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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-633

**Clinical Pharmacology and Biopharmaceutics
Review**

Clinical Pharmacology and Biopharmaceutics Review

NDA	21,633
Submission Date	October 21, 2003
Brand Name	Femtrace
Generic Name	Estradiol acetate
Reviewer	Stephan R. Ortiz, R.Ph., Ph.D.
Team Leader	Ameeta Parekh, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM Division	Division of Reproductive & Urologic Drug Products
Sponsor	Warner Chilcott
Submission Type; Code	Original NDA; 3S
Dosing regimen	Once daily
Indication	Treatment of moderate and severe vasomotor symptoms associated with the menopause and treatment of vulvar vaginal atrophy associated with the menopause

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2 Executive Summary

NDA 21633 was submitted for Femtrace oral tablets, which contains the pro-drug estradiol acetate. This pro-drug is quickly hydrolyzed *in vivo* to estradiol. Estradiol is currently indicated for the treatment of moderate to severe vasomotor symptoms related to menopause and vulvar vaginal atrophy related to menopause. The sponsor seeks approval for 0.45, 0.90 and 1.8mg estradiol acetate oral tablets for both indications.

Sponsor Proposed Dissolution Specifications

Reviewer Proposed Dissolution Specifications

USP Paddles @ 75 rpm

500 ml of — SLS in water, purified, USP @ 37°C ± 0.5 °C

Measuring Estrone sulfate by []

Q = [] at 20 minutes

A. Recommendation

The submission of NDA 21633 for Femtrace (estradiol acetate) tablets is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

B. Phase IV Commitments

None.

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

- **PK Highlights**

Following administration, estradiol acetate was rapidly hydrolyzed to estradiol; systemic exposure to estradiol acetate was not significant. Administration of estradiol acetate enhances estradiol bioavailability, as measured by AUC, by 19%, compared to an equivalent dose of estradiol (Estrace®). Estradiol C_{max} for one EA tablet was more than double (46.75 pg/mL vs. 22.72 pg/mL) the C_{max} of one micronized E2 tablet. According to the medical reviewer, this C_{max} difference is not expected to pose a safety concern. Estradiol disposition and elimination are not affected by estradiol acetate administration.

Administration of a 1.8 mg estradiol acetate tablet with food decreased the rate but not the extent of estradiol bioavailability. Estradiol was rapidly absorbed following oral administration of estradiol acetate tablets. Estradiol and estrone exposure increased dose-proportionally with increasing dose. The corresponding estradiol C_{avg} values were 23.5, 44.4, and 92.1 pg/mL for the 0.45, 0.90 and 1.8mg doses, respectively.

Increase in sex hormone binding globulin (SHBG) concentration depended on the estradiol acetate dose; SHBG concentration was not significantly changed by single- or multiple-dose administration of 0.45- and 0.9-mg tablets, but 7 days of multiple-dose administration of 1.8-mg

estradiol acetate tablets resulted in a 73.2% increase in SHBG concentration. Estradiol was extensively metabolized to estrone and estrone sulfate; baseline-adjusted serum estrone and estrone sulfate concentrations were 4-5 times and approximately 140 times higher than serum estradiol concentrations, respectively. Estradiol apparent elimination half-life values were 21 to 26 hours.

The 3 doses of estradiol acetate tablets (0.45, 0.9 and 1.8 mg) administered in single- and multiple-dose regimens were generally well tolerated. The spectrum of adverse events was similar to what would be expected from oral estrogen.

- ***Dose-Response***

No formal dose-response or dose ranging studies were performed for this submission. The sponsor relied on extensive knowledge of estradiol dose-response characteristics to determine dose selection of estradiol acetate in the safety and efficacy trials.

- ***Intrinsic Factors***

All studies to characterize the pharmacokinetics of estradiol acetate tablets were conducted in the target population, postmenopausal women. No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

- ***Extrinsic Factors***

The sponsor did not perform any drug interaction studies. However, the following is the language used in all estrogen-containing labels (and is proposed by sponsor for this label):

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 decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma — concentrations of estrogens and may result in side effects.

- ***Formulation***

Other than a minor change to the formulation of the 0.45mg tablet, no changes have been made from the clinical to the to-be-marketed formulations. This minor change to the formulation of the to-be-marketed 0.45 mg tablet is classified as a Level 1 change according to the SUPAC IR guidance and as such, does not warrant bridging studies.

