilcoxon rank sum test (van Elteren test), or a post hoc Responder Analysis with p-values calculated from Fisher's Exact test].

The first issue, pertinent to the nonapproval recommendation of Femtrace 0.45 mg in Study PR 01502 for moderate to severe VMS, is that on April 3, 2003 by altering the Statistical Analysis Plan, the sponsor created a modified ITT (ITT*) study population for the primary efficacy analysis by excluding 24 patients due to unblinding at Site 62. Using ANOVA on the modified ITT* population, the efficacy of Femtrace 0.45 mg for **frequency** of moderate to severe VMS compared to baseline was not demonstrated at Week 4 ($p=0.113$), was demonstrated at Week 12 ($p=0.049$), and was demonstrated at 4 of the 12 weekly time points; see **Table 1** on pg. 11. Using ANOVA on a true ITT population (i.e., all randomized patients who received at least one dose of study medication) as the primary efficacy analysis, the efficacy of Femtrace 0.45 mg for **frequency** of moderate to severe VMS compared to baseline was not demonstrated at Week 4 ($p=0.167$), was not demonstrated at Week 12 ($p=0.095$) and was demonstrated at 3 of the 12 weekly time points; see **Table 2** on pg. 12. Regarding the study population issue, the Division advised the sponsor during the February 12, 2003 preNDA meeting (as documented in the meeting minutes): “For Protocol 1502, those 24 subjects inadvertently unblinded should be included in the Intent-to-treat population (provide with and without those 24 subjects in the statistical analyses).” Whether a true ITT or a modified ITT population was selected as the population for the primary efficacy analysis, Femtrace 0.45 mg did not achieve statistical significance for the treatment of moderate to severe vasomotor symptoms by Week 4 and through Week 12 for **frequency** using ANOVA. In contrast, Femtrace 0.9 and 1.8 mg achieved statistical significance for the treatment of moderate to severe vasomotor symptoms by Week 4 and through Week 12 for **frequency** (see **Table 3** on pg. 13) for an ITT population using ANOVA.

Using ANOVA on the modified ITT* population, the efficacy of Femtrace 0.45 mg for **severity** of moderate to severe VMS was not demonstrated at Week 4 ($p=0.259$), was demonstrated at Week 12 ($p<0.001$) and was demonstrated at 8 of the 12 weekly time points; see **Table 4** on pg. 14. Using ANOVA on a true ITT population (i.e., all randomized patients who received at least one dose of study medication) as the primary efficacy analysis, the efficacy of Femtrace 0.45 mg for **severity** of moderate to severe VMS was not demonstrated at Week 4 ($p=0.188$), was demonstrated at Week 12 ($p=0.006$) and was demonstrated at 8 of the 12 weekly time points; see **Table 5** on pg. 15. In contrast, Femtrace 0.9 and 1.8 mg achieved statistical significance for the treatment of moderate to severe vasomotor symptoms by Week 4 and through Week 12 for **severity** see **Table 6** on pg. 16) using ANOVA.

The second issue, is that the sponsor performed an ANOVA model with p-values based on Fisher’s least significant differences for the primary efficacy analysis, while the CDER statistician performed an ANCOVA model with p-values based on the Wilcoxon rank sum test (van Elteren test) for the primary efficacy analysis. This issue is pertinent to all three doses of Femtrace and to both the VMS and vulvar and vaginal atrophy (VVA) indications. A regulatory letter to IND 63,188 for Femtrace dated October 18, 2002 regarding the submissions dated April 18, 2002 (Serial No. 005) and dated June 13, 2002 (Serial No. 007) stated that “the statistical analysis plan for Protocol 01502.0 and revisions to Protocol 00501.3 are acceptable”. Neither the January 2003 “Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendations for Clinical Evaluation” nor the 1995 “Guidance for Industry: Guidance for Clinical Evaluation Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women” specifically recommends an ANOVA or an ANCOVA efficacy analysis. However, for consistency with other estrogen drug products and per the DRAFT Guidance for Reviewers: Analysis of Covariance in Randomized Clinical Trials dated March 12, 1998, an ANCOVA primary efficacy analysis was performed by the CDER statistician. It was also stated in the CDER statistical review for NDA 21-633 that ANCOVA was selected since it reduced the variability of the estimated treatment effects. In addition, when

analyzing the ANCOVA results, the CDER statistical reviewer found that the model residuals failed tests for normality, and thus a stratified Wilcoxon rank sum test was used as the basis for testing the significance of treatment effects. When an ANCOVA model with p-values based on the Wilcoxon rank sum test (van Elteren test) was selected for the primary efficacy analysis in the **modified ITT*** population, Femtrace 0.45 mg achieved statistical significance for the treatment of moderate to severe vasomotor symptoms by Week 4 and through Week 12 for **frequency**, but not for **severity**; see **Table 7** on pg. 17 and **Table 8** on pg. 18. When an ANCOVA model with p-values based on the Wilcoxon rank sum test (van Elteren test) was selected for the primary efficacy analysis in the **ITT** population, Femtrace 0.45 mg achieved statistical significance for the treatment of moderate to severe vasomotor symptoms by Week 4 and through Week 12 for **frequency**, but not for **severity**; see **Table 9** on pg. 19 and **Table 10** on pg. 20.

The third issue is regarding the post hoc Responder Analysis requested by the Division. On July 9, 2004, a Responder Analysis was submitted by the Sponsor that detailed the **frequency** of moderate to severe VMS in the modified ITT* population for Femtrace 0.45 mg. In this analysis, a responder was defined as demonstrating a 75% or more decrease in the number of hot flushes when compared to baseline. When a modified ITT* population was selected for the efficacy analysis, Femtrace 0.45 mg achieved a statistically significant change from baseline for the treatment of moderate to severe vasomotor symptoms by Week 4 and through Week 12 for **frequency** using a Responder Analysis; see **Table 11** on pg. 11. After a request from the Division, a Responder Analysis was received on July 23, 2004 that detailed the **severity** of moderate to severe VMS in the modified ITT* population for Femtrace 0.45 mg. In this analysis, a responder was defined as demonstrating a 75% or more decrease in the severity of hot flushes when compared to baseline. When a modified ITT* population was selected for the efficacy analysis, Femtrace 0.45 mg did not achieve statistical significance for the treatment of moderate to severe vasomotor symptoms by Week 4 and through Week 12 for **severity** using a Responder Analysis; see **Table 12** on pg. 21. The Sponsor did not provide a Responder Analysis for the ITT population. This reviewer agrees with the statistical reviewer that analyses based on responders should be considered exploratory, for descriptive purposes only, and should not be supportive of any labeling for this indication.

Thus, this reviewer recommends non-approval of Femtrace 0.45 mg for the treatment of moderate to severe vasomotor symptoms since it did not achieve statistical significance by Week 4 and through Week 12 for all four vasomotor co-primary efficacy endpoints. If the prespecified and Division accepted Statistical Analysis Plan analysis was performed (i.e. modified ITT population using an ANOVA model with p-values based on Fisher's least significant differences), Femtrace 0.45 mg did not achieve statistical significance on either of the two Week 4 co-primary efficacy endpoints; see **Table 1** on pg. 11 and **Table 4** on pg. 14). In addition to the delayed onset of efficacy until Week 6 for frequency using the above analysis plan, Femtrace 0.45 mg did not demonstrate efficacy from Week 6 through Week 12 for frequency; see **Table 1** on pg. 11. If the CDER proposed ANCOVA model with p-values based on the Wilcoxon rank sum test (van Elteren test) analysis on the modified ITT population was used, Femtrace 0.45 mg did not achieve statistical significance for one of the four co-primary efficacy endpoints, i.e., Week 4 for severity; see **Table 8** on pg. 18. In addition to the delayed onset of efficacy until Week 7 for severity by the CDER proposed analysis, Femtrace 0.45 mg did not demonstrate efficacy from Week 7 through Week 12 for severity; see **Table 8** on pg. 18.

In addition, this reviewer recommends non-approval for all three proposed doses of Femtrace™ (estradiol acetate 0.45 mg, 0.9 mg, and 1.8 mg) for the treatment of moderate to severe vulvar and vaginal atrophy associated with the menopause. This recommendation is L.

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..... If in the future the sponsor amends NDA [] for
VVA, this reviewer recommend []
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Thus, this reviewer recommends non-approval for all three proposed doses of Femtrace™ (estradiol acetate 0.45 mg, 0.9 mg, and 1.8 mg) for the treatment of moderate to severe vulvar and vaginal atrophy associated with the menopause.

Recommendations on Postmarketing Studies and/or Risk Management Steps

No specific postmarketing commitments and/or risk management steps are recommended.

II. SUMMARY OF CHEMISTRY FINDINGS

Per the Chemistry review #1 finalized on July 26, 2004, NDA 21-633 may be approved pending resolution of labeling issues (i.e., container/carton, trade name, patient information, and package insert). A two-year expiration dating period has been granted. The labeling changes recommended in the Chemistry review have been incorporated into the Division proposed DRAFT Package Insert (PI) and Division proposed DRAFT Patient Information (PPI). No Phase 4 commitments, agreements, and/or risk management steps have been requested by Chemistry.

Per the Chemistry review #2 finalized on August 18, 2004, NDA 21-633 may be approved. All Chemistry issues have been resolved.

III. SUMMARY OF PHARMACOLOGY/TOXICOLOGY FINDINGS

The Pharmacology/Toxicology review finalized on June 28, 2004 recommended approval of NDA 21-633 based on the established efficacy of estradiol at equivalent or higher doses. Two studies were reviewed as follows:

- Study determining the rate of conversion of estradiol-3-acetate to estradiol *in vitro* in human serum and human whole blood: results indicated that the concentration of estradiol acetate was negligible within 2 minutes (4 half-lives) following absorption.
- Study determining reverse mutation in four histidine-requiring strains of *Salmonella typhimurium* and two tryptophan-requiring strains of *Escherichia coli*: results indicated that estradiol acetate and estradiol hemihydrate were negative in the Bacterial Reverse Mutation Assay.

The labeling changes recommended in the Pharmacology/Toxicology review (i.e. "Labeling should be consistent with current estrogen class labeling.") have been incorporated into the Division proposed DRAFT Package Insert (PI) and Division proposed DRAFT Patient Information (PPI) and have been approved by Pharmacology/Toxicology. All Pharmacology/Toxicology issues have been resolved.

IV. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The Clinical Pharmacology and Biopharmaceutics review finalized on July 30, 2004 stated that "The submission of NDA 21-633 for Femtrace (estradiol acetate) tablets is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective". No recommendation regarding approvability of NDA 21-633 was given. Three studies were reviewed as follows:

- Study **PR 05000**: a single center, single dose, 3-period crossover PK study in 9 healthy volunteers
- Study **PR 09601**: a single center, single dose, 2-period crossover food effect study in 16 healthy volunteers
- Study **PR 00102**: a single center, single and multiple dose, 3-period crossover PK study in 18 healthy volunteers

Most of the labeling changes recommended in the Clinical Pharmacology and Biopharmaceutics review have been incorporated into the Division proposed DRAFT Package Insert (PI) and Division proposed DRAFT Patient Information (PPI). Specifically, changes to the generic name (i.e. changing "estradiol acetate tablets" to "estradiol tablets", as recommended by DDMAC, were not accepted by Chemistry and are not included in the Division proposed DRAFT Package Insert (PI) and Division proposed DRAFT Patient Information (PPI). All Clinical Pharmacology and Biopharmaceutics issues have been resolved.

V. SUMMARY OF STATISTICAL FINDINGS

The Statistical review finalized on August 17, 2004 made no recommendation regarding approvability of NDA 21-633. The following conclusions from the Statistical review are all using the CDER proposed ANCOVA model with p-values based on the Wilcoxon rank sum test since the data did not meet the normality assumption:

- Subjects treated with estradiol acetate (EA) 0.45, 0.9, and 1.8 showed both clinically and statistically significant change from baseline in frequency of moderate to severe vasomotor symptoms (MSVS) as compared to placebo at weeks 4 and 12.
- Subjects treated with EA 0.9 mg and 1.8 mg showed a statistically significant change from baseline in severity compared to placebo at weeks 4 and 12.
- Subjects treated with EA 0.45 mg failed to show a statistically significant change in severity at week 4; however, a statistical difference was reached at week 7 but not maintained to week 12.
- For moderate to severe vulvar and vaginal atrophy (VVA). [

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- For moderate to severe VVA, [

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- For moderate to severe VVA [

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VI. SUMMARY OF CLINICAL FINDINGS

Brief Overview of the Clinical Program

The clinical program for estradiol acetate development consisted of three supportive Phase 1 clinical studies (PR 05000, PR 09601, and PR 00102) designed to characterize the pharmacokinetic profile of estradiol acetate tablets and two Phase 3 clinical trials (PR 00501 evaluated Femtrace 0.9 and 1.8 mg; PR 01502 evaluated Femtrace 0.45 mg) to demonstrate safety and efficacy.

See the primary Medical Officer review for details regarding the five clinical studies. Only three of the 30 tables in the primary Medical Officer reviewer are replicated in this review: **Table 10** on pg. 20, **Table 11** on pg. 21, and **Table 16** on pg. 23.

Efficacy

Vasomotor Symptoms

The primary Medical Officer review finalized on August 13, 2004 recommends approval of estradiol acetate (EA) 0.45, 0.9, and 1.8 mg for VMS and nonapproval of EA 0.45, 0.9, and 1.8 mg for VVA.

The recommendation of approval by the primary Medical Officer of the EA 0.45 mg dose for VMS in the primary Medical Officer review is based upon the Sponsor's analysis of the modified ITT* Population (i.e. excluding subjects from Site 62) using LOCF and a 2-way ANOVA model with interaction (treatment and center effects) and basing the p-value on Fisher's least significant differences. Subjects administered oral EA 0.45 mg once daily for 12 weeks experienced statistically significantly greater reduction in the **frequency** of moderate to severe hot flashes compared to placebo treated subjects at weeks 6 and 12 ($p=0.042$ and $p=0.049$ respectively) but not at week 4 ($p=0.113$); see **Table 1** on pg. 11. Subjects administered oral EA 0.45 mg once daily for 12 weeks experienced statistically significantly greater reduction in the **severity** of moderate to severe hot flashes compared to placebo treated subjects by Week 5 ($p=0.010$) through Week 12 ($p<0.001$) but not at Week 4 ($p=0.259$); see **Table 4** on pg. 14. The primary Medical Officer noted that EA 0.45 did not meet the two co-primary endpoints for frequency and severity at Week 4; however, he considers these findings sufficient to support approval. This reviewer disagrees with the primary Medical Officer and does not recommend approval of Femtrace 0.45 mg., due to it failing to demonstrate efficacy for frequency and severity by Week 4 in the modified ITT populations using an ANOVA model and basing the p-value on Fisher's least significant differences and due to inconsistent demonstration of efficacy from Week 4 through Week 12. After considering the entire body of data for both study populations and all three analysis methods, this reviewer continues to recommends nonapproval of EA 0.45 mg for VMS.

This reviewer is in agreement with the primary Medical Officer review in recommending approval of EA 0.9 and 1.89 mg for VMS.

Vulvar and Vaginal Atrophy

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Safety

The safety data for the two primary Phase 3 clinical trials presented in the submission shows that the overall safety profile of Femtrace™ given daily in doses of 0.45 mg, 0.9 mg, or 1.8 mg is acceptable: see **Table 16** on pg. 23.

Dosing, Regimen, and Administration

The continuous daily oral treatment regimen for which approval is sought is a standard regimen for estrogen-only oral therapy. This reviewer considers that the Sponsor has determined that Femtrace 0.9 mg is the lowest effective dose by determining that the 0.45 mg dose was ineffective.