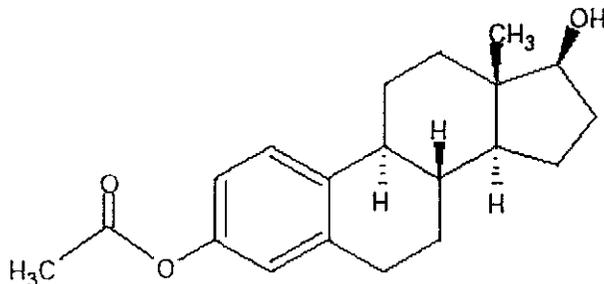
3 Question Based Review

A. General Attributes

What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Estradiol acetate is chemically described as estra-1,3,5(10)-triene-3,17 β -diol-3-acetate. The molecular formula of estradiol acetate is C₂₀H₂₆O₃ and the structural formula is:

Structural Formula of Estradiol Acetate



The molecular weight of estradiol acetate is 314.42.

Estradiol acetate is only slightly soluble in water (3.6 μ g/ml) and has an estimated pK_a of greater than 16. As such, dissolution is not expected to be pH dependent. The composition of the estradiol acetate tablets is presented in the following table (note that the 1.152mg tablet was not developed for market consideration).

Composition of Estradiol Acetate Tablets

Component	Amount Per Tablet (mg)			
	1.152 mg Tablet	0.45 mg Tablet	0.9 mg Tablet	1.8 mg Tablet
Estradiol acetate ^a	1.152	0.450	0.900	1.800
Iron Oxide Color (Yellow)				
Povidone				
Lactose Monohydrate				
Microcrystalline Cellulose				
Croscarmellose Sodium				
Silicon Dioxide				
Magnesium Stearate				
Acetic Acid				
Purified Water ^b	-	-	-	-
Total	90.0	90.0	90.0	90.0

What is the proposed mechanism of drug action and therapeutic indications?

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal

intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500µg 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 are thought to act through binding to nuclear receptors in estrogen-responsive tissues. Circulating estrogens modulate the pituitary secretion of gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism. Estrogen replacement therapy acts to reduce the elevated levels of these gonadotropins seen in postmenopausal women.

Estradiol acetate is rapidly hydrolyzed *in vivo* to estradiol.

What is the proposed dosage and route of administration?

The sponsor proposes the trade name Femtrace for the estradiol acetate tablets. Femtrace therapy consists of a single tablet to be taken orally once daily. The sponsor has submitted three dosage strengths for review; 0.45, 0.9 and 1.8mg which is equivalent (molar equivalence) to 0.39, 0.78 and 1.56mg of 17β-estradiol, respectively.

What efficacy and safety information contribute to the assessment of clinical pharmacology and biopharmaceutics study data?

Two 12-week double-blind, placebo-controlled clinical trials were conducted to evaluate the efficacy of Femtrace in the treatment of moderate to severe vasomotor symptoms in postmenopausal women who had at least 7 moderate to severe hot flushes daily or at least 60 moderate to severe hot flushes per week before randomization. In one study, 289 postmenopausal women were randomized to receive either placebo, Femtrace 0.9 mg/day or Femtrace 1.8 mg/day. In the second study, 221 postmenopausal women were randomized to receive either placebo or Femtrace 0.45 mg/day.

Additionally, for purposes of determining efficacy in treating postmenopausal women for vulvar vaginal atrophy, ζ \int were measured.

B. General Clinical Pharmacology

Were appropriate clinical endpoints, surrogate endpoints or pharmacodynamic (PD) biomarkers selected, adequately measured and used to assess efficacy and safety in clinical pharmacology studies?

The proposed intended uses for Femtrace are for the treatment of moderate to severe vasomotor symptoms associated with menopause and for the treatment of vulvar and vaginal atrophy. The following markers were selected to assess efficacy in clinical pharmacology studies: the effects on vasomotor symptoms (frequency and severity of daily hot flushes at 4 and 12 weeks of therapy), ζ \int

To assess safety, incidence of endometrial hyperplasia was recorded along with measuring effects on metabolism, bleeding and assorted quality of life indicators.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The moieties measured in the assorted studies include estradiol (E2), estrone (E1), estrone sulfate (E1S), sex hormone binding globulin (SHBG) and estradiol acetate (EA). E2, E1 and E1S concentrations were measured using a validated ^{125}I assay, SHBG concentrations were measured using a commercially available ^{125}I and EA concentrations were measured using a validated ^{125}I method. More details on these assays are provided in the analytical section of this review.

Was a mass balance determination performed?

No mass balance appears to have been performed by the sponsor. However, the metabolic pathway of estradiol is generally well characterized.

What is the metabolic pathway of the drug?

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to E1, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic circulation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially E1S, which serves as a circulating reservoir for the formation of more active estrogens. The estrogenic potency is as follows: estradiol > estrone > estriol.

Estradiol acetate hydrolysis is catalyzed by esterases which are found in serum, liver, intestinal mucosa and other tissues. The hydrolysis of EA to E2 was explored both *in vitro* and *in vivo*.

In human serum, *in vitro*, EA was very rapidly hydrolyzed to E2; the hydrolysis half-life was 28 seconds (Study RR-06801). *In vivo*, following administration of a 1.8-mg EA tablet, EA was not detected in serum samples (Study RR-06703). Estradiol acetate was rapidly hydrolyzed to E2, and systemic exposure to EA was not considered to be significant. The studies are summarized below.