Special Populations

Femtrace™ is only indicated for use in postmenopausal women. The protocols in Study PR 00501 and Study PR 01502 included subjects greater than 45 years of age. Median ages for each study were 53.2 years and 52.4 years respectively. There is no data available from the studies to determine efficacy for the indications sought for those women under age 45. Regarding the use of Femtrace in a geriatric population, insufficient numbers of patients were enrolled aged 65 years and older to support the findings in patients aged less than 65 years: 4 subjects in Study PR 00501 and 9 subjects in PR 01502 were aged 65 years or older. Femtrace™ has not been studied in women with liver disease or renal impairment. Femtrace™ should not be used in pregnant women.

Additional Consults:

- Consult Response from HFD-410 Division of Surveillance, Research, and Communication Support (DSRCS), Office of Drug Safety, finalized on April 29, 2004, provided recommendations for the Patient Labeling.
- Consult Response from HFD-42 Division of Drug Marketing, Advertising, and Communications finalized on May 27, 2004 provided recommendations for the Package Insert.
- Consult Response from HFD-420 Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety, finalized on July 8, 2004, stated that DMETS did not recommend the use of the proprietary name Femtrace and DIMAC found the proprietary name Femtrace acceptable from a promotional perspective. It also included recommendations regarding the label.

These consult responses were considered in preparing the Division proposed PI and PPI. The Division carefully reviewed the tradename issue, including the July 1, 2003 [] report entitled "Market Research for Proposed Name FEMTRACE™" and the sponsor's response regarding the issue submitted as Amendment 18 to NDA 21-633 and faxed to the Division on August 4, 2004. The tradename "Femtrace" was found to be clinically acceptable to the Division and to this reviewer. The sponsor was notified of this decision on August 6, 2004.

Labeling

The Statistical review recommended changing the four sponsor proposed ANOVA efficacy tables to contain the efficacy data from the Statistical review Tables #3-6 using ANCOVA model with p-values based on the Wilcoxon rank sum test. The Division concurred with the Statistical recommendation, since this would be consistent with labeling for similar products. Division proposed labeling was sent to the sponsor on August 11, 2004 and contained efficacy data from 4 tables in this review; **Table 7** on pg. 17, **Table 8** on pg. 18, **Table 17** on pg. 23 and **Table 18** on pg. 24. A t-con regarding the labeling was held on August 12, 2004. Revised Sponsor proposed labeling was sent to the Division on August 16, 2004. Two t-cons regarding the labeling was held on August 18, 2004, resulting in Femtrace PI and PPI labeling acceptable to both the Division and the Sponsor.

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Appendix 2: Tables**Table 1: Study PR 01502 mean change from baseline in the number of moderate to severe hot flushes at each study week using LOCF (ITT* Population, ANOVA)**

Study Visit	Placebo (n=108)	EA 0.45 mg (n=113)	p-value: EA 0.45 vs. placebo
Baseline Mean (SD)	85.8 (37.8)	86.2 (34.8)	0.691
Week 1 Mean change (SD)	-18.5 (42.2)	-21.1 (25.3)	0.555
Week 2 Mean change (SD)	-26.5 (47.3)	-30.0 (29.79)	0.385
Week 3 Mean change (SD)	-30.2 (49.0)	-36.2 (32.6)	0.217
Week 4 Mean change (SD)	-34.3 (50.0)	-42.1 (33.8)	0.113
Week 5 Mean change (SD)	-35.8 (50.2)	-44.8 (34.5)	0.076
Week 6 Mean change (SD)	-36.8 (49.2)	-47.5 (33.8)	0.042**
Week 7 Mean change (SD)	-38.1 (49.4)	-47.2 (35.2)	0.094
Week 8 Mean change (SD)	-40.1 (48.3)	-50.4 (35.4)	0.048**
Week 9 Mean change (SD)	-40.7 (48.6)	-51.4 (31.4)	0.038**
Week 10 Mean change (SD)	-42.3 (49.1)	-51.8 (31.6)	0.064
Week 11 Mean change (SD)	-42.8 (48.7)	-51.9 (31.6)	0.058
Week 12 Mean change (SD)	-42.8 (49.2)	-52.2 (32.1)	0.049**

Per Text Table 12 in Vol. 52 on pg. 10980

* ITT* Population excluded 24 subjects from Site 62

**p<0.05 and statistically significant

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On Original*

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

Study Visit	Placebo (n=120)	EA 0.45 mg (n=125)	p-value: EA 0.45 vs. placebo
Baseline Mean (SD)	84.5 (36.5)	85.1 (33.5)	0.893
Week 1 Mean change (SD)	-19.9 (41.1)	-21.9 (25.3)	0.645
Week 2 Mean change (SD)	-27.1 (45.8)	-30.2 (29.3)	0.528
Week 3 Mean change (SD)	-30.4 (47.2)	-35.9 (31.9)	0.291
Week 4 Mean change (SD)	-33.9 (48.1)	-41.2 (33.0)	0.167
Week 5 Mean change (SD)	-35.5 (48.4)	-44.2 (33.3)	0.100
Week 6 Mean change (SD)	-36.6 (47.7)	-47.1 (32.6)	0.047*
Week 7 Mean change (SD)	-37.7 (47.9)	-46.9 (33.9)	0.081
Week 8 Mean change (SD)	-39.8 (46.9)	-50.1 (34.1)	0.049*
Week 9 Mean change (SD)	-40.4 (47.1)	-51.1 (34.6)	0.043*
Week 10 Mean change (SD)	-42.4 (47.6)	-51.6 (33.8)	0.079
Week 11 Mean change (SD)	-42.8 (47.4)	-51.9 (34.1)	0.086
Week 12 Mean change (SD)	-43.4 (47.7)	-52.3 (34.8)	0.095

Per Table 14.2.1.1 in Vol. 53 on pg. 11056

*p<0.05 and statistically significant

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On Original*

Table 3: Study PR 00501 mean change from baseline in the number of moderate to severe hot flushes at each study week using LOCF (ITT Population, ANOVA)

Study Visit	Placebo (n=94)	EA 0.9mg (n=100)	EA 1.8 mg (n=95)	p-value: EA 0.9 vs. placebo	p-value: EA 1.8 vs. placebo
Baseline Mean (SD)	86.1 (40.2)	78.5 (24.9)	82.4 (39.1)	0.188	0.596
Week 1 Mean change (SD)	-19.8 (35.2)	-14.0 (22.1)	-24.5 (33.0)	0.447	0.145
Week 2 Mean change (SD)	-30.3 (38.3)	-34.4 (28.9)	-43.8 (39.6)	0.155	0.005*
Week 3 Mean change (SD)	-33.0 (36.9)	-46.3 (32.0)	-54.9 (38.7)	0.003*	<0.001*
Week 4 Mean change (SD)	-34.6 (43.0)	-54.2 (30.8)	-60.5 (39.9)	<0.001*	<0.001*
Week 5 Mean change (SD)	-35.2 (42.1)	-56.8 (30.6)	-66.0 (40.4)	<0.001*	<0.001*
Week 6 Mean change (SD)	-36.2 (45.1)	-57.4 (30.2)	-70.3 (40.9)	<0.001*	<0.001*
Week 7 Mean change (SD)	-38.2 (46.0)	-57.0 (32.0)	-72.3 (40.6)	<0.001*	<0.001*
Week 8 Mean change (SD)	-40.0 (47.4)	-59.3 (31.5)	-73.1 (41.3)	<0.001*	<0.001*
Week 9 Mean change (SD)	-39.4 (49.1)	-60.8 (31.4)	-73.2 (40.7)	<0.001*	<0.001*
Week 10 Mean change (SD)	-40.1 (47.6)	-61.0 (31.6)	-73.9 (41.2)	<0.001*	<0.001*
Week 11 Mean change (SD)	-38.4 (51.0)	-61.7 (31.6)	-74.3 (41.0)	<0.001*	<0.001*
Week 12 Mean change (SD)	-39.3 (52.3)	-61.0 (32.1)	-75.0 (40.0)	<0.001*	<0.001*

From Text Table 12 in Vol. 36 pg. 4124

*p<0.05 and statistically significant

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On Original

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

Study Visit	Placebo (n=108)	EA 0.45 mg (n=113)	p-value: EA 0.45 vs. placebo
Baseline Mean (SD)	2.55 (0.2)	2.54 (0.2)	0.621
Week 1 Mean change (SD)	-0.0 (0.1)	-0.0 (0.1)	0.409
Week 2 Mean change (SD)	-0.1 (0.4)	-0.1 (0.4)	0.9865
Week 3 Mean change (SD)	-0.1 (0.3)	-0.1 (0.5)	0.679
Week 4 Mean change (SD)	-0.2 (0.5)	-0.3 (0.7)	0.259
Week 5 Mean change (SD)	-0.1 (0.5)	-0.3 (0.8)	0.010**
Week 6 Mean change (SD)	-0.2 (0.6)	-0.5 (0.9)	0.006**
Week 7 Mean change (SD)	-0.2 (0.7)	-0.5 (0.9)	0.025**
Week 8 Mean change (SD)	-0.2 (0.6)	-0.5 (0.9)	<0.001**
Week 9 Mean change (SD)	-0.2 (0.7)	-0.5 (0.9)	0.012**
Week 10 Mean change (SD)	-0.3 (0.8)	-0.5 (1.0)	0.015**
Week 11 Mean change (SD)	-0.2 (0.7)	-0.7 (1.1)	<0.001**
Week 12 Mean change (SD)	-0.3 (0.8)	-0.7 (1.1)	<0.001**

Per Table 14.2.5 in Vol. 53 on pg. 11073

ITT Population excluded 24 subjects from Site 62

**p<0.05 and statistically significant

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Table 5: Study PR 01502 mean change from baseline in the severity of moderate to severe hot flushes at each study week using LOCF (ITT Population, ANOVA)

Study Visit	Placebo (n=108)	EA 0.45 mg (n=113)	p-value: EA 0.45 vs. placebo
Baseline Mean (SD)	2.55 (0.2)	2.55 (0.2)	0.928
Week 1 Mean change (SD)	-0.0 (0.1)	-0.0 (0.2)	0.316
Week 2 Mean change (SD)	-0.1 (0.4)	-0.1 (0.4)	0.969
Week 3 Mean change (SD)	-0.1 (0.3)	-0.1 (0.5)	0.464
Week 4 Mean change (SD)	-0.2 (0.5)	-0.2 (0.67)	0.188
Week 5 Mean change (SD)	-0.1 (0.5)	-0.3 (0.7)	0.020*
Week 6 Mean change (SD)	-0.2 (0.6)	-0.4 (0.9)	0.004*
Week 7 Mean change (SD)	-0.2 (0.7)	-0.4 (0.9)	0.027*
Week 8 Mean change (SD)	-0.2 (0.6)	-0.5 (0.9)	0.002*
Week 9 Mean change (SD)	-0.2 (0.7)	-0.4 (0.9)	0.042**
Week 10 Mean change (SD)	-0.3 (0.7)	-0.5 (0.9)	0.023*
Week 11 Mean change (SD)	-0.3 (0.7)	-0.6 (1.0)	0.001*
Week 12 Mean change (SD)	-0.3 (0.8)	-0.7 (1.0)	0.006*

Per Table 14.2.5.1 in Vol. 53 on pg. 11078

*p<0.05 and statistically significant

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Table 6: Study PR 00501 mean change from baseline in the severity of moderate to severe hot flushes at each study week using LOCF (ITT Population, ANOVA)

Study Visit	Placebo (n=94)	EA 0.9mg (n=100)	EA 1.8 mg (n=95)	p-value: EA 0.9 vs. placebo	p-value: EA 1.8 vs. placebo
Baseline Mean (SD)	2.5 (0.2)	2.5 (0.2)	2.5 (0.2)	0.572	0.526
Week 1 Mean change (SD)	-0.0 (0.2)	-0.0 (0.3)	-0.1 (0.4)	0.997	0.839
Week 2 Mean change (SD)	-0.1 (0.4)	-0.2 (0.5)	-0.3 (0.7)	0.341	0.044*
Week 3 Mean change (SD)	-0.1 (0.4)	-0.4 (0.7)	-0.4 (0.7)	0.020*	0.034*
Week 4 Mean change (SD)	-0.2 (0.6)	-0.7 (1.0)	-0.7 (1.0)	0.003*	0.004*
Week 5 Mean change (SD)	-0.2 (0.6)	-1.0 (1.1)	-0.9 (1.1)	<0.001*	<0.001*
Week 6 Mean change (SD)	-0.2 (0.6)	-0.9 (1.1)	-1.0 (1.0)	<0.001*	<0.001*
Week 7 Mean change (SD)	-0.3 (0.8)	-1.0 (1.1)	-1.2 (1.2)	<0.001*	<0.001*
Week 8 Mean change (SD)	-0.3 (0.8)	-1.0 (1.1)	-1.3 (1.2)	<0.001*	<0.001*
Week 9 Mean change (SD)	-0.4 (0.9)	-1.1 (1.2)	-1.2 (1.2)	<0.001*	<0.001*
Week 10 Mean change (SD)	-0.4 (0.9)	-1.1 (1.1)	-1.3 (1.2)	<0.001*	<0.001*
Week 11 Mean change (SD)	-0.3 (0.8)	-1.2 (1.2)	-1.4 (1.2)	<0.001*	<0.001*
Week 12 Mean change (SD)	-0.3 (0.8)	-1.1 (1.2)	-1.5 (1.2)	<0.001*	<0.001*

Per Table 14.2.5 in Vol. 37 on pg. 4215-4219.

*p<0.05 and statistically significant

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Table 7: 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)

Sources: SAS dataset received 8/2/04

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

^aLOCF=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

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Table 8: Study PR 01502 mean change from baseline in the severity of moderate to severe hot flushes at each study week using LOCF* (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)

Sources: SAS dataset received 8/4/04

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

*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)

CI's 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.

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Table 9: Study PR 01502 mean change from baseline in the number of moderate to severe hot flushes at each study week using LOCF* (ITT Population, ANCOVA)

Study Visit	Placebo (n=120)	EA 0.45 mg (n=125)	p-value (95% CI Femtrace – Placebo) [1]
Baseline Mean (SD)	84.5 (36.5)	85.1 (33.5)	
Week 1 Mean (SE) change	-19.2 (2.7)	-20.9 (2.6)	0.1956 (-8.9, 5.6)
Week 2 Mean change (SE)	-26.3 (3.1)	-29.5 (3.3)	0.1309 (-11.7, 5.3)
Week 3 Mean change (SE)	-29.7 (3.2)	-35.1 (3.2)	0.0339* (-14.2, 3.4)
Week 4 Mean change (SE)	-33.5 (3.2)	-40.6 (3.2)	0.0161* (-15.9, 1.8)
Week 5 Mean change (SE)	-35.0 (3.2)	-43.4 (3.2)	0.0038* (-17.3, 0.5)
Week 6 Mean change (SE)	-36.1 (3.2)	-46.1 (3.1)	0.0004* (-18.7, -1.4)
Week 7 Mean change (SE)	-37.0 (3.2)	-45.8 (3.2)	0.0016* (-17.7, -0.07)
Week 8 Mean change (SE)	-39.0 (3.2)	-49.1 (3.1)	0.0003* (-18.7, -1.4)
Week 9 Mean change (SE)	-39.5 (3.2)	-50.1 (3.1)	0.0008* (-19.3, -1.8)
Week 10 Mean change (SE)	-41.4 (3.2)	-50.6 (3.2)	0.0019* (-18.0, -0.3)
Week 11 Mean change (SE)	-41.5 (3.2)	-50.7 (3.2)	0.0031* (-18.1, -0.3)
Week 12 Mean change (SE)	-42.0 (3.3)	-51.1 (3.5)	0.0047* (-18.0, -0.1)

Sources: SAS dataset received 8/2/04

ITT: Intent-to-Treat population

*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)

CI's were calculated from an ANCOVA with baseline, treatment, center at weekly

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Table 10: Study PR 01502 mean change from baseline in the severity of moderate to severe hot flushes at each study week using LOCF* (ITT Population, ANCOVA)

Study Visit	Placebo (n=120)	EA 0.45 mg (n=125)	p-value (95% CI Femtrace – Placebo) [1]
Baseline Mean (SD)	2.4 (0.3)	2.4 (0.3)	
Week 1 Mean (SE) change	-0.03 (0.02)	-0.09 (0.02)	0.2251 (-0.12, 0.01)
Week 2 Mean change (SE)	-0.1 (0.04)	-0.2 (0.04)	0.4069 (-0.15, 0.05)
Week 3 Mean change (SE)	-0.2 (0.04)	-0.2 (0.04)	0.7406 (-0.2, 0.06)
Week 4 Mean change (SE)	-0.3(0.05)	-0.2 (0.05)	0.1811 (-0.3, 0.02)
Week 5 Mean change (SE)	-0.4 (0.05)	-0.2 (0.05)	0.1077 (-0.3, -0.07)
Week 6 Mean change (SD)	-0.4 (0.05)	-0.2 (0.05)	0.0182* (-0.4, -0.04)
Week 7 Mean change (SE)	-0.3 (0.06)	-0.4 (0.06)	0.0266* (-0.3, -0.003)
Week 8 Mean change (SE)	-0.2 (0.06)	-0.5 (0.06)	0.0120* (-0.4, -0.1)
Week 9 Mean change (SE)	-0.3 (0.06)	-0.5 (0.06)	0.0266* (-0.4, -0.03)
Week 10 Mean change (SE)	-0.3 (0.06)	-0.5 (0.06)	0.1752 (-0.4, -0.004)
Week 11 Mean change (SE)	-0.3 (0.07)	-0.6 (0.07)	0.0152* (-0.5, -0.1)
Week 12 Mean change (SE)	-0.3 (0.07)	-0.6 (0.07)	0.0550 (-0.5, -0.1)

Sources: SAS dataset received 8/4/04

ITT: Intent-to-Treat, *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 $SSI = (2 * nr_mod + 3 * nr_sev) / nr_ms$

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.

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Table 11: Study PR 01502 responder rates for decrease in frequency of moderate to severe hot flushes (ITT* Population)

	Placebo n=108	EA 0.45mg n=113	p-value*
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%)	0.039²
Week 4	20 (18.5%)	33 (29.2%)	0.083
Week 5	22 (20.4%)	39 (34.5%)	0.024²
Week 6	23 (21.3%)	43 (38.1%)	0.008²
Week 7	23 (21.3%)	46 (40.7%)	0.002²
Week 8	23 (21.3%)	47 (41.6%)	0.001²
Week 9	27 (25.0%)	53 (46.9%)	<.001²
Week 10	26 (24.1%)	54 (47.8%)	<.001²
Week 11	29 (26.9%)	52 (46.0%)	0.003²
Week 12	29 (26.9%)	53 (46.9%)	0.002²

Source: Submitted by Sponsor as Amendment No. 13 to NDA 21-633 on July 9, 2004

Note: Responder = 75% or more decrease in the number of hot flushes when compared to baseline

ITT* Population excluded 24 subjects from Site 62

¹p-value is from Fisher's Exact Test.

²p<0.05 and statistically significant

Table 12: Study PR 01502 responder rates for severity of moderate to severe hot flushes (ITT* Population)

	Placebo n=108	EA 0.45 mg n=113	p-value ¹
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%)	0.012²
Week 7	8 (7.4%)	17 (15.0%)	0.090
Week 8	5 (4.6%)	17 (15.0%)	0.012²
Week 9	8 (7.4%)	16 (14.2%)	0.131
Week 10	9 (8.3%)	20 (17.7%)	0.047²
Week 11	7 (6.5%)	26 (23.0%)	<0.001²
Week 12	10 (9.3%)	27 (23.9%)	0.004²

Source: Submitted by Sponsor as Amendment No. 15 to NDA 21-633 on July 23, 2004

Note: Responder = 75% or more decrease in the severity of hot flushes when compared to baseline

ITT* Population excluded 24 subjects from Site 62

¹p-value is from Fisher's Exact Test

²p<0.05 and statistically significant

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 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Table 16: Incidence of AEs Occurring in $\geq 2\%$ of Subjects in Any Treatment Group Presented in Descending Frequency of Preferred Term

Adverse Event ^a	Placebo	Femtrace 0.45	Femtrace	Femtrace
	(n = 221)	mg/day (n = 132)	0.9 mg/day (n = 100)	1.8 mg/day (n = 95)
	n (%)	n (%)	n (%)	n (%)
Headache (NOS)	12 (5.4)	4 (3.0)	5 (5.0)	4 (4.2)
Vaginal Bleeding	3 (1.4)	1 (0.8)	4 (4.0)	7 (7.4)
Breast Tenderness	3 (1.4)	1 (0.8)	0 (0.0)	6 (6.3)
Influenza	3 (1.4)	3 (2.3)	0 (0.0)	4 (4.2)
Vaginal Discharge	0 (0.0)	3 (2.3)	4 (4.0)	3 (3.2)
Abdominal Pain (NOS)	4 (1.8)	1 (0.8)	0 (0.0)	3 (3.2)
Fungal Infection (NOS)	2 (0.9)	4 (3.0)	1 (1.0)	1 (1.1)
Nasopharyngitis	5 (2.3)	2 (1.5)	0 (0.0)	1 (1.1)
Nausea	3 (1.4)	3 (2.3)	0 (0.0)	2 (2.1)
Intermenstrual Bleeding	2 (0.9)	0 (0.0)	2 (2.0)	3 (3.2)
Sinusitis (NOS)	3 (1.4)	2 (1.5)	1 (1.0)	1 (1.1)
Upper Respiratory Tract Infection (NOS)	3 (1.4)	1 (0.8)	3 (3.0)	0 (0.0)
Back Pain	1 (0.5)	0 (0.0)	3 (3.0)	2 (2.1)
Bronchitis (NOS)	1 (0.5)	2 (1.5)	2 (2.0)	1 (1.1)

AE = adverse event; NOS = not otherwise specified

^a Regardless of drug relationship

Table 17: Study PR 00501 mean change from baseline in the number of moderate to severe hot flushes (MSVS) per week using LOCF (ITT^a Population, ANCOVA)

Week	Placebo (N=94)	Femtrace 0.9 mg (N=100)	Femtrace 1.8 mg (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-values (95% CI Femtrace – Placebo) [2]		< 0.0001 (-35.5, -17.4)	< 0.0001 (-38.5, -19.8)
Week 8			
Mean (SD)	46.1 (51.6)	19.2 (29.4)	9.3 (15.5)
Mean (SE) change from baseline	-37.4 (3.4)	-62.5 (3.3)	-73.3 (3.4)
(95% CI Femtrace – Placebo)		(-25.1, -34.5)	(-35.9, -45.3)
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-values (95% CI Femtrace – Placebo) [2]		< 0.0001 (-37.3, -17.9)	< 0.0001 (-48.5, -28.5)

Sources: SAS dataset

^aITT=Intent-to-Treat, ^bLOCF=Last Observation Carried Forward

Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval

* : Primary endpoint

[1]: The number of MSVS at baseline was the weekly average number of MSVS during the 2-week between screening and randomization

[2]:P-values were based on Wilcoxon rank sum test (van Elteren test)

Table 18: Study PR 00501 mean change from baseline in the severity of moderate to severe hot flushes (MSVS) per week using LOCF (ITT^a Population, ANCOVA)

Week	Placebo (N=94)	Femtrace 0.9 mg (N=100)	Femtrace 1.8 mg (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-values (95% CI Femtrace – Placebo) [2]		0.0005 (-0.8, -0.2)	0.002 (-0.7, -0.2)
Week 8			
Mean (SD)	2.2 (0.8)	1.5 (1.2)	1.2 (1.2)
Mean (SE) change from baseline (95% CI Femtrace – Placebo)	-0.3 (0.1)	-1.0 (0.1) (-1.0, -0.4)	-1.3 (0.1) (-1.2, -0.6)
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-values (95% CI Femtrace – Placebo) [2]		< 0.0001 (-1.1, -0.5)	<0.0001 (-1.5, -0.9)

Sources: SAS dataset

^aITT=Intent-to-Treat, ^bLOCF=Last Observation Carried Forward

Mean=Arithmetic Mean, SD=Standard Deviation, SE= Standard Error, CI=Confidence Interval

* : Primary endpoint

[1]: The number of MSVS at baseline was the weekly average number of MSVS during the 2-week between screening and randomization.

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

Change from baseline in the severity defined as $SS1 = (2 * nr_mod + 3 * nr_sev) / nr_ms$

Where $nr_ms = nr_mod + nr_sev$ is the total number of moderate to severe hot flushes.

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/s/

Brenda Gierhart
8/20/04 09:44:14 AM
MEDICAL OFFICER

Daniel A. Shames
8/20/04 11:28:19 AM
MEDICAL OFFICER

NDA 21-633

Date NDA Submitted: 10/14/03

Date NDA Received: 10/14/03

Review Completed: 8/05/04

Review Finalized: 8/13/04

**Medical Officer's Review
(Original Review)**

Sponsor: Warner Chilcott Company, Inc.
Rockaway 80 Corporate Center
100 Enterprise Drive, Suite 280
Rockaway, New Jersey 07866

Drug Name:

Generic: Estradiol Acetate
Trade: Femtrace™
Chemical: Estra-1,3,5(10)-triene-3, 17β-diol-3-acetate

Pharmacologic category: Estrogen

Dosage Form: Oral tablet

Dosage Strength: Estradiol acetate 0.45 mg once daily
Estradiol acetate 0.9 mg once daily
Estradiol acetate 1.8 mg once daily

Proposed Indications:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Related Submission: IND 63,188

Related Documents: NDA 21-633 Amendments dated 12/16/03, 2/03/04, 2/19/04, 3/17/04, 7/01/04, and 7/09/04.

Medical Reviewer: Ronald J. Orleans, M.D.
Medical Officer

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The Executive Summary of the Primary Clinical Review

1. RECOMMENDATION

1.1. Recommendations on Approvability

This reviewer recommends approval of all three proposed doses of Femtrace™ (estradiol acetate 0.45 mg, 0.9 mg, and 1.8 mg) for the treatment of moderate to severe vasomotor symptoms associated with the menopause. This recommendation is based upon an analysis of the efficacy and safety data from the two Phase 3, placebo-controlled clinical trials (Study PR 00501 and Study PR 01502) submitted in the Original NDA 21-633.

This reviewer does not recommend approval of any of the three proposed doses of Femtrace™ (estradiol acetate 0.45 mg, 0.9 mg, and 1.8 mg) for the treatment of moderate to severe vulvar and vaginal atrophy associated with the menopause. ☐

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1.2. Recommendations on Postmarketing Studies and/or Risk Management Steps Where Appropriate

No specific postmarketing commitments and/or risk management steps are recommended.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of the Clinical Program

The clinical program for estradiol acetate (EA) development consisted of two primary Phase 3 clinical trials (PR 00501 and PR 01502) to demonstrate safety and efficacy and three Phase 1 clinical studies (PR 05000, PR 09601, and PR 00102) designed to characterize the pharmacokinetic profile of EA tablets.

Study PR 00501 was a multicenter, double-blind, placebo-controlled, randomized, parallel group study planned to be conducted at 44 U.S. study sites. A total of 293 subjects were randomized at 41 study sites. This study compared two doses of daily, continuous regimens of EA (0.9 mg and 1.8 mg) against placebo. 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.

Study PR 01502 was a multicenter, double-blind, placebo-controlled, randomized, parallel group study planned to be conducted at 40 U.S. study sites. A total of 259 subjects were randomized at 36 study sites. The study compared one dose of a daily, continuous regimen of EA (0.45 mg) against placebo. 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.

Study PR 05000 was a single center, single dose, three period crossover pharmacokinetic study in nine healthy volunteers.

Study PR 09601 was a single center, single dose, two period crossover food effect study in 16 healthy volunteers.

Study PR 00102 was a single center, single and multiple dose three period crossover pharmacokinetic study in 18 healthy volunteers.

2.2. Efficacy

Vasomotor Symptoms

The ANOVA results submitted by the Sponsor from the two Phase 3 clinical trials demonstrate the effectiveness of EA tablets in doses of 0.45 mg, 0.9 mg, and 1.8 mg administered once daily for the treatment of postmenopausal moderate to severe hot flushes.

- Subjects administered oral EA 0.45 mg once daily for 12 weeks experienced statistically significantly greater reduction in the number of moderate to severe hot flushes compared to placebo treated subjects at week 6 ($p=0.042$), week 8 ($p=0.048$), week 9 ($p=0.038$), and week 12 ($p=0.049$) but not statistically significant at week 4 ($p=0.113$).
- Subjects administered oral EA 0.45 mg once daily for 12 weeks experienced statistically significantly greater reduction in the severity of moderate to severe hot flushes compared to placebo treated subjects at week 5 ($p=0.010$), week 6 ($p=0.006$), week 7 ($p=0.025$), week 8 ($p<0.001$), week 9 ($p=0.012$), week 10 ($p=0.015$), week 11 ($p<0.001$), and week 12 ($p<0.001$), but not at week 4 ($p=0.259$).
- Subjects administered oral EA 0.9 mg and EA 1.8 mg once daily for 12 weeks experienced a statistically significantly greater reduction in the number of moderate to severe hot flushes compared to placebo treated subjects at weeks 4 and 12 ($p<0.001$ for both treatment groups at both time points).
- Subjects administered oral EA 0.9 mg and EA 1.8 mg once daily for 12 weeks experienced statistically a significantly greater reduction in the severity of moderate to severe hot flashes compared to placebo treated subjects at weeks 4 and 12 (EA 0.9 mg: $p=0.003$ and $p<0.001$, respectively and EA 1.8 mg: $p=0.004$ and $p<0.001$, respectively).

Vulvar and Vaginal Atrophy

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2.3. Safety

The safety data for the two primary Phase 3 clinical trials presented in the submission shows that the overall safety profile of Femtrace™ given daily in doses of 0.45 mg, 0.9 mg, or 1.8 mg is acceptable.

Once daily oral treatment for 12 weeks with Femtrace™ in all doses tested was well tolerated in this study. The majority of adverse events (AEs) reported were mild to moderate in intensity and most were considered not related or unlikely related to study drug. The most commonly reported AEs during the study were primarily those that were expected with the use of orally administered estradiol (e.g., headache, nausea, vaginal bleeding and/or spotting, vaginal discharge, breast tenderness), and those caused by infectious agents (e.g., nasopharyngitis, fungal infection, influenza).

Of the 548 subjects who received study medication, 236 (43.1%) reported one or more adverse events. At least one AE was experienced by 38.6%, 48.0%, and 51.6% of subjects receiving EA 0.45 mg, 0.9 mg, and 1.8 mg, respectively, compared with 39.8% of placebo-treated subjects.

2.4. Dosing, Regimen, and Administration

Estrogens alone or combined with a progestin are approved for the treatment of vasomotor symptoms (oral tablets) and vulvar and vaginal atrophy (vaginal cream, vaginal tablets or oral tablets) associated with the menopause. The continuous daily oral treatment regimen for which approval is sought is a standard regimen for estrogen-only oral therapy. The Food and Drug Administration's 2003 draft Guidance for Industry document, entitled "Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendations for Clinical Evaluation", encourages Sponsors to develop the lowest doses and exposures for estrogens (and progestins) for indications being sought.