***In Vitro* Hydrolysis in Serum and Blood**

The objective of Study RR 06801 was to determine the rate of estradiol acetate hydrolysis in human serum and blood *in vitro*. Briefly, estradiol acetate was added to the sample matrix at initial concentrations of 500 pg/mL, 2000 pg/mL and 5000 pg/mL in serum and 5000 pg/mL in blood. Studies were performed in triplicate, trials A3, A5, A6 (serum) and trials A11, A12, A13 (blood). Serial samples were taken for estradiol acetate and estradiol concentration determination by a validated ^{125}I assay. Samples were collected at 0.25, 0.50, 1.0, 1.5, 2, 3, 5 and 10 minutes after estradiol acetate was added to the sample matrix. Concentration data

was evaluated to characterize the hydrolysis reaction for estradiol acetate in human serum and blood *in vitro*.

Stripped human serum (pooled from 75 male subjects) was supplied by [] Whole blood (containing lithium heparin anticoagulant) was supplied by [] Estradiol acetate (Lot number 38052685, [] was supplied by Galen.

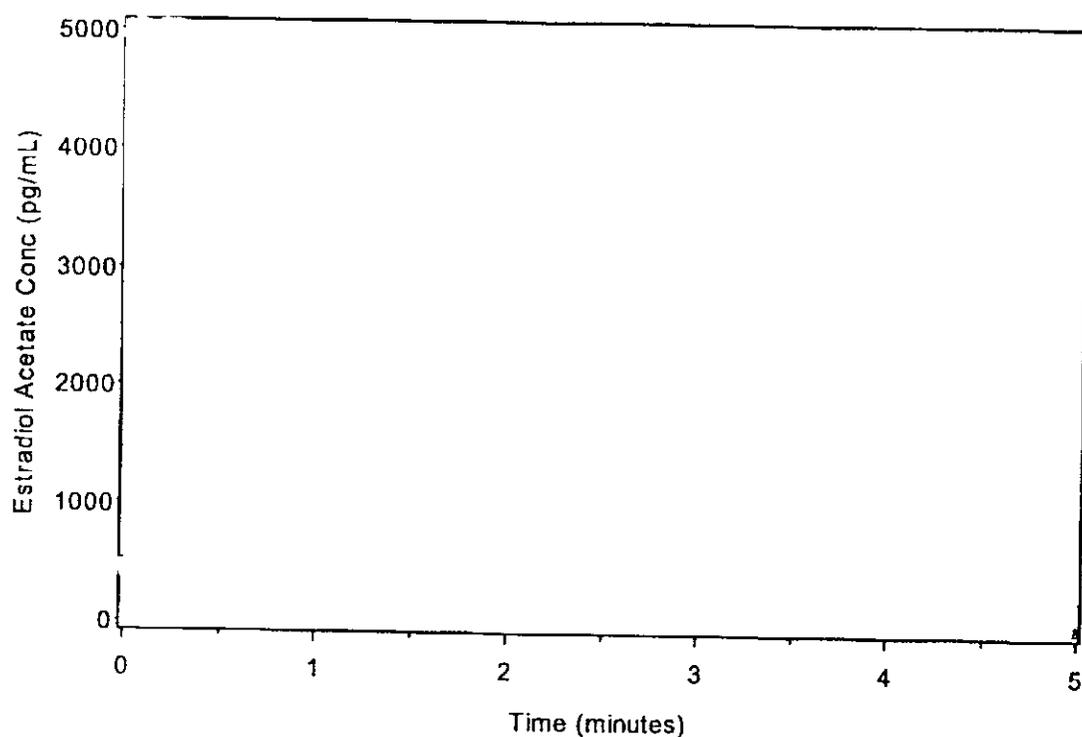
Results in serum

Estradiol acetate concentrations in serum decreased with time. Individual serum estradiol acetate concentrations are detailed in the following table and shown in the following figure.

Serum estradiol acetate concentrations as a function of time									
Sample time (Minutes)	Serum Estradiol Acetate Concentration (pg/mL) by Trial Number								
	A3	A5	A6	A3	A5	A6	A3	A5	A6
0	500	500	500	2000	2000	2000	5000	5000	5000
0.25									
0.5									
1									
1.5									
2									
3									
5									
10									
Values below the limit of quantitation (— pg/mL) were reported as zero.									
^{a,b,c} Actual sample time ^a 14 seconds, ^b 13 seconds, ^c 12 seconds.									
Data source, — report 1450/011-D1145									

Serum Estradiol Acetate Concentration as a function of time; Trial Number (O) A3, (Δ) A5, (□) A6.