Since the onset of efficacy by ANOVA was delayed for the vasomotor symptom indication to five and six weeks for the EA 0.45 mg once daily dose and since the EA 0.45 mg dose did not show a sustained statistically significant decrease in the frequency of moderate to severe hot flushes to week 12, this reviewer considers EA 0.45 mg to be the lowest effective dose. This reviewer does not recommend conducting another study to demonstrate an ineffective dose of EA.

2.5. Drug-Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogen and may result in side effects. This information is provided in estrogen class labeling.

2.6. Special Populations

Femtrace™ is only indicated for use in postmenopausal women. The protocols in Study PR 00501 and Study PR 01502 included subjects greater than 45 years of age. Median ages for each study were 53.2 years and 52.4 years respectively. There is no data available from the studies to determine efficacy for the proposed indications in women under age 45. Femtrace™ has not been studied in women with liver disease or renal impairment. Femtrace™ should not be used in pregnant women.

Study PR 00501 only enrolled four subjects above the age of 65. Three subjects were randomized to EA 0.9 mg treatment arm and one subject randomized to placebo. The oldest enrolled subject in the study was 68 years of age.

Study PR 01502 only enrolled nine subjects above the age of 65. Seven subjects were randomized to the EA 0.45 mg treatment arm and one subject randomized to placebo. The oldest enrolled subject in the study was 79 years of age.

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Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication (s), Dose, Regimen

Endogenous estrogens are responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estrinol at the receptor level. Estradiol acetate (EA) is the 3-acetate ester of estradiol. It is rapidly hydrolyzed to estradiol, the prevalent sex steroid produced by the ovarian follicle which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women. Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Femtrace™, the product described in this application is an oral tablet containing estradiol acetate; henceforth in this review referred to as EA. The Division of Medication Errors and Technical Support (DMETS) did not recommend the use of the proprietary name Femtrace™ because of concerns regarding the look-alike and/or sound-alike confusion with other drugs such as Estrace, Premphase, Femtrol, and FemHRT. In addition, DMETS was concerned regarding the confusion with the dosing of similar products. After internal discussions however, the Division of Reproductive and Urologic Drug Products (DRUDP) decided the name Femtrace™ was sufficiently distinctive so as not to become clinically problematic.

EA is a prodrug which is rapidly hydrolyzed to estradiol, the prevalent sex steroid produced by the ovary before menopause. EA has been shown to have a half-life of 28 seconds *in vitro* in human serum and whole blood cells. The proposed indications for EA are:

- The treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause.
- The treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) associated with the menopause.

The Sponsor stated that because EA is approximately 15% more orally bioavailable than estradiol, the 0.9 and 1.8 mg tablets are expected to have efficacy similar to 1.0 and 2.0 mg of estradiol. The Sponsor also stated that estradiol 0.5 mg is not believed to be effective in the treatment of menopausal symptoms. The 0.45 mg tablet is therefore expected to be marginally or not effective and was included in the development program to define the lowest effective dose.

EA was originally developed to facilitate intravaginal delivery of estrogen. The EA intravaginal ring (IVR) is the subject of IND 58,488 submitted by Galen Limited (now Warner Chilcott Company Inc.). EA is considerably more soluble in the elastomeric polymer IVR than estradiol, thus allowing an IVR to be formulated to deliver the equivalent of 0.05 mg and 0.1 mg of

estradiol per day (Study PR 05000). The EA IVR, Femring™, was approved by the Agency on 3/20/03 (NDA 21-367) for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

Vasomotor symptoms in postmenopausal women are commonly known as hot flashes or hot flashes. 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 DRUDP recommends conducting one or more randomized, double-blinded, placebo-controlled clinical trials of 12-week duration to support safety and efficacy. These recommendations emphasize that adequate dose ranging studies be conducted to identify the doses to be studied in the proof of efficacy studies. Studies should identify the lowest effective dose by inclusion of an ineffective dose as one of the doses evaluated.

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

DRUDP recommends that the primary efficacy analysis show a clinically and statistically significant reduction in the frequency and severity of hot flashes in the treated group compared to the control group. This reduction in the frequency and severity of hot flashes 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, although objective measures (e.g., thermography) can be used as primary efficacy endpoints and as validation of subjective endpoints.

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1.2. State of Armamentarium for Indication(s)

Other oral estrogen-alone drug products currently approved for the treatment of VMS and/or VVA include:

- Cenestin® (synthetic conjugated estrogens, A) 0.3 mg is approved for the treatment of VVA and 0.625 mg, 0.9 mg, and 1.25 mg are approved for the treatment of VMS.
- Estinyl® (ethinyl estradiol) 0.02 mg, and 0.05 mg for the treatment of VMS.
- Estrace® (micronized estradiol) 0.5 mg, 1.0 mg, and 2.0 mg
- Estratab® (esterified estrogens) 0.3 mg, and 0.625 mg
- Menest® (esterified estrogens) 0.3 mg, 0.625 mg, 1.25 mg, and 2.5 mg
- Ogen® (estropipate) 0.625 mg, 1.25 mg, and 2.5 mg
- Ortho-Est® (estropipate) 0.625 mg and 1.25 mg
- Premarin® (conjugated equine estrogens) 0.3 mg, 0.45 mg, 0.625 mg, 1.25 mg, and 2.5 mg is approved for the treatment of VMS and VVA (0.3 mg to 1.25 mg/day).
- Enjuvia® (synthetic conjugated estrogens; B) 0.625 mg and 1.25 mg

The approximate equivalent estrogen doses for menopausal use are:

- Conjugated equine estrogens: 0.625 mg
- Ethinyl estradiol: 0.005-0.015 mg
- Micronized estradiol: 1.0 mg
- Estropipate (piperazine estrogen sulfate): 1.25 mg
- Esterified estrogens: 0.625 mg

Femring™ is an estradiol acetate vaginal ring which was approved on March 20, 2003 for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause (NDA 21-367). Two dosage forms are available, 0.05 mg/day and 0.10 mg/day.

Other approved estrogen-only drug products include:

- A transdermal gel: EstroGel (estradiol)
- Vaginal creams: Estrace® (micronized estradiol), Ogen® (estropipate), Premarin® (conjugated estrogens)
- A vaginal tablet: Vagifem® (estradiol)
- A topical lotion: Estrasorb™ (estradiol topical emulsion)
- Transdermal patches: Alora® (estradiol), Climara® (estradiol), Esclim™ (estradiol), Estraderm® (estradiol), FemPatch® (estradiol), Vivelle® (estradiol), Vivelle Dot® (estradiol)
- Vaginal rings: Estring® (estradiol), FemRing™ (estradiol acetate)

1.3. Important Milestones in Product Development

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 two issues:

- Inclusion of the 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 (PR 01502) to investigate a lowest effective dose was initiated and submitted to the FDA on 4/18/02. Both Phase 3 studies, PR 00501 and PR 01502 had the same primary and secondary efficacy endpoints.

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1.4. Important Issues with Pharmacologically Related Agents

The January, 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms - Recommendations for Clinical Evaluation" "encourages sponsors to develop the lowest doses and exposures for both estrogens and progestins for indications sought, even though specific relationships between dose, exposure, and risk of adverse events may not be known". In addition, the Agency recommends that "studies identify the lowest effective dose by including an ineffective dose as one of the doses evaluated." Therefore, demonstrating the lowest effective dose of EA for the indications sought is an issue for this review.

Another significant issue with pharmacologically related agents is the question of how many primary endpoints must be met before approval is given for the VMS and VVA indications. The issue of whether a Sponsor must show success in meeting all of the four co-primary endpoints to obtain a VMS indication and [is uncertain.

Reviewer's Comment

Since the publication of the Women's Health Initiative (WHI) study results in 2002, the Agency has recommended that estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks. The definition of what constitutes the "lowest effective dose" is unclear with regards to therapy for VMS and VVA.

2. SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND STATISTICS

2.1. Chemistry, Manufacturing and Controls

The drug substance estradiol acetate is synthesized [redacted] It is present as a white to off-white powder at room temperature. It is slightly soluble in aqueous solvents and highly soluble in organic solvents. Femtrace™ is manufactured in three strengths: 0.45 mg (cream), 0.9 mg (white), and 1.8 mg (yellow). The EA 0.45 mg dose is molar equivalent (but not bioequivalent) to 0.39 mg of 17β estradiol; the EA 0.9 mg dose is molar equivalent to 0.78 mg of 17β estradiol; and the EA 1.8 mg dose is molar equivalent to 1.56 mg of 17β estradiol.

The Sponsor has listed two sites for EA manufacturing. The first site [redacted] is located in [redacted] and the second site [redacted] is located in [redacted] Commercial production of the drug product will be done at the [redacted] site while the pivotal Phase 1 and 3 clinical supplies were manufactured using EA from the [redacted] site.

Please see the Chemistry, Manufacturing and Controls Review by the Chemistry reviewer for a more complete discussion

2.2. Animal Pharmacology and Toxicology

No nonclinical development program was conducted due to the rapid hydrolysis of estradiol acetate to estradiol resulting in no significant systemic exposure to estradiol acetate. One *in vitro* study in human serum and whole blood cells (Study 1450/011) showed that estradiol acetate was very rapidly hydrolyzed to estradiol with a hydrolysis half-life of 28 seconds. In a confirmatory study (Study PR-09601), 1.8 mg estradiol acetate was given orally to healthy postmenopausal women and was not detected in subsequent serum samples confirming that estradiol acetate was rapidly hydrolyzed to estradiol *in vivo*. Therefore, the absorption, distribution, metabolism and excretion of estradiol acetate are essentially the same as those of estradiol.

In an Ames study, estradiol acetate is non-genotoxic.

Please see the Pharmacology/Toxicology Review for a more complete discussion.

Reviewer's Comment

Because estradiol-3-acetate is rapidly hydrolyzed to estradiol, estradiol is the relevant compound with respect to toxicity. The safety of this new formulation delivering estradiol-3-acetate is based on the extensive experience of human exposure to estradiol.

2.3 Statistics

There were several statistical issues that arose during the course of this review.

In Study PR 00501, the first 50 subjects enrolled in the study were not asked to record their most bothersome urogenital symptom at baseline. This was handled in two different ways in the tables: One table had imputations made that the most severe urogenital symptom at screening was considered to be the most bothersome and the other table had no imputations made and these 50 subjects were excluded from the analysis.

In the course of monitoring Study PR 01502, it was discovered that at one study site (Site 62), subject medication labels were mistakenly unblinded for all 24 subjects randomized at that site. The study protocol was then amended (Amendment 1) to replace the 24 subjects and to exclude them from the primary efficacy analysis. The original analysis population is designated "ITT" and the revised, final, analysis population is designated "ITT*".

For evaluation of efficacy, the Sponsor used analysis of variance (ANOVA) model with effects of treatment, center, and treatment-by-center interaction performed for each of the target variables at each post-treatment week as planned in the protocol. The treatment-by-center interaction was dropped from the model if the interaction term was not significant. All efficacy analyses were based on an intent-to-treat (ITT) population and a modified intent-to-treat (ITT*).

The statistical reviewer applied an analysis of covariance (ANCOVA) as the primary efficacy analysis. The variables included baseline, treatment, center, and treatment-by-center interaction. The treatment-by-center interaction was dropped from the model if it showed no significance ($p > 0.05$).

Please refer to the Statistical Review and Evaluation for a more complete discussion.

Reviewer's Comment

This review will evaluate efficacy based on the Tables included in the submission which used analysis of variance (ANOVA) as the model.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

Estradiol is a lipophilic molecule that is absorbed readily across cellular membranes including skin, vaginal mucosa, and the gastrointestinal tract. Estradiol is highly lipid-soluble, will accumulate in fatty tissue, and is distributed throughout the body. Estradiol binds extensively to albumin, sex hormone binding globulin (SHBG), cortisol binding globulin (CBG), and α -glycoproteins. The main site of estradiol metabolism is in the liver although estradiol is metabolized in the gut wall. The plasma elimination half-life of estradiol is approximately one hour, independent of the route of administration.

Three pharmacokinetic studies were conducted to characterize the pharmacokinetic profile of EA tablets (See Section 4.2 for summaries of each study).

The following conclusions were reached:

- Estradiol acetate was rapidly hydrolyzed to E2 so that systemic exposure to EA was not significant. The administration of EA enhances E2 bioavailability by 19%. In addition, E2 disposition and elimination are not affected by EA administration.
- Administration of a 1.8 mg EA tablet with food decreased the rate but not the extent of E2 bioavailability.
- Estradiol was rapidly absorbed following oral administration of EA tablets. Estradiol and estrone (E1) exposure increased dose-proportionately with increasing dose of EA. Estradiol was metabolized to the less active metabolites E1 and E1 sulfate with an apparent half-life of 21 to 26 hours.

3.2. Pharmacodynamics

No specific pharmacodynamic studies were included in the submission.

Reviewer's Comment

Estradiol acetate is rapidly and completely hydrolyzed to estradiol. Because EA is approximately 1.15 times as bioavailable as estradiol (Study PR 05000) the doses of EA that were studied in this submission (0.45 mg, 0.9 mg, and 1.8 mg) were expected to produce serum estradiol levels approximating those produced by the oral administration of 0.5 mg, 1 mg, and 2 mg of estradiol, respectively. The molar equivalent amount of 17 β estradiol in each EA tablet is 0.39 mg, 0.78 mg, and 1.56 mg respectively.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Source of Clinical Data

Warner Chilcott Company, Inc. in Rockaway, New Jersey, is the Sponsor of NDA 21-633. NDA 21-633/ 000 was submitted on October 14, 2003.

The clinical program for EA development consisted of three Phase 1 clinical studies (PR 05000, PR 09601, and PR 00102) designed to characterize the pharmacokinetic profile of EA. tablets and two primary Phase 3 clinical trials (PR 00501 and PR 01502) to demonstrate safety and efficacy.

4.2. Overview of Clinical Trials

See Table 1 for a summary of studies in the clinical development program.

Table 1: Summary of All Studies in NDA 21-633 Clinical Development Program

Phase 1 Clinical Studies

Study Number	Country/No. of Sites	Study Design	Number Enrolled/ Complete	Age Range	Dosages/Dosage Forms/Duration
PR 05000	UK/1	Open label, single dose, 3-period, 3-treatment randomized cross-over study in healthy volunteers. 7-day washout period.	9/9	47-70	1 x 1.152 mg EA tablet 2 x 1.152 mg EA tablet 1 x 1 mg estradiol tablet
PR 09601	US/1	Open label, single dose, 2-period, 2-treatment, randomized crossover study in healthy volunteers.	16/16	47-75	1.8 mg EA tablet fasted vs. fed

		14-day washout period.			
PR 00102	US/1	Open label, single- and multiple-dose, 3-period, 3-treatment crossover study in healthy volunteers. 14-day washout period.	18/18	47-75	1 x 0.45 mg EA tablets x 7 days 1 x 0.09 mg EA tablets x 7 days 1 x 1.8 mg EA tablets x 7 days

Phase 3 Clinical Studies

Study Number	Country/No. of Sites	Study Design	Number Enrolled/Complete	Age Range	Dosages/Dosage Forms/Duration
PR 00501	US/44	Multicenter, double-blind, placebo-controlled, randomized, parallel group	293/263	41-67	0.9 mg/day EA tablets 1.8 mg/day EA tablets Placebo x 12 weeks
PR 01502	US/40	Multicenter, double-blind, placebo-controlled, randomized, parallel group	258/218	36-80	0.45 mg/day EA tablets Placebo x 12 weeks

Source: Adapted from ND 21-633, PR 00501, Final Study Report, Volume 36, Section 8.4.1, Page 4039.

Study PR 05000 was a single dose pilot pharmacokinetic study to compare the bioavailability of estradiol and estradiol acetate tablets following oral administration to postmenopausal women volunteers. Each subject received each of the following three treatments in random order (A) one 1.152 mg EA tablet (molar equivalent to 1 mg E2), (B) two 1.152 mg EA tablets (molar equivalent to 2 mg E2) and (C) one 1 mg micronized E2 tablet (Estrace®) with a 1-week washout period between treatments. Serum samples were collected from each subject before and following treatment. It was found that administration of EA enhances E2 bioavailability by 19% and that E2 disposition or elimination was not affected by EA administration. Serum E2 concentrations increased rapidly ($t_{max} = 2-3$ hours) following administration of EA tablets, then decreased to relatively constant E2 concentrations over 3 to 24 hours post dose. In comparison, serum E2 concentrations increased slowly over six hours following administration of micronized E2, then remained relatively constant over 6 to 24 hours.

Reviewer's Comment

EA is rapidly absorbed and hydrolyzed to E2 ($t_{max} = 2-3$ hours), while the profile for E2 indicates slower absorption ($t_{max} = 6$ hours). The similar E2 levels at times > 6 hours for both EA and E2 oral administration suggests that disposition and elimination are not affected by EA administration.

Study PR 09601 was a study to determine the effect of food on estradiol bioavailability following oral administration of a single dose of estradiol acetate in healthy postmenopausal women. Sixteen healthy postmenopausal women were enrolled and each received one 1.8 mg EA tablet with 240 mL of water in each of two treatment periods. In period 1, half the subject received treatment following an overnight fast and the other half received treatment within five minutes of consuming a high-fat, high calorie, test meal. After a two week washout, each subject received the alternative treatment. It was concluded that administration of a 1.8 mg EA tablet with food decreased the rate but not the extent of E2 bioavailability.

Study PR 00102 was a study to determine the pharmacokinetics of estradiol following oral administration of single- and multiple-doses of estradiol acetate tablets to healthy postmenopausal

women. Each subject received single- (one tablet) and multiple-doses (one tablet per day for six days) of EA tablets containing 0.45 mg, 0.9 mg, or 1.8 mg EA for a total of seven tablets administered in each of three treatment periods. There was a two week washout between treatment periods. Progestin therapy was administered to all non-hysterectomized women. It was found that estradiol was rapidly absorbed following oral administration of EA tablets and that estradiol and estrone exposure increased proportionally with increasing dose. Estradiol was extensively metabolized to the less active estrone and estrone sulfate and that the apparent elimination half-life values of 21 to 26 hours reflected enterohepatic circulation of E2.

Study PR 00501 was a multicenter, double-blind, placebo-controlled, randomized, parallel group study conducted in 44 U.S. study sites (three of these sites were initiated but did not enroll any subjects). A total of 293 subjects were randomized at 41 study sites. This study compared two continuous regimens of EA (0.9 mg and 1.8 mg) against placebo. All subjects being considered for enrollment were to discontinue estrogen/hormone therapy prior to the screening period. Both hysterectomized and non-hysterectomized women could be screened. Date first subject enrolled: 10/03/01. Date last subject completed: 11/19/02.

Study PR 01502 was a multicenter, double-blind, placebo-controlled, randomized, parallel group study conducted in 40 U.S. study sites (four of these sites were initiated but did not enroll any subjects). A total of 259 subjects were randomized at 36 study sites. The study compared one continuous regimen of EA (0.45 mg) against placebo. All subjects being considered for enrollment were to discontinue estrogen/hormone therapy prior to the screening period. Both hysterectomized and non-hysterectomized women could be screened. Date first subject enrolled: 6/26/02. Date last subject completed 2/26/03.

4.3. Postmarketing Experience

Estradiol acetate tablets are not approved for use in the U.S. so there is no postmarketing experience.

4.4. Literature Review

References are provided in the submission that pertain to the overall risks and benefits of estradiol administration. No additional FDA literature review was conducted.

5. CLINICAL REVIEW METHODS

5.1. Describe How Review was Conducted

NDA 21-633/000 was submitted in paper format on 10/14/2003. SAS transport files and draft labeling have been submitted electronically to the Electronic Document Room. The two primary Phase 3 studies submitted (PR 00501 and PR 01502) to support safety and efficacy were reviewed in their entirety. Safety data from the three Phase 1 studies (PR 05000, PR 09601, and PR 00102) were also reviewed.

The safety data submitted in the 4-Month Safety Update was reviewed upon receipt.

5.2. Overview of Materials Consulted in Review

The following materials were consulted during the conduct of this review:

- NDA 21-633/000; Volumes 25 to 64; Submission date of October 14, 2003
- NDA 21-633; Amendment No. 1; Clinical/Statistical and Chemistry, Manufacturing, and Controls Information; Submission date of December 16, 2003
- NDA 21-633; Amendment No. 2; Chemistry, Manufacturing and Controls Information; Submission date of December 18, 2003
- NDA 21-633; Amendment No. 3; Clinical Site Information; Submission date of February 3, 2004
- NDA 21-633; Amendment No. 4; The 4-Month Safety Update; Submission date of February 19, 2004
- NDA 21-633; Amendment No. 5; Revised Labeling; Submission date of March 17, 2004
- NDA 21-633; Amendment No. 13; Requested Clinical and CMC Information; Submission date of July 9, 2004
- NDA 21-633; Amendment No. 15; Requested Statistical Information; Submission date of July 23, 2004
- Consultation obtained from the Division of Medication Errors and Technical Support (DMETS) dated April 15, 2004
- Consultation obtained from the Division of Surveillance, Research, and Communication Support (DSRCS) dated April 29, 2004
- Consultation obtained from the Division of Drug Marketing, Advertising, and Communications (DDMAC) dated May 27, 2004
- IND 63,188/SN-000; Submission date of September 4, 2001
- IND 63,188/SN-005; Submission date of April 18, 2002
- NDA 21-367/SN-000; Submission date of December 28, 2001

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity

No Division of Scientific Investigation (DSI) audit was requested. Estradiol acetate has a 3S classification (new formulation, standard 10 month priority).

Reviewer's Comment

Estradiol is an approved drug and longstanding efficacy and safety data are available for vaginal creams, transdermal systems, oral tablets, and a vaginal ring. As such, this is not an application for which we would routinely request a clinical inspection.

5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards

The informed consent documents proposed for Study PR 00501 and PR 01502 were appropriate. Appropriate standards of patient care were administered during the conduct of the clinical trials in accordance with regulations pertaining to Good Clinical Practice (GCP).

In Study PR 00501, the first 50 subjects enrolled in the study were not asked to record their most bothersome urogenital symptom at baseline. This was handled in two different ways in the tables: One table had imputations made that the most severe urogenital symptom at screening was considered to be the most bothersome and the other table had no imputations made and these 50 subjects were excluded from the analysis.

In the course of monitoring Study PR 01502, it was discovered that at one study site (Site 62), subject medication labels were mistakenly unblinded for all 24 subjects randomized at that site.

The study protocol was then amended (Amendment 1) to replace the 24 subjects and to exclude them from the primary efficacy analysis. The original analysis population is designated "ITT" and the revised, final, analysis population is designated "ITT*".

5.5. Evaluation of Financial Disclosure

There were a total of 161 principal investigators and subinvestigators at 44 sites for Study PR 0501 and a total of 181 principal investigators and subinvestigators at 40 sites for Study PR 01502. FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was submitted by all investigators and subinvestigators. One investigator had disclosable information. Dr. [redacted] at Site [redacted] (Study [redacted]) and Site [redacted] (Study [redacted]) reported equity interest in the Sponsor that exceeded \$50,000.00 during the time he carried out the study. Dr. [redacted] at Site number [redacted] for Study [redacted] did not enroll any subjects due to timing of IRB approval. Dr. [redacted] at Site [redacted] enrolled [redacted] subjects in Study [redacted] ([redacted] of the study population). [redacted] was a double-blinded, multicenter trial with 44 participating investigators. The blind was not broken until after the database was locked.

Reviewer's Comment

Due to the small number of enrolled subjects at Site 24, no concerns arise from this financial disclosure information.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

The results from the two Phase 3 clinical trials demonstrate the effectiveness of EA tablets in single daily doses of 0.45 mg, 0.9 mg, and 1.8 mg in the treatment of postmenopausal moderate to severe hot flashes associated with the menopause.

Study PR 00501

Mean change in the four co-primary endpoints recommended for treatment of menopausal vasomotor symptoms at weeks 4 and 12:

Subjects administered oral EA 0.9 mg and EA 1.8 mg once daily for 12 weeks experienced statistically significantly greater reduction in the number of moderate to severe hot flashes compared to placebo treated subjects at weeks 4 and 12 ($p < 0.001$ for both treatment groups at both time points).

Subjects administered oral EA 0.9 mg and EA 1.8 mg once daily for 12 weeks experienced statistically significantly greater reduction in the severity of moderate to severe hot flashes compared to placebo treated subjects at weeks 4 and 12 (EA 0.9 mg: $p = 0.003$ and $p < 0.001$, respectively and EA 1.8 mg: $p = 0.004$ and $p < 0.001$, respectively).

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Study PR 01502

Mean change in the four co-primary endpoints recommended for treatment of menopausal vasomotor symptoms at weeks 4 and 12:

Subjects administered oral EA 0.45 mg once daily for 12 weeks experienced statistically significantly greater reduction in the number of moderate to severe hot flashes compared to placebo treated subjects at week 6 (p=0.042), week 8 (p=0.048), week 9 (p=0.038), and week 12 (p=0.049) but not statistically significant at week 4 (p=0.113).

Subjects administered oral EA 0.45 mg once daily for 12 weeks experienced statistically significantly greater reduction in the severity of moderate to severe hot flashes compared to placebo treated subjects at week 5 (p=0.010), week 6 (p=0.006), week 7 (p=0.025), week 8 (p<0.001), week 9 (p=0.012), week 10 (p=0.015), week 11 (p<0.001), and week 12 (p<0.001), but not at week 4 (p=0.259).

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6.2. General Approach to Review of the Efficacy of the Drug

Two Phase 3 double-blind, placebo-controlled clinical trials are included in the submission. Study PR 00501 and Study PR 01502 were performed to demonstrate the effectiveness of continuous administration of EA compared with placebo in decreasing the frequency and severity of moderate to severe hot flushes in postmenopausal women and in treating the moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. No other studies are included in the efficacy analysis.

6.3. Detailed Review of Trials by Indication

Study PR 00501 and Study PR 01502 were nearly identical studies which incorporated different dosages of EA. Subjects considered for enrollment, pre-screen and screening period requirements, eligibility criteria, and study procedures were identical in both studies. The protocol for Study PR 00501, using dosage strengths of EA 0.9 mg and 1.8 mg, was originally submitted to the DRUDP on August 31, 2001. As a result of subsequent discussions, a second study to investigate a lowest effective dose (PR 01502) was initiated. It evaluated a dosage strength of EA 0.45 mg and was submitted to IND 63,188 on April 18, 2002. Both studies were multicenter, double-blind, placebo-controlled, parallel group, and randomized with the common primary objective to determine 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. In addition, both Study PR 00501 and Study PR 01502 had identical secondary objectives. This was to evaluate the effectiveness of the treatment regimen in relieving urogenital symptoms (vaginal dryness, dyspareunia, urinary urgency, dysuria, urinary incontinence, nocturia, vaginal irritation/itching, and bleeding after intercourse) [

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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 42 study sites as follows:

- 100 subjects to the EA 0.9 mg study group
- 98 subjects to the EA 1.8 mg study group
- 95 subjects to the placebo group

A total of 263 (89.8%) subjects completed the study as follows:

- 88 (88.0%) subjects in the EA 0.9 mg study group
- 90 (91.8%) subjects in the EA 1.8 mg study group
- 85 (89.5%) subjects in the placebo study group

For all target variables an intent-to-treat (ITT) analysis was performed. Additionally, a per protocol analysis was done for the primary and secondary target variables. 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). A subject was included in the Per Protocol Population provided she had no protocol deviations that might have affected the primary target variable.

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 as follows:

- 132 subjects to the EA 0.45 mg study group
- 127 subjects to the placebo group

A total of 218 (84.2%) subjects completed the study as follows:

- 116 (87.9%) subjects in the EA 0.45 mg study group
- 102 (80.3%) subjects in the placebo study group

For all target variables an intent-to-treat (ITT) analysis was also performed. This population and the Per Protocol Population were similarly defined as in Study PR 00501.

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. The originally planned ITT data set including Site 62 subjects was analyzed in a supplementary analysis for the primary efficacy variables only.

Reviewer's Comment

It is only the ITT analysis (Study PR 00501) and the ITT* analysis (Study PR 01502) that this reviewer will use to determine efficacy of the estradiol acetate relating to the indications of treatment of postmenopausal vasomotor symptoms and vulvar and vaginal atrophy.

The originally planned ITT data set for Study PR 01502 was only analyzed for the primary efficacy variables which were the change from baseline in the frequency and severity of moderate to severe and total hot flushes, particularly at weeks 4 and 12. No other data regarding the ITT Population (including Site 62) was submitted to this NDA.

Inclusion and Exclusion Criteria

Women must satisfy the following inclusion criteria:

1. Age \geq 45 years of age.
2. Amenorrhea for > 12 months or amenorrhea for at least 6 months and serum FSH > 40 mIU/mL and serum estradiol < 20 pg/mL or 2 weeks post bilateral oophorectomy (if unable to confirm removal of both ovaries, must have serum FSH > 40 mIU/mL and serum estradiol < 20 pg/mL).
3. Seven or more moderate or severe hot flushes daily for 1 week or 60 or more hot flushes per week during the two week screening period prior to study entry.
4. Endometrial biopsy without evidence of endometrial hyperplasia or cancer (for non-hysterectomized women). A valid negative endometrial biopsy performed within 6 months prior to the study will be accepted if the report is available. Women with bleeding must have an endometrial biopsy at screening. Amenorrheic women with uteri with insufficient endometrial tissue for diagnosis at screening may be enrolled if a transvaginal ultrasound (TVU) shows a double-wall endometrial thickness of < 5mm.
5. Negative pregnancy test (if less than 12 months of amenorrhea without bilateral oophorectomy).
6. Signed an informed consent form.

Women must not have any of the following exclusion criteria:

1. Oral hormone therapy within 8 weeks, transdermal hormone therapy within 4 weeks, intramuscular therapy within 6 months of start of study, and estrogen implants still implanted or removed within 4 weeks of start of study.
2. Abnormal Pap smear (low grade squamous intraepithelial lesion or worse).
3. Known or suspected premalignant or malignant disease (successfully treated skin cancers are excluded) or a history of steroid-dependent malignancy.
4. Myocardial infarction within 6 months prior to start of study, coronary heart disease requiring antiarrhythmic or antianginal drugs, congestive heart failure, uncontrolled hypertension.
5. History of stroke or transient ischemic attacks, recent or past history of thrombophlebitis or thromboembolic disorders, and treatment with anticoagulants.
6. Uncontrolled thyroid disorders, insulin-dependent diabetes mellitus, or severe systemic disease that might interfere with the conduct of the study.
7. Increased frequency or severity of headaches including migraines during previous estrogen therapy.
8. Any disease or condition that compromises the function of the body systems resulting in altered absorption, excessive accumulation, impaired metabolism, or altered excretion.
9. Urinary tract infection.
10. Fasting baseline cholesterol \geq 300 mg/dL, triglycerides \geq 300 mg/mL, or glucose \geq 140 mg/dL.

11. History of drug addition or alcohol abuse (within last 2 years).
12. Current or significant past history of depression.
13. Participation in another clinical trial within one month or have received investigational drug within the last three months prior to study entry.