Appears This Way
On Original



The first order rate constant value was independent of substrate concentration, confirming that the hydrolysis of estradiol acetate in human serum *in vitro* is a first order reaction over the range of concentrations studied (up to 5000 pg/mL). The mean $-k_1$ value for the nine trials was 1.48 min^{-1} ; the corresponding harmonic mean half-life value was 0.47 minutes or 28 seconds. These results indicate that estradiol acetate will be very rapidly hydrolyzed upon absorption, and by approximately 2.5 minutes (five half-lives) after absorption, concentration of estradiol acetate will be negligible.

Results in Blood

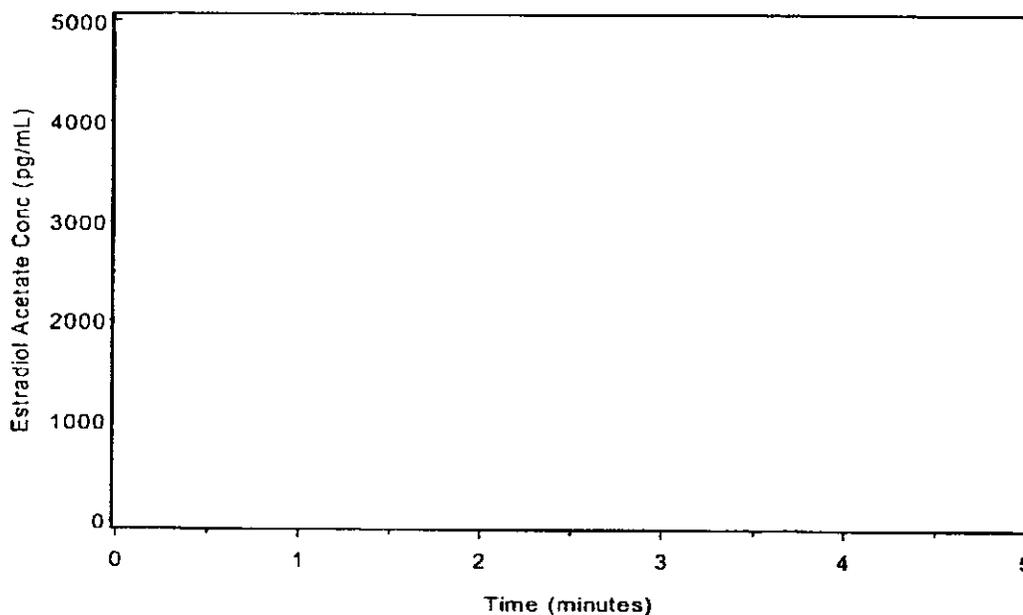
Estradiol acetate concentrations in blood decreased with time. Individual serum estradiol acetate concentrations are detailed in the following table and shown in the following figure.

Appears This Way
On Original

Blood estradiol acetate concentration as a function of time			
Blood Estradiol Acetate concentration (pg/mL) by Trial Number			
Sample time (minutes)	A11	A12	A13
0.00	5000.0	5000.0	5000.0
0.25			
0.50			
1.00			
1.50			
2.00			
3.00			
5.00			
10.00			

Values below the limit of quantitation (— ng/mL) were reported as zero.
^{a,b}Actual sample time ^a13 seconds, ^b14 seconds
 Data source: [] report 1450/011-D1145

Blood estradiol acetate concentration as a function of time; Trial Number:
 (O) A11, (Δ) A12, (□) A13.



Results indicated that the hydrolysis of estradiol acetate in human blood *in vitro* is a first order reaction. The mean $-k_1$ value for the three trials was 0.71 min^{-1} ; this corresponds to a harmonic mean half-life of 0.98 minutes or 59 seconds. The apparent hydrolysis rate was slower in blood than in serum. This was probably due to inhibition of esterases in the blood by the anti-coagulant lithium heparin. Heparin has been shown to reduce acetylcholinesterase activity. As such, the observed half-life is not representative of the estradiol acetate hydrolysis rate in blood.

***In Vivo* Hydrolysis**

The objective of Study PR-09601 was to characterize the concentration of estradiol acetate in serum samples from a food-effect study, titled "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.” Samples were collected from this study in an effort to determine the rate of estradiol acetate hydrolysis *in vivo* (Report RR-06703). This was a single-center, randomized, balanced, single-dose, 2 treatment, 2 period, 2 sequence crossover study in which 18 healthy postmenopausal women with screening serum estradiol concentrations less than 20 pg/mL each received one 1.8-mg estradiol acetate tablet in each of 2 treatment periods; one in the fasted state and the other in the fed state. There was a 2-week washout period between treatment periods. The results of the food effect study will be reported later in this review.

Samples were selected for analysis based upon availability of sufficient sample volume for analysis of serum estradiol acetate concentration. A total of 21 serum samples from 7 subjects were selected for analysis. The following table describes the samples used in this analysis.