Reviewer's Comment

The inclusion and exclusion criteria and study design utilized in Studies PR 00501 and PR 01502 were based on the FDA's "Guidance for the Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women", March 1995. This has been replaced by the Agency's 2003 draft Guidance for Industry entitled "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms-Recommendations for Clinical Evaluation". The inclusion/exclusion criteria used by the Sponsor are consistent with the 2003 draft Guidance for the vasomotor symptom indication. ☐

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Study Visits

Visit 1 (Screening):

The following safety evaluations were performed during the screening visit (Visit 1) in both Studies PR 00501 and PR 01502:

- Subject information and informed consent.
- A medical history and physical examination, including breast and pelvic exam, blood pressure, heart rate, and weight.
- A Pap smear and maturation index were performed. If the Pap smear presents cellular abnormalities other than ASCUS the subject cannot be enrolled into the study.
- A mammogram was performed (unless a written report of a normal mammogram within the previous one year was available).
- An endometrial biopsy was obtained. If insufficient tissue was obtained, a transvaginal ultrasound (TVS) was performed.
- Laboratory evaluations will be performed including hematology, blood chemistry, liver enzymes, lipid profile, urinalysis, pregnancy test and hormone assays (FSH, estradiol, TSH).
- Screening diary cards dispensed. Vasomotor symptoms were to be reported daily and the presence or absence of urogenital symptoms were to be recorded weekly.

Subsequent subject visits and evaluations were identical in both Studies PR 00501 and PR 01502.

Visit 2 (Baseline):

- Blood pressure, heart rate, weight
- TVU if the endometrial biopsy indicates insufficient tissue
- Adverse events

- Concomitant medication
- Screening diary card returned
- Randomization
- Diary cards dispensed
- Cycles 1 and 2 medication dispensed

Visit 3 (Week 4):

- Blood pressure, heart rate, weight
- Adverse events
- Concomitant medication
- Cycle 1 diary card reviewed
- Cycle 1 medication returned
- Cycle 3 medication dispensed

Visit 4 (Final Visit Week 12):

- Physical Examination
- Gynecological examination
- Vaginal cytology for maturation index
- General laboratory and urinalysis
- Blood pressure, heart rate, weight
- Adverse events
- Concomitant medication
- Diary cards returned
- Cycles 2 and 3 medication returned
- End of study evaluation
- At the completion of the study, all women who had not had a hysterectomy received a course of progestin. The choice of drug and dose of treatment was left to the discretion of the investigator; the duration of treatment was to be at least 12 days (per Amendment 1 dated August 7, 2001).

Subject Disposition

A total of 820 subjects were screened for Study PR 00501 and 691 subjects were screened for Study PR 01502.

The disposition of subjects by treatment groups is presented in Tables 2 and 3.

Table 2: Disposition of Subjects by Treatment Groups for Study PR 00501

Parameter	Study PR 00501			Total
	Placebo	EA 0.9 mg	EA 1.8 mg	
Randomized Subjects (%)	95 (32.4)	100 (34.1)	98 (33.4)	293 (100)
Completed Study (%)	85 (89.5)	88 (88.0)	90 (91.8)	263 (89.8)
Discontinued Early (%)	10 (10.5)	12 (12.0)	8 (8.16)	30 (10.2)
Adverse Event	2 (2.10)	4 (4.0)	1 (1.02)	7 (2.38)
Lack of Efficacy	4 (4.21)	2 (2.0)	2 (2.04)	8 (2.73)

Loss to Follow-Up	2 (2.10)	2 (2.0)	3 (3.06)	7 (2.38)
Withdrew Consent	1 (1.05)	2 (2.0)	1 (1.02)	4 (1.36)
Protocol Violation	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Other	1(1.05)	1 (1.0)	1 (1.02)	3 (1.02)

Source: Adapted from PR 00501 Final Study Report, Section 14.1, Table 14.1.2.

Reviewer's Comment

Of the 293 subjects randomized in Study PR 0051 four subjects were excluded from the ITT Population because they never returned to the study site and had no post-baseline efficacy data. Thus the ITT Population totaled 289 subjects.

A total of 30 subjects (10.2%) discontinued early from this study. Overall, lack of efficacy (2.73%, 8 subjects) was the most common reason for discontinuation.

The protocol violation in the EA 0.9 mg group, assessed by the Sponsor, involved the use of hormone products during the study other than the investigational drug.

All treatment groups of the ITT Population were comparable at baseline with regard to the efficacy parameters.

Table 3: Disposition of Subjects by Treatment Groups for Study PR 01502

Parameter	Study PR 01502		Total
	Placebo	EA 0.45 mg	
Randomized Subjects (%)	127 (49.0)	132 (50.9)	259 (100)
Completed Study (%)	102 (80.3)	116 (87.8)	218 (84.1)
Discontinued Early (%)	25 (19.6)	16 (12.1)	41 (15.8)
Adverse Event	4 (3.1)	0 (0.0)	4 (1.5)
Lack of Efficacy	9 (7.0)	5 (3.7)	14 (5.4)
Loss to Follow-Up	7 (5.5)	8 (6.0)	15 (5.7)
Withdrew Consent	4 (3.1)	1 (0.7)	5 (1.9)
Death	0 (0.0)	1 (0.7)	1 (.00)
Other	1 (0.7)	1 (0.7)	2 (.07)

Source: Adapted from PR 01502 Final Study Report, Section 14.1, Table 14.1.2.

Reviewer's Comment

Of the 259 subjects randomized in Study PR 01502, 24 subjects from Site 62 were excluded because subject medication labels were mistakenly unblinded. Another 14 subjects were excluded from the ITT Population analysis because of no post-baseline observations. Thus the ITT* Population consisted of 221 subjects.

In Study 01502, a total of 41 subjects (15.8%) discontinued early from the study. Overall, the most common reasons were lack of efficacy (5.4%, n=14) and loss to follow-up (5.7%, n=15).

All treatment groups of the ITT* Population were comparable at baseline with regard to the efficacy parameters.

Subject Demographics

Table 4: Demographic Information for Study PR 00501 (ITT Population)

Parameter	Placebo (n=94)	EA 0.9 mg (n=100)	EA 1.8 mg (n=95)	p-value*	Overall (N=289)
Age, years					
Mean (SD)	53.7 (4.8)	53.5 (4.7)	53.0 (4.1)	0.560	53.4 (4.5)
Median	53.3	53.2	53.0		53.2
Range	41.3-66.6	46.0-68.4	45.0-62.3		41.3-68.4
Race, n (%)				0.660	
Caucasian	71 (75.5%)	78 (78.0%)	77 (81.1%)		226 (78.2%)
Non-Caucasian	23 (24.5%)	22 (22.0%)	18 (18.9%)		63 (21.8%)
Height, inches				0.985	
Mean (SD)	64.0 (3.1)	64.1 (2.9%)	64.0 (2.9)		64.0 (2.9)
Median	64.0	64.0	64.0		64.0
Range	53.0-70.0	53.0-72.0	54.5-71.0		53.0-72.0
Weight, pounds				0.660	
Mean (SD)	163 (32.5)	164 (39.0)	168 (36.7)		165 (36.1)
Median	159	156	159		158
Range	106.5-265.0	97.8-313.4	105.0-276.9		97.8-313.4

Source: Adapted from Study PR 00501, Final Study Report, Section 11.2.1, Text Table 4.
SD = standard deviation.

* p-values are from a 1-way ANOVA for continuous parameters; Fisher's Exact test for categorical variables.

ITT = intent-to-treat

Reviewer's Comment

As can be seen in Table 4, the treatment groups were comparable at baseline with regard to demographics for the ITT Population.

Table 5: Demographic Information for Study PR 01502 (ITT* Population)

Parameter	Placebo (n=108)	EA 0.45 mg (n=113)	p-value**	Overall (N=221)
Age, years			0.524	
Mean (SD)	51.9 (6.5)	52.5 (7.5)		52.2 (7.0)
Median	52.4	52.4		52.4
Range	36.2-71.4	36.0-79.6		36.0-79.6
Race, n (%)			0.868	
Caucasian	86 (79.6%)	91 (80.5%)		177 (80.1%)
Non-Caucasian	22 (20.4%)	22 (19.5%)		44 (19.9%)
Height, inches			0.074	
Mean (SD)	64.3 (3.1)	63.6 (3.2)		63.9 (3.2)
Median	64.0	64.0		64.0
Range	56.0-76.0	50.0-69.0		50.0-76.0

Weight, pounds				
Mean (SD)	162 (35.9)	166 (38.7)	0.479	164 (37.3)
Median	158	160		159
Range	99.0-293.0	106.9-282.0		99.0-293.0

Source: Adapted from Study PR 01502, Final Study Report, Section 11.2.1, Text Table 4.

SD = standard deviation.

** p-values are from a 1-way ANOVA for continuous parameters; Fisher's Exact test for categorical variables.

ITT* = intent-to-treat but excluding Site 62.

Reviewer's Comment

As can be seen in Table 5, the treatment groups were comparable at baseline with regard to demographics for the ITT* Population.

Effects on Vasomotor Symptoms

- Frequency

Subjects recorded the occurrences of hot flushes in diary cards on a daily basis during the screening period and once enrolled in the study. Subjects were instructed that for each day of treatment they would enter the number of hot flushes experienced by severity (mild, moderate, or severe) in the space indicated on the diary card.

During the screening period, hot flush intensity and number were recorded for two weeks in order to determine eligibility for the trial. Subjects experiencing seven hot flushes per day or at least 60 per week during any seven day period were eligible for study enrollment. If more than 14 days of hot flush diary information was collected, the first 14 days of data were used to determine eligibility and baseline values.

The primary target variable that defined treatment efficacy for vasomotor symptoms was the change from baseline in the weekly number of moderate to severe hot flushes. The number of hot flushes during each week of the two week baseline period and the 12 week treatment period was determined by severity (mild, moderate or severe) from the subject diary card. These data were then analyzed as total hot flushes (sum of mild, moderate, and severe). The weekly number of moderate to severe hot flushes was analyzed for each of the 12 treatment weeks as change from baseline, with the primary tests of treatment efficacy being at weeks 4 and 12.

Table 6: Mean Change from Baseline to Weeks 4, 8, and 12 in the Number of Moderate to Severe Hot Flushes Per Week During Therapy Using LOCF (ITT Population) for Study PR 00501.

Study Visit	Placebo (n=94)	EA 0.9 mg (n=100)	EA 1.8 mg (n=95)	p-values*		
				Overall	EA 0.9 vs. PBO	EA 1.8 mg vs. PBO
Baseline						
Mean Number	86.1	78.5	82.4	0.414	0.188	0.596
Week 4						
Mean Number	51.5	24.3	21.9			
Mean Change	-34.6	-54.2	-60.5	<0.001	<0.001	<0.001

Week 8						
Mean Number	46.1	19.2	9.3			
Mean Change	-40.0	-59.3	-73.1	<0.001	<0.001	<0.001
Week 12						
Mean Number	46.8	17.5	7.3			
Mean Change	-39.3	-61.0	-75.0	<0.001	<0.001	<0.001

Source: Adapted from Study PR 00501, Final Study Report, Section 11.4.1.1.1.1, Text Table 11 on page 80 of 6859.

LOCF = last observation carried forward

ITT = intent-to-treat

PBO = placebo

* p-values are from a 2-way ANOVA interaction with treatment and center effects as factors.

Reviewer's Comment

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 (p<0.001 for both dosages at both timepoints).

The mean changes from baseline at weeks 4, 8, and 12 in the number of moderate to severe hot flushes using LOCF for the ITT* Population for Study PR 01502 are presented in Table 7. The mean decreases from baseline in the number of moderate to severe hot flushes at weeks 8 and 12 were statistically significantly greater in the EA 0.45 mg group compared to the placebo group (p=0.048 and p=0.049, respectively). At week 4 the difference between treatment groups was not statistically significant (p=0.113). Mean change from baseline in the number of moderate to severe hot flushes in the EA 0.45 mg group first achieved statistical significance compared to placebo at week 6 (p=0.042).

Table 7: Mean Change from Baseline in the Number of Moderate to Severe Hot Flushes Per Week During Therapy Using LOCF (ITT*Population) for Study PR 01502.

Study Visit	Placebo (n=108)	EA 0.45 mg (n=113)	p-values*
Baseline			
Mean Number	85.8	86.2	0.691
Week 4			
Mean Number	51.5	44.1	
Mean Change	-34.3	-42.1	0.113
Week 5			
Mean Number	50.0	41.4	
Mean Change	-35.8	-44.8	0.076
Week 6			
Mean Number	49.0	38.7	
Mean Change	-36.8	-47.5	0.042
Week 7			
Mean Number	47.7	39.0	
Mean Change	-38.1	-47.2	0.094
Week 8			
Mean Number	45.7	35.9	
Mean Change	-40.1	-50.4	0.048
Week 9			
Mean Number	45.1	34.8	

Mean Change	-40.7	-51.4	0.038
Week 10			
Mean Number	43.5	34.4	
Mean Change	-42.3	-51.8	0.064
Week 11			
Mean Number	43.0	34.3	
Mean Change	-42.8	-51.9	0.058
Week 12			
Mean Number	43.1	34.1	
Mean Change	-42.8	-52.2	0.049

Source: Adapted from Study PR 01502, Final Study Report, Section 11.4.1.1.1.1, Text Table 11 and Volume 53, Page 11050, Table 14.2.1

LOCF = last observation carried forward

ITT* = intent-to-treat but excluding Site 62

^ap-values are from a 2-way ANOVA interaction with treatment and center effects as factors.

Reviewer's Comment

The draft Guidance states that the primary efficacy analyses show a clinically and a statistically significant reduction in the frequency of moderate to severe hot flushes within four weeks of initiation of treatment that is maintained throughout 12 weeks of treatment. The EA 0.45 mg dosage in the ITT* Population did not show a statistically significant reduction in the frequency of moderate to severe hot flushes at the four week time point. The EA 0.45 mg treatment group first achieved statistical significance compared to placebo at week 6 (p=0.042). However the EA 0.45 mg ITT* treatment did not achieve statistical significance compared to placebo at week 7 (p=0.094), week 10 (p=0.064) or week 11 (p=0.058). The EA 0.45 mg ITT* treatment group achieved statistical significant reduction in the frequency of moderate to severe hot flushes compared to placebo during four of the 12 weeks of treatment: at week 6 (p=0.042), week 8 (p=0.048), week 9 (p=0.038) and week 12 (p=0.049).

The originally planned ITT data set including Site 62 subjects was analyzed in a supplementary analysis (see Volume 53, page 11055). In this analysis, the EA 0.45 mg dosage in the ITT Population also first achieved a statistically significant reduction in the frequency of moderate to severe hot flushes at week 6 (p=0.047) but not at week 12 (p=0.095). The EA 0.45 mg ITT treatment group achieved a statistically significant reduction in the frequency of moderate to severe hot flushes only during three of the 12 weeks of treatment: at week 6 (p=0.047), week 8 (p=0.049) and week 9 (p=0.043).

- Severity

The severity of hot flushes was analyzed as the change from baseline in the average weekly severity of hot flushes, where, for this purpose, mild, moderate, and severe hot flushes were assigned scores of 1, 2, and 3, respectively. In each case, the baseline severity was the mean weekly severity of hot flushes reported during the 2 week screening period.

In the EA 0.9 mg group, the mean changes from baseline in the severity of moderate to severe hot flushes at weeks 4 and 12 were statistically significantly greater compared to the placebo group (p=0.003 and p<0.001, respectively). In the EA 1.8 mg group, the mean change from baseline in the severity of moderate to severe hot flushes at weeks 4 and 12 were also statistically significantly greater compared to the placebo group (p=0.004 and p<0.001, respectively).

Table 8: Mean Change from Baseline to Weeks 4, 8, and 12 in the Severity of Moderate to Severe Hot Flushes During Therapy Using LOCF (ITT Population) for Study PR 00501.