Serum Samples Collected During Study PR-09601 and Analyzed for Serum Estradiol Acetate (EA) Concentration

Subject Number	Treatment	Post-dose samples analyzed
01	1 × 1.8-mg EA tablet in fasted state	0.25, 0.5 and 1.0 h
03 ^a	1 × 1.8-mg EA tablet in fed state	0.25, 0.5 and 1.0 h
07	1 × 1.8-mg EA tablet in fasted state	0.25, 0.5 and 1.0 h
11	1 × 1.8-mg EA tablet in fasted state	0.25, 0.5 and 1.0 h
13	1 × 1.8-mg EA tablet in fasted state	0.25, 0.5 and 1.0 h
15	1 × 1.8-mg EA tablet in fasted state	0.25, 0.5 and 1.0 h
16	1 × 1.8-mg EA tablet in fasted state	0.25, 0.5 and 1.0 h

^a Samples from fed treatment were analyzed for this subject

Serum estradiol acetate analysis was performed by \square using a validated \square assay. The limit of quantification for estradiol acetate was \square pg/mL. The following table shows that estradiol acetate was not detected in any of the serum samples.

Serum Estradiol Acetate (EA) Concentrations following Oral Administration of 1.8mg Estradiol Acetate Tablet to Healthy Postmenopausal Women

Subject Number	Serum Estradiol Acetate Concentration by Nominal Sampling Time (h)		
	0.25	0.5	1.0
01	0.0	0.0	0.0
03 ^a	0.0	0.0	0.0
07	0.0	0.0	0.0
11	0.0	0.0	0.0
13	0.0	0.0	0.0
15	0.0	0.0	0.0
16	0.0	0.0	0.0

Concentrations were BLQ; limit of quantitation was — pg/mL

^a Samples from fed treatment were analyzed for this subject

These results indicate that following oral administration of a 1.8 mg estradiol acetate tablet in the fasted state to healthy postmenopausal women, estradiol acetate was not detected in serum samples 15 minutes after administration. These *in vivo* results confirm the results obtained from

the previous *in vitro* studies of estradiol acetate hydrolysis. Additionally, upon analysis of the fed samples, food did not appear to significantly affect the rate of EA hydrolysis

How much of the drug is bound to plasma proteins?

Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Approximately 1.3% of E2 circulates unbound; about 40% of the bound fraction is bound to SHBG, while the remaining E2 is bound to albumin. Literature reports indicate that induction of SHBG by oral estrogen administration is dose-dependent. Low estrogen doses are not sufficient to induce SHBG production, but oral doses of 2-mg/day E2 for 13 days increases SHBG concentration by 76%.

1. Pharmacokinetics/Bioavailability

Two pharmacokinetic studies were conducted to characterize the pharmacokinetic profile of EA tablets. The first study, Study PR-05000, was a pilot study designed to compare the oral bioavailability of E2 following EA tablet administration to that following an approved, micronized E2 tablet administration. The second study, Study PR-09601, characterized the pharmacokinetics following both single- and multiple-doses of EA tablets for all three strengths.

(i) The objective of Study PR-05000 was to compare the oral bioavailability of E2 following EA oral administration to that following an approved micronized E2 oral administration. Briefly, this single-center, open-label, single-dose, randomized, 3-treatment, 3-period, crossover study was conducted in 9 healthy postmenopausal female volunteers. Each subject received each of the following 3 treatments in random order with a 1-week washout period between treatments:

- (A) one 1.152-mg EA tablet (equivalent to 1 mg E2),
- (B) two 1.152-mg EA tablets (equivalent to 2 mg E2) and
- (C) one 1-mg micronized E2 (Estrace®) tablet.

Serial serum samples were collected from each subject from 48 hours before and up to 48 hours following treatment in Period 1 and from 24 hours before and up to 48 hours following treatment in Periods 2 and 3.

Nine subjects completed the study; data from 8 subjects were evaluable. The subjects had a median (range) age of 57 (47-70) years, median (range) weight of 68.5 (55.0-89.0) kg, and a median (range) height of 156 (149-165) cm. All subjects were Caucasian.

The following table contains a summary of pharmacokinetic results for E2 and E1; mean baseline-corrected serum E2 and E1 concentration-time profiles are shown in the following figures. One 1.152-mg EA tablet contains an equimolar amount of E2 to one 1-mg micronized E2 tablet. As such, E2 bioavailability (rate and extent of absorption) of EA can be compared to that for micronized E2.

Summary of Pharmacokinetic Parameters Derived from Baseline-Corrected Serum E2 and E1 Concentrations Following Oral Administration of One or Two 1.152-mg EA Tablets or One 1-mg Micronized E2 (Estrace®) Tablet (n=8)

Parameter	Treatment Mean (%CV)		
	One x 1.152-mg EA Tablet	Two x 1.152-mg EA Tablets	One x 1-mg Micronized Estradiol Tablet
Estradiol			
C _{max}	52.8 (53)	77.7 (50)	24.0 (30)
t _{max}	1.9 (141)	3.0 (180)	10.1 (54)
AUC(0-t _l dc)	825.7 (23)	1463.9 (23)	703.8 (28)
λ _z	0.0305 (17) ^a	0.0325 (18) ^a	0.0331 (42)
t _{1/2}	22.7 ^a	21.3 ^a	20.9
Estrone			
C _{max}	172.4 (24)	310.9 (30)	151.7 (33)
t _{max}	6.8 (27)	6.3 (27)	7.3 (29)
AUC(0-t _l dc)	3815.9 (24)	7106.7 (33)	3316.7 (34)
λ _z	0.0516 (20)	0.0420 (20)	0.0521 (44) ^a
t _{1/2}	13.4	16.5	13.3 ^a

^an=7

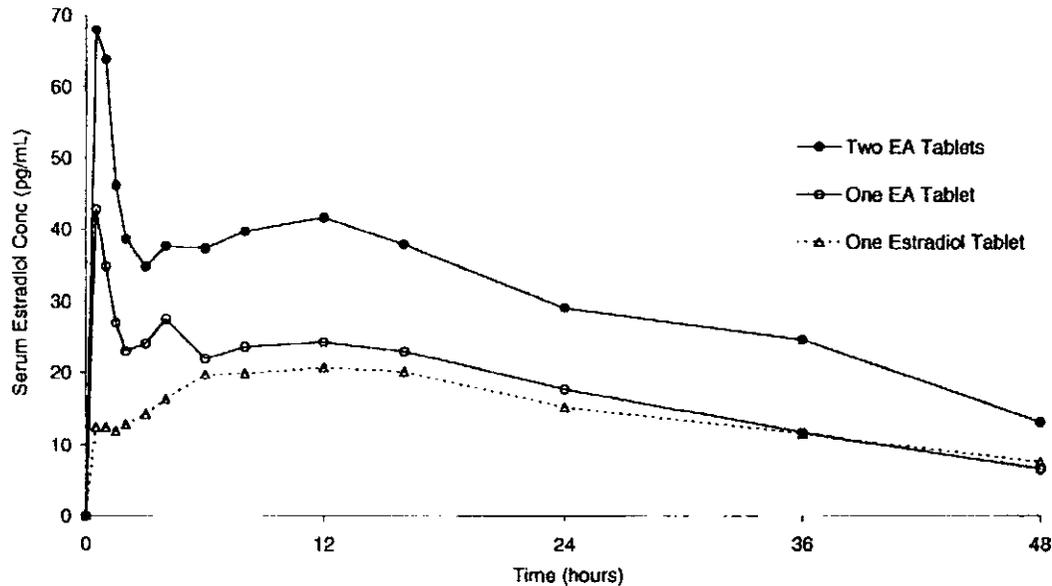
C_{max} = Maximum serum concentration (pg/mL); t_{max} = time of C_{max} (h)

AUC(0-t_ldc) = AUC from time zero to time of last determinable concentration (pg h/mL);

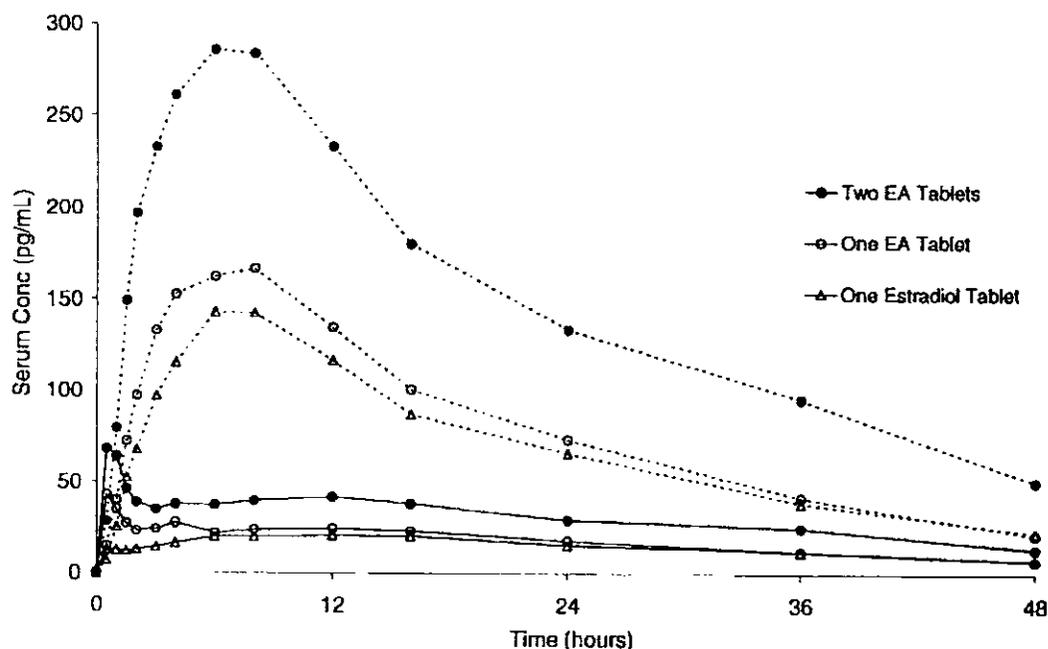
λ_z - terminal phase rate constant (1/h); t_{1/2} = harmonic mean half-life (h) = 0.693 divided by mean λ_z value