Study Visit	Placebo (n=94)	EA 0.9 mg (n=100)	EA 1.8 mg (n=95)	p-values*	
				EA 0.9 vs. PBO	EA 1.8 mg vs. PBO
Baseline Mean Severity	2.5	2.5	2.5	0.572	0.526
Week 4 Mean Severity Mean Change	2.3 -0.2	1.8 -0.7	1.9 -0.7	0.003	0.004
Week 8 Mean Severity Mean Change	2.2 -0.3	1.5 -1.0	1.2 -1.3	<0.001	<0.001
Week 12 Mean Severity Mean Change	2.2 -0.3	1.4 -1.1	1.0 -1.5	<0.001	<0.001

Source: Adapted from Study PR 00501, Final Study Report, Section 11.4.1.1.2.1, Text Table 13.

LOCF = last observation carried forward

ITT = intent-to-treat

SD = standard deviation

PBO = placebo

* p-values are from a 2-way ANOVA interaction with treatment and center effects as factors.

Reviewer's Comment

Mean decrease from baseline in the severity of moderate-to-severe hot flashes 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.

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 ($p=0.259$); however, starting at week 5 and continuing through 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 (week 5, $p=0.010$; week 12, $p<0.001$).

Table 9: Mean Change from Baseline in the Severity of Moderate to Severe Hot Flushes During Therapy Using LOCF (ITT*Population) for Study PR 01502.

Study Visit	Placebo (n=108)	EA 0.45 mg (n=113)	p-values ^a
Baseline Mean Severity	2.6	2.5	0.621
Week 4 Mean Severity Mean Change	2.4 -0.2	2.3 -0.3	0.259
Week 5 Mean Severity Mean Change	2.4 -0.1	2.2 -0.3	0.010

Week 6			
Mean Severity	2.4	2.1	
Mean Change	-0.2	-0.5	0.006
Week 7			
Mean Severity	2.3	2.1	
Mean Change	-0.2	-0.5	0.025
Week 8			
Mean Severity	2.4	2.1	
Mean Change	-0.2	-0.5	<0.001
Week 9			
Mean Severity	2.3	2.1	
Mean Change	-0.2	-0.5	0.012
Week 10			
Mean Severity	2.3	2.0	
Mean Change	-0.3	-0.5	0.015
Week 11			
Mean Severity	2.3	1.9	
Mean Change	-0.2	-0.7	<0.001
Week 12			
Mean Severity	2.3	1.9	
Mean Change	-0.3	-0.7	<0.001

Source: Adapted from Study PR 01502 Final Study Report, Section 11.4.1.1.2.1, Text Table 13.

LOCF = last observation carried forward

ITT* = intent-to-treat but excluding Site 62

*p-values are from a 2-way ANOVA interaction with treatment and center effects as factors.

Reviewer's Comment

In the ITT* Population, mean decrease from baseline in the severity of moderate to severe hot flushes achieved statistical significance compared to placebo at weeks 5 and 12 for the EA 0.45 mg treatment group. Statistical significance was not achieved by week 4 in this group.

In the ITT Population, mean decrease from baseline in the severity of moderate to severe hot flushes also achieved statistical significance compared to placebo at weeks 5 (p=0.020) and 12 (p=0.006) for the EA 0.45 mg treatment group.

Post hoc Responder Analysis

Due to the delayed effect of the EA 0.45 mg dose in Study PR 01502 on the improvement in the frequency and severity of moderate to severe hot flushes, the Sponsor performed 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. In order to better define a "responder", the results of Study PR 00501 were reviewed to determine the responder rates to the effective EA 0.9 mg dose. The mean percent decrease in the weekly frequency of moderate to severe hot flushes from baseline to week 12 for the EA 0.9 mg treatment group in Study PR 00501 was 77.7%. Based on this information, a subject with a 75% or greater decrease in weekly frequency 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.

Table 10: 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

Source: Received by facsimile from Sponsor on July 8, 2004

Note: Responder = 75% or more decrease in the number of hot flushes when compared to baseline

ITT* = Intent-to-Treat but excluding Site 62

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

Reviewer's Comment

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. The Sponsor did not provide a responder analysis for the ITT Population.

Table 11: 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

Source: Document submitted by Sponsor July 23, 2004

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.

Reviewer's Comment

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.

Effects on Vulvar and Vaginal Atrophy

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7 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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6.4. Efficacy Conclusions

- For decrease in frequency and severity of hot flushes from baseline to week 4 and week 12 (Four Co-Primary Endpoints):

The results from the Phase 3 clinical trials (Study PR 00501 and Study PR 01502) demonstrate the effectiveness of EA tablets in single daily doses of 0.45 mg, 0.9 mg, and 1.8 mg in the treatment of postmenopausal moderate to severe hot flushes because the Sponsor has shown that:

1. EA 0.9 mg, and 1.8 mg each show a clinically and a statistically significant reduction, within four to six weeks of initiation of treatment and maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flushes in the treated groups compared to the control groups.
2. The EA 0.45 mg treatment group first achieved statistical significance compared to placebo at week 6 ($p=0.042$) instead of week 4 ($p=0.113$) in reducing the frequency of hot flushes and also (with the exception of week 7 $p=0.094$, week 10 $p=0.064$, and week 11 $p=0.058$) in maintaining efficacy through week 12 ($p=0.049$). In this same group, statistical significance was achieved in reducing the severity of moderate to severe hot flushes by week 5 ($p=0.010$) and maintaining the reduction through week 12 ($p<0.001$).

Reviewer's Comment

Regarding the EA 0.45 mg dosage, this reviewer does not believe that the delay of one week (week 4 to week 5) in significantly reducing the severity of moderate to severe hot flushes is of importance in a clinical setting. This reviewer also does not believe that a delay of two weeks (week 4 to week 6) in significantly reducing the frequency of moderate to severe hot flushes is clinically meaningful. In addition, in the Responder Analysis submitted by the Sponsor as Amendment 13, significance in decreasing the frequency of moderate to severe hot flushes 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).

Because the EA 0.45 mg dosage form is not as efficient in reducing the frequency and severity of hot flushes as the two higher dosage forms, I believe that the Sponsor has established this dose as the lowest effective dose of EA.

- For treatment of vulvar and vaginal atrophy

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Summary of Primary Efficacy Analysis

Table 25: Indication: Treatment of Vasomotor Symptoms Associated with the Menopause

Co-Primary Endpoints (4)	EA 0.45 mg vs. PBO p-values	EA 0.9 mg vs. PBO p-values	EA 1.8 mg vs. PBO p-values
Decrease in Frequency			
1. Week 4	0.113	<0.001	<0.001
Week 6	0.042		
2. Week 12	0.049	<0.001	<0.001
Decrease in Severity			
3. Week 4	0.259	0.003	0.004
Week 5	0.010		
4. Week 12	<0.001	<0.001	<0.001

Table 26: Indication: Treatment of Vulvar and Vaginal Atrophy Associated with the Menopause

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Conclusions

Once daily oral treatment for 12 weeks with EA in all doses tested (0.45 mg, 0.9 mg or 1.8 mg) was well tolerated in this study. The majority of adverse events (AEs) reported were mild to moderate in intensity and most were considered not related or unlikely related to study drug. The most commonly reported AEs during the study were primarily those that were expected with the use of orally administered estradiol (e.g., headache, nausea, vaginal bleeding and/or spotting, vaginal discharge, breast tenderness), and those caused by infectious agents (e.g., nasopharyngitis, fungal infection, influenza).

7.2. Materials Utilized in the Review

The data from three completed Phase 1 studies (PR 05000, PR 09601, and PR 00102) and two large, completed, prospective, randomized, placebo-controlled Phase 3 studies (PR 00501 and PR 01502) were reviewed for safety outcomes (n=595 subjects enrolled). In addition, the 4-Month Safety Update was reviewed.

The three Phase 1 studies, while presented in the Integrated Summary of Safety (ISS), are not included in the integrated database.

Study PR 05000 studied the oral bioavailability of estradiol following oral administration of one EA 1.152 mg tablet, then 2 EA 1.152 mg tablets then 1 EA 1mg tablet in a single-dose, randomized, open-label, 3-way cross-over study. Nine subjects were enrolled. A total of 20 AEs were recorded in the nine subjects. The most common were AEs were headaches (six subjects), hot flushes (five subjects), and nausea (three subjects). No serious AEs occurred and the frequency of all AEs was similar for all treatments. In addition, no clinically significant abnormalities in laboratory evaluations, vital signs, or physical examinations were observed.

Study PR 09601 studied the effect of food on estradiol bioavailability following oral administration of EA 1.8 mg in a single dose cross-over study. Sixteen subjects were enrolled. A total of seven AEs were reported by five subjects. Two cases of vaginal bleeding were reported by two subjects. No serious AEs occurred and no clinically significant abnormalities in laboratory evaluations, vital signs, or physical examinations were observed.

Study PR 00102 studied 18 healthy, female, postmenopausal volunteers in a multiple-dose, 3-treatment, 3-period, cross-over pharmacokinetic study using tablets containing 0.45 mg, 0.9 mg, and 1.8 mg EA/day for seven days. A total of 72 adverse events were reported by 13 (72%) subjects; seven subjects following the 0.45 mg dose, 12 subjects following the 0.9 mg dose, and seven subjects following the 1.8 mg dose. The majority of AEs were mild in severity and, in the opinion of the investigator, not related to study medication. Headache was the AE reported by the greatest number of subjects (33%) followed by abdominal pain (28%) and nausea (22%). No serious AEs occurred and no clinically significant abnormalities in laboratory evaluations, vital signs, or physical examinations were observed.

The Sponsor is conducting an ongoing Phase 3 study of postmenopausal women comparing the efficacy of 0.9 mg EA, 1 mg of estradiol, and 0.625 mg of Premarin®, administered once daily, in the treatment of vasomotor symptoms. The study is ongoing and the Sponsor states that no serious AEs have been reported thus far in this study.

7.3. Description of Patient Exposure

In the two Phase 3 studies, a total of 548 of the 552 randomized subjects received either EA tablets (0.45 mg, 0.9 mg or 1.8 mg; 327 subjects) or placebo (221 subjects). Among all treatment groups, the mean number of days on study medication was comparable. Subjects had a mean exposure between 77 and 81 days, with a total duration of treatment ranging from five to 98 days. Almost all subjects (>98%) subjects in each treatment group were exposed to study medication for at least 63 days. Among EA treatment groups, the majority ($\geq 85\%$) of subjects were exposed to study medication for 63 to 85 days.

Table 27: Summary of Duration of Treatment Exposure of all Subjects by Treatment Intent-to-Treat Population (n=548)

Duration Of Treatment (days)	Placebo (n=221) n (%)	EA 0.45 mg (n=132) n (%)	EA 0.9 mg (n=100) n (%)	EA 1.8 mg (n=95) n (%)
<42	24 (11.3)	6 (4.9)	7 (7.1)	3 (3.2)
42-62	4 (1.9)	2 (1.6)	6 (6.1)	3 (3.2)
63-85	183 (85.9)	113 (91.9)	84 (84.8)	87 (92.6)
>85	2 (0.9)	2 (1.6)	2 (2.0)	1 (1.1)
Mean (SD)	76.7 (19.3)	81.0 (13.9)	77.1 (17.5)	80.2 (13.4)
Median	84.0	85.0	84.0	84.0
Range	9.0 to 90.0	12.0 to 86.0	5.0 to 98.0	7.0 to 86.0

Source: Adapted from NDA 21-633, Integrated Summary of Safety, Section 8.7.4.1.1, Text Table 2, Volume 64, Page 16020.

SD = standard deviation

Of the 552 subjects randomized, 71 (12.9%) discontinued the study. Of those, 11 (2%) subjects discontinued due to AEs. One subject in the EA 0.45 mg group died (suicide). Discontinuations due to AEs did not appear to be associated with the dose of EA. The highest rates of discontinuation were seen in the placebo group and were due to lack of efficacy and AEs (See Tables 2 and 3).

All subjects were female and ranged from 36 to 80 years of age with a mean age of 53 years. Mean and median ages were comparable among treatment groups. Of the 548 treated subjects, 75.7% were Caucasian. Approximately half (49.5%) of the subjects had had hysterectomies and the majority (70.3%) of subjects had not had bilateral oophorectomies. Height and weight data were comparable among treatment groups.

Reviewer's Comment

Overall, 87.1% of subjects in the two Phase 3 trials completed the study. The percent of subjects (12.9%) who discontinued participation in the two Phase 3 studies is lower than that reported in other 12-week VVS and VMA clinical trials.

7.4. Safety Findings from Clinical Studies

Of the 548 subjects who received study medication, 236 (43.1%) reported one or more adverse events. At least one AE was experienced by 38.6%, 48.0%, and 51.6% of subjects receiving EA

0.45 mg, 0.9 mg, and 1.8 mg, respectively, compared with 39.8% of placebo-treated subjects.

Table 28: Incidence of Adverse Events Occurring in $\geq 1\%$ or More of the Overall Population of Subjects by Preferred Term and Treatment Group in Decreasing Order of Overall Incidence (All Treated Subjects), Study PR 00501

Adverse Event Preferred Term	EA 0.9 mg (n=100) n (%)	EA 1.8 mg (n=95) n (%)	Placebo (n=94) n (%)	Overall (n=289) n (%)
Vaginal Hemorrhage	4 (4.0)	7 (7.4)	3 (3.2)	14 (4.8)
Headache NOS	5 (5.0)	4 (4.2)	3 (3.2)	12 (4.2)
Breast Tenderness	0 (0.0)	6 (6.3)	2 (2.1)	8 (2.8)
Vaginal Discharge	4 (4.0)	3 (3.2)	0 (0.0)	7 (2.4)
Abdominal Pain NOS	0 (0.0)	3 (3.2)	3 (3.2)	6 (2.1)
Influenza	0 (0.0)	4 (4.2)	2 (2.1)	6 (2.1)
Intermenstrual Bleeding	2 (2.0)	3 (3.2)	1 (1.1)	6 (2.1)
Back Pain	3 (3.0)	2 (2.1)	0 (0.0)	5 (1.7)
Sinusitis NOS	1 (1.0)	1 (1.1)	3 (3.2)	5 (1.7)
Arthralgia	1 (1.0)	2 (2.1)	1 (1.1)	4 (1.4)
Breast Pain	3 (3.0)	0 (0.0)	1 (1.1)	4 (1.4)
Bronchitis NOS	2 (2.0)	1 (1.1)	1 (1.1)	4 (1.4)
Fungal Infection NOS	1 (1.0)	1 (1.1)	2 (2.1)	4 (1.4)
Bladder Infection NOS	0 (0.0)	2 (2.1)	1 (1.1)	3 (1.0)
Genital Pruritis	1 (1.0)	2 (2.1)	0 (0.0)	3 (1.0)
Nasopharyngitis	0 (0.0)	1 (1.1)	2 (2.1)	3 (1.0)
Nausea	0 (0.0)	2 (2.1)	1 (1.1)	3 (1.0)
Rash NOS	3 (3.0)	0 (0.0)	0 (0.0)	3 (1.0)
Upper Respiratory Tract Infection NOS	3 (3.0)	0 (0.0)	0 (0.0)	3 (1.0)
Urinary Tract Infection NOS	0 (0.0)	1 (1.1)	2 (2.1)	3 (1.0)

Source: Adapted from Study PR 00501, Final Study Report, Volume 36, Text Table 22, Page 4147.