Source Data: RR-01001, Tables 14-19.

Mean Baseline-corrected Serum E2 Concentrations Following Oral Administration of One 1.152-mg EA Tablet, Two 1.152-mg EA Tablets or One 1-mg Micronized E2 (Estrace) Tablet in Healthy Postmenopausal Women (n=8)



Mean Baseline-Corrected Serum E2 (solid line) and E1 (dashed line) Concentration-time Profiles Following Oral Administration of 1.152-mg EA Tablets and 1-mg Micronized E2 (Estrace®) Tablets (n=8)



Serum E2 concentration-time profiles following administration of EA and E2 suggested differences in absorption. Shorter E2 t_{max} values following EA tablet administration indicated rapid EA absorption and conversion to E2 while longer t_{max} values following micronized E2 administration revealed slower E2 absorption from the micronized E2 tablet. Similarity of E2 profiles at later times (>6 hours) suggest that disposition and elimination were not affected by prodrug (EA) administration. The following table contains a summary of the statistical comparison of the treatments.

Summary of Statistical Comparison (Ratio, 90% Confidence Interval) of E2 and E1 Pharmacokinetic Parameters Following Oral Administration of 1.152-mg EA Tablets and 1-mg Micronized E2 (Estrace) Tablets (n~8)

Comparison (Test vs Reference)	Analyte	Parameter	Geometric Least Square Mean		Ratio	90% Confidence Interval
			Reference	Test		
One EA tablet vs 1 E2 tablet	Estradiol	Cmax	22.72	46.75	205.79%	163% to 260%
		AUC(0-t _{ldc})	684.85	817.57	119.38%	107% to 134%
	Estrone	Cmax	143.51	166.89	116.29%	103% to 132%
		AUC(0-t _{ldc})	3190.0	3767.1	118.09%	103% to 136%
2 EA tablets vs 1 EA tablet	Estradiol	Cmax	46.75	69.92	149.58%	118% to 189%
		AUC(0-t _{ldc})	817.57	1438.5	175.95%	158% to 209%
	Estrone	Cmax	166.89	294.58	176.52%	156% to 200%
		AUC(0-t _{ldc})	3767.1	6835.9	181.46%	158% to 209%

Ratio = Ratio of Log-transformed least-square means of pharmacokinetic parameter derived from baseline corrected serum concentration, Test/reference

The rate of E2 absorption was higher from EA tablets as compared to the micronized E2 tablet; E2 Cmax values following administration of one EA tablet were double (206%) those following

administration of one micronized E2 tablet, and tmax values were shorter for EA (1.9 hours) as compared to micronized E2 (10.1 hours).

Reviewers comments:

- Estradiol relative bioavailability as indicated by ratio of E2 AUC values was 19% higher for one EA tablet as compared to one micronized E2 tablet. Estradiol C_{max} for one EA tablet was more than double (46.75 pg/mL vs. 22.72 pg/mL) the C_{max} of one micronized E2 tablet. According to the medical reviewer, this C_{max} difference is not expected to pose a safety concern.
- Estrone results were consistent with those for E2; E1 C_{max} and AUC(0-t) values following administration of one EA tablet were 16% and 18% higher, respectively, than those following one micronized E2 tablet. Rate of E1 formation was not different between treatments as indicated by similar t_{max} values.
- Estradiol C_{max} values following administration of 2 EA tablets were 50% higher than those following one EA tablet. E2 AUC(0-t) values were 76% higher following administration of 2 EA tablets as compared to one EA tablet. Estrone results were similar to those for E2; E1 C_{max} and AUC(0-t) values following administration of 2 EA tablets were 77% and 81% higher, respectively, than those following one EA tablet.
- The mean ratio of E2 AUC to E1 AUC value was 0.22, 0.21, and 0.22 following administration of one EA tablet, 2 EA tablets and one micronized E2 tablet, respectively. No difference in E2 to E1 ratio was observed between treatments.
- Administration of EA improved E2 bioavailability but did not affect E2 disposition or elimination.
- Estradiol acetate tablets were generally well tolerated.