NOS = Not Otherwise Specified

Table 29: Incidence of Adverse Events Occurring in $\geq 1\%$ or More of the Overall Population of Subjects by Preferred Term and Treatment Group in Decreasing Order of Overall Incidence (All Treated Subjects), Study PR 01502

Adverse Event Preferred Term	EA 0.45 mg (n=132) n (%)	Placebo (n=127) n (%)	Overall (n=259) n (%)
Headache NOS	4 (3.0)	9 (7.1)	13 (5.0)
Nasopharyngitis	2 (1.5)	3 (2.4)	5 (1.9)
Nausea	3 (2.3)	2 (1.6)	5 (1.9)
Blood Cholesterol Increased	3 (2.3)	1 (0.8)	4 (1.5)
Fungal Infection NOS*	4 (3.0)	0 (0.0)	4 (1.5)
Influenza	3 (2.3)	1 (0.8)	4 (1.5)
Upper Respiratory Tract Infection NOS	1 (0.8)	3 (2.4)	4 (1.5)
Asthma	3 (2.3)	0 (0.0)	3 (1.2)
Blood Triglycerides Increased	1 (0.8)	2 (1.6)	3 (1.2)
Depression	2 (1.5)	1 (0.8)	3 (1.2)
Diarrhea NOS	2 (1.5)	1 (0.8)	3 (1.2)

Dizziness	0 (0.0)	3 (2.4)	3 (1.2)
Dry Mouth	2 (1.5)	1 (0.8)	3 (1.2)
GGT Increased	1 (0.8)	2 (1.6)	3 (1.2)
Urinary Tract Infection NOS	2 (1.5)	1 (0.8)	3 (1.2)
Vaginal Discharge	3 (2.3)	0 (0.0)	3 (1.2)
Vomiting NOS	1 (0.8)	2 (1.6)	3 (1.2)
Weight Increased	1 (0.8)	2 (1.6)	3 (1.2)

Source: Adapted from Study PR 01502, Final Study Report, Volume 52, Text Table 22, Page 11001.

NOS = Not Otherwise Specified

* = Vaginal Yeast Infections

The frequency of AEs reported by 1% or more of subjects was not consistently higher for subjects in one treatment group compared with another. Overall, headache was the AE reported most often. However, among all treatment groups, headache was most frequently reported in the placebo group. Vaginal hemorrhage was reported most often for subjects who received EA 1.8 mg. The frequency of vaginal hemorrhage and intermenstrual bleeding seem to be dose related.

Table 30: Incidence of AEs Occurring in $\geq 2\%$ of Subjects in Any Treatment Group Presented in Descending Frequency of Preferred Term

Adverse Event ^a	Placebo	Femtrace	Femtrace	Femtrace
	(n = 221)	0.45 mg/day (n = 132)	0.9 mg/day (n = 100)	1.8 mg/day (n = 95)
	n (%)	n (%)	n (%)	n (%)
Headache (NOS)	12 (5.4)	4 (3.0)	5 (5.0)	4 (4.2)
Vaginal Bleeding	3 (1.4)	1 (0.8)	4 (4.0)	7 (7.4)
Breast Tenderness	3 (1.4)	1 (0.8)	0 (0.0)	6 (6.3)
Influenza	3 (1.4)	3 (2.3)	0 (0.0)	4 (4.2)
Vaginal Discharge	0 (0.0)	3 (2.3)	4 (4.0)	3 (3.2)
Abdominal Pain (NOS)	4 (1.8)	1 (0.8)	0 (0.0)	3 (3.2)
Fungal Infection (NOS)	2 (0.9)	4 (3.0)	1 (1.0)	1 (1.1)
Nasopharyngitis	5 (2.3)	2 (1.5)	0 (0.0)	1 (1.1)
Nausea	3 (1.4)	3 (2.3)	0 (0.0)	2 (2.1)
Intermenstrual Bleeding	2 (0.9)	0 (0.0)	2 (2.0)	3 (3.2)
Sinusitis (NOS)	3 (1.4)	2 (1.5)	1 (1.0)	1 (1.1)
Upper Respiratory Tract Infection (NOS)	3 (1.4)	1 (0.8)	3 (3.0)	0 (0.0)
Back Pain	1 (0.5)	0 (0.0)	3 (3.0)	2 (2.1)
Bronchitis (NOS)	1 (0.5)	2 (1.5)	2 (2.0)	1 (1.1)

AE = adverse event; NOS = not otherwise specified

^a Regardless of drug relationship

Reviewer's Comment

August 13, 2004 (Final)

Generally, the incidence of adverse events was comparable among all active treatment groups. Among EA treatment groups, adverse events occurred most frequently in the Infections and Infestations category in the 0.45 mg group. In the 0.9 mg and 1.8 mg group adverse events occurred most frequently in the Reproductive System and Breast Disorders category.

Most AEs were classified as mild to moderate in intensity. A total of 7.6%, 6.0%, and 3.2% of subjects who received 0.45 mg, 0.9 mg, and 1.8 mg EA, respectively, reported at least one adverse event that was classified as severe. The proportion of placebo subjects who reported at least one severe adverse event was 5.9%.

Seven placebo-treated subjects compared with six EA-treated subjects discontinued due to adverse events. Among subjects treated with EA, four subjects in the 0.9 mg group discontinued study drug because of (1) palpitations and chest tightness, (2) pelvic pain NOS, (3) edema NOS and (4) generalized pruritis. One subject in the 0.45 mg group committed suicide and one subject in the 1.8 mg group discontinued the study due to depression.

Deaths

No deaths occurred during Study PR 00501. There was one study death in Study PR 01502. Subject 51-001 was a 59 year old woman who received EA 0.45 mg. She was randomized to treatment on 8/27/02. When she did not return to the clinic for her scheduled visit on 10/11/02 the site called and was informed that she had committed suicide on 10/9/02. In the opinion of the investigator, the suicide was not considered to be related to the study medication.

Other Serious Adverse Events (SAE)

SAEs were reported for one placebo-treated subject in Study PR 00501, and one 0.45 mg EA-treated subject in Study PR 01502.

Study PR 00501:

Subject #18-017, a 54 year old woman in the placebo group, was diagnosed with moderate cholelithiasis approximately six weeks after randomization and subsequently underwent a laparoscopic cholecystectomy during the study. She recovered and continued in the study for another few weeks before discontinuing early because of continuous hot flush symptoms. The SAE was considered to be possibly related to study drug by the investigator.

Two additional subjects had SAEs within 30 days after study completion and therefore not included in the database.

Subject #38-004, a 53 year old woman in the EA 1.8 mg study group, who had discontinued study medication after five weeks on treatment because of depression and nausea, developed a symptomatic hepatic cyst two weeks after discontinuing the study medication. The cyst was resected and a cholecystectomy was done. The patient had a full recovery. This SAE was considered by the investigator as unlikely related to study treatment.

Subject #18-014, a 51 year old woman in the EA 0.9 mg group, discontinued study medication after approximately eight weeks on treatment because of edema of the lower extremities and

cough. Approximately two weeks after study discontinuation, the edema and cough did not resolve and subsequent investigations revealed a high grade epitheloid hemangiosarcoma with metastasis. This condition, diagnosed after study completion, was considered unrelated to treatment.

Study PR 01502:

Subject #67-020, a 42 year old women who received EA 0.45 mg, was hospitalized due to severe abdominal pain and anxiety disorder for five days after approximately three weeks on treatment. Study medication was temporarily interrupted and she was discharged with the diagnosis of an anxiety disorder. No pathology was identified and ultimately it was determined that the subject was trying to escape an abusive spouse. In the opinion of the investigator, neither of these events was related to study medication. The subject completed the study two months after her hospitalization.

Reviewer's Comment

The reported serious adverse events (two in Study PR 00501 and one in Study PR 01502) do not indicate a higher number of SAEs than observed in other clinical trials with estrogen-alone drug products, and do not represent safety-related concerns for this reviewer.

Clinical Laboratory Assessments

Hematology (red blood cell count, hemoglobin, hematocrit, white blood cell count and differential, and platelet count) was obtained at screening and at the end of the study. An elevated eosinophil count in one placebo subject was the only hematology value considered to be clinically significant by the investigator.

Chemistry values (sodium, potassium, blood glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total bilirubin, total protein, albumin, uric acid, alkaline phosphatase, gamma-glutamyl transferase [GGT], alanine aminotransferase[ALY]/serum glutamic pyruvic transaminase, aspartate aminotransferase [AST]/serum glutamic oxaloacetic transaminase, lactate dehydrogenase, serum cholesterol, serum triglycerides, low density lipoprotein [LDL], high density lipoprotein) were also obtained at screening and at the end of the study.

Among all three EA treatment groups, the most clinically significant lab values were total cholesterol, LDL cholesterol, and triglycerides. A comparable number of subjects in each of the EA treatment groups had clinically significant elevations at baseline and screening. Subjects were not excluded from studies if they had lipid disorders or were taking lipid lowering agents therefore no clinically significant trends were apparent over the course of the studies in any treatment group with regard to lipids or other clinical laboratory values.

No clinically significant changes occurred over the course of the studies in any treatment group with regard to urinalyses, vital signs, body weights, or physical examination findings.

Reviewer's Comment

Across the two Phase 3 studies, the number of subjects with chemistry or hematological values that were considered to be clinically significant was comparable between the placebo and all treatment groups. Therefore, no consistent trend or pattern was evident in the data from both these trials.

7.5. Miscellaneous Studies

No additional studies were conducted that contribute to either the historical information regarding the product development or actual safety and efficacy data.

7.6. Literature Review for Safety

No literature review was conducted by this reviewer. The Sponsor provided 19 pertinent scientific articles identified during their literature review for new safety information relevant to the product.

7.7. Postmarketing Surveillance – If Applicable

Estradiol acetate tablets are not marketed in the US or internationally. However, estradiol, the active moiety, has been approved and marketed in numerous formulations for many years. Therefore no specific postmarketing commitments and/or risk management steps are recommended

7.8. Safety Update

4-Month Safety Update

One Safety Update was submitted for this NDA. This 4-Month Safety Update, dated February 19, 2004, provides an update of the safety information from Study [] This study was a 12-week randomized, double-blind, parallel group study of postmenopausal women comparing the efficacy in the treatment of vasomotor symptoms of three oral estrogen preparations (EA 0.9 mg/day, estradiol 1mg/day, and conjugated equine estrogens 0.625 mg/day). At the time of the NDA submission, this study was ongoing. Safety data from [] and Phase 1 studies were presented in the Integrated Summary of Safety (ISS) but were not part of the integrated data base.

The 4-Month Safety Update discusses the one subject in the [] data base who experienced a serious adverse event. Subject #37-476, a 56 year old woman in the estradiol 1 mg treatment group, was diagnosed with severe metrorrhagia approximately eight weeks after randomization that was determined to be probably related to study treatment. She recovered but discontinued the study due to this event.

Two SAEs were also reported during the screening period in subjects who were never randomized and were not included in the database. One screen failure was hospitalized for pancreatitis and one was hospitalized for pneumonia. There were no SAEs reported after study completion.

No deaths were reported in Protocol []

The 4-Month Safety Update provides no further information on Studies PR 00501 or PR 01502.

7.9. Drug Withdrawal, Abuse, and Overdose Experience

No serious adverse events were reported as a result of EA withdrawal, abuse or overdose during clinical trials. Overdose of estrogens may cause nausea and vomiting and withdrawal bleeding in postmenopausal women with a uterus.

7.10. Adequacy of Safety Testing

Prestudy safety assessments were appropriate for this three month study. A complete physical and gynecological examination was performed at Visit 1 (screening) and Visit 4 (final visit). The gynecological examination included a breast examination, pelvic examination and a Pap smear.

Further screening at Visit 1 included a medical and surgical history; and gynecological history. A medication history included any medication usage (including previous use of sex hormones) over the last three months, with start and stop dates, total daily dosage and indications.

In women with a uterus, an endometrial biopsy was performed at Visit 1. If insufficient tissue was obtained, a transvaginal ultrasound was performed. Endometrial biopsies were analyzed by a central laboratory. All treated subjects with a uterus received a course of progestin at the conclusion of the study. The choice of drug and dose of treatment was left to the discretion of the investigator; the duration of treatment was to be at least 12 days.

Bilateral mammography was also performed at Visit 1. If a negative mammography had been reported within the previous nine months, and the report was available, then the screening mammography was not necessary.

General laboratory tests and hormone assays were performed at a central laboratory. General laboratory tests were performed at Visit 1 (screening) and Visit 4 (final visit) but hormone assays were only performed at Visit 1. For all laboratory tests, fasting blood and urine specimens were collected. The following laboratory tests were performed:

- Blood chemistries included: electrolytes, glucose, blood urea nitrogen, creatinine, calcium, phosphorus, total bilirubin, total protein, albumin and uric acid.
- Liver enzymes
- Urinalysis (performed by dipstick)
- Hormone assays included: estradiol, FSH, TSH
- Hematology included: red blood cell count, hematocrit, hemoglobin, platelet count and white blood cell count.
- Lipid profile
- Pregnancy test

Reviewer's Comment

The procedures and laboratory performed were appropriate and adequate.

7.11. Labeling Safety Issues and Postmarketing Commitments

Proposed labeling was included in the NDA submission. Consultations were obtained from the Division of Drug Marketing, Advertising, and Communications (DDMAC); the Division of Surveillance, Research, and Communication Support (DSRCS); and the Division of Medication Errors and Technical Support (DMETS).

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

DSRCS has reviewed the patient labeling to ensure consistency with the February 10, 2004 revised 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 Healthcare Providers and Patient Labeling.

DMETS does not recommend the use of the proprietary name Femtrace. One of the primary concerns is the look-alike and/or sound-alike confusion with Estrace, Premphase, Femtrol, and FemHRT. In addition, DMETS is concerned regarding the confusion with the dosing of similar products. They prefer the product be labeled "estradiol tablets" with equivalent strengths to 17β estradiol of 0.39 mg, 0.78 mg, and 1.56 mg.

No specific postmarketing commitments and/or risk management steps are being proposed by the Sponsor.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

No estradiol acetate tablets are approved for use in the U.S. Femring™, an estradiol acetate vaginal ring, is currently approved in two dosage forms 0.05 mg/day and 0.10 mg/day for the treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause (NDA 21-367).

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity. Comment on Adequacy of Applicant's Analyses.

EA is indicated for use in postmenopausal women with or without a uterus. EA is not indicated for use in a pediatric population.

9.2. Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

A request for a full waiver of pediatric studies was submitted for NDA 21-633 on October 14, 2003. Femtrace™ is only recommended for use in postmenopausal women.

9.3. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy

The EA dosage strengths were only investigated in healthy postmenopausal women. No data is available for other special populations. EA should not be used during pregnancy.

10. CONCLUSIONS AND RECOMMENDATIONS, AND LABELING

10.1. Conclusions Regarding Safety and Efficacy

The safety and efficacy data presented in NDA 21-633 support the approval of Femtrace™ (estradiol acetate 0.45 mg, 0.9 mg, and 1.8 mg) for the treatment of moderate to severe vasomotor symptoms associated with the menopause. The data presented in this new drug application (NDA) provides evidence from two placebo-controlled clinical trials (Study PR 00501 and Study PR 01502) to support the safety and efficacy of each daily dosage formulation for this indication.

Although the safety data presented in NDA 21-633 show that Femtrace™ in doses of 0.45 mg, 0.9 mg, and 1.8 mg administered once daily orally was well tolerated and generally safe, this

reviewer does not support the approval of Femtrace™ (estradiol acetate 0.45 mg, 0.9 mg, and 1.8 mg) for the treatment of moderate to severe vulvar and vaginal atrophy associated with the menopause []

10.2. Recommendations on Approvability

Pending approval of final labeling, from a clinical perspective, the daily use of estradiol acetate in dosage strengths of 0.45 mg, 0.9 mg and 1.8 mg can be approved for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

[

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10.3. Labeling

At this time, labeling for this drug product has not been finalized.

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/s/

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