(ii) The objective of study PR-00102 (N=18) was to characterize E2 pharmacokinetics following oral administration of single- and multiple-doses of EA tablets to healthy postmenopausal women. Briefly, this single-center, single- and multiple-dose, non-blinded, 3-treatment, 3-period crossover study was conducted in 18 postmenopausal women under medical supervision. Each subject received single- (1 tablet) and multiple-doses (1 tablet per day for 6 days) of EA tablets containing 0.45, 0.9 or 1.8 mg EA for a total of 7 tablets administered in each of 3 treatment periods.

Test Drug(s)

Estradiol Acetate Dose (mg estradiol acetate)	Equivalent Estradiol Dose (mg estradiol)	Batch #
0.45	0.39	2506.004
0.9	0.78	2504.02.001
1.8	1.56	2505.01.001

Treatment was administered with 240 mL (8 fluid ounces) of water. Subjects were fasted for 10 hours (overnight) before dosing and for 4 hours following the first dose. During the multiple dosing phase of each treatment subjects were fasted for at least 4 hours before and for 1 hour

after each dose. There was a 2-week washout between treatment periods. Progestin therapy [C] was administered to all non-hysterectomized subjects on completion of the study.

Serum E2, E1, E1S and sex hormone binding globulin (SHBG) were determined. At screening, complete physical and gynecological examinations were performed. Laboratory safety parameters (hematology, biochemistry and urinalysis) were determined at screening and at the end of the study. Adverse events and concomitant medication were recorded at all visits.

All 18 subjects completed the study; pharmacokinetic data from all subjects were evaluable. The subjects had a median (range) age of 54 (47-75) years, median (range) weight of 70.9 (47.2-82.6) kg, and a median (range) height of 160 (150-173) cm. Twelve subjects were Caucasian; 6 were Hispanic.

Mean E2, E1 and E1S pharmacokinetic parameter values are summarized in the following tables.

E2, E1 and E1S pharmacokinetic parameter values following single-dose administration of 0.45-, 0.9- and 1.8-mg EA tablets in postmenopausal women (n=18)

Analyte	Parameter	Arithmetic Mean (%CV) by EA Dose		
		0.45 mg	0.9 mg	1.8 mg
Estradiol	C _{max}	45.4 (80)	66.6 (70)	91.5 (62)
	t _{max}	0.34 -	0.52 -	0.75 -
	AUC(0-t _{lde})	565.3 (22)	892.7 (21)	1496.5 (23)
	AUC(0-24)	337.5 (21)	554.8 (24)	924.4 (22)
	AUC _{inf}	973.5 (40) ^b	1375.6 (23) ^c	2271.7 (36) ^b
	kel	0.0229 (48) ^b	0.0239 (26) ^c	0.0256 (29) ^b
	t _{1/2}	30.3 ^b -	29.0 ^c -	27.1 ^b -
Estrone ^a	C _{max}	99.9 (34)	192.8 (26)	351.3 (39)
	t _{max}	6.0 -	6.0 -	6.0 -
	AUC(0-t _{lde})	2027.0 (30)	3601.4 (28)	7217.9 (28)
	AUC(0-24)	1432.7 (27)	2589.5 (22)	5111.0 (25)
	AUC _{inf}	2524.4 (40)	4360.8 (33) ^c	9107.4 (36)
	kel	0.0427 (39)	0.0473 (45) ^c	0.0399 (34)
	t _{1/2}	16.2 -	14.7 ^c -	17.4 -
Estrone Sulfate ^a	C _{max}	- -	- -	15242.2 (48)
	t _{max}	- -	- -	3.0 -
	AUC(0-t _{lde})	- -	- -	219521.5 (42)
	AUC(0-24)	- -	- -	172634.1 (43)
	AUC _{inf}	- -	- -	251848.6 (47)
	kel	- -	- -	0.0528 (37)
	t _{1/2}	- -	- -	13.1 -
SHBG (nmol/L)	Pre-Dose 1	37.3 (18)	29.3 (19)	33.2 (16)
	48-h Concentration	37.3 (18)	36.5 (19)	34.4 (16)

C_{max} : Maximum serum concentration following single dosing, pg/mL

t_{max} : Time of C_{max}, median, h

AUC(0-t_{lde}) : AUC from time 0 to time of last determinable concentration, pg-h/mL

AUC(0-24) : AUC from time 0 to 24 hours post-dose, pg-h/mL

AUC_{inf} : AUC from time 0 to extrapolated to infinity, pg-h/mL

kel : Apparent elimination rate constant, 1/h

t_{1/2} : Apparent elimination half-life. Harmonic mean values are reported (0.693 / mean kel value), h

^a Pharmacokinetic parameters have been calculated from baseline-adjusted concentrations

^b n=16, ^c n=17; parameters could not be calculated for all subjects

E2, E1 and E1S pharmacokinetic parameter values following multiple- dose administration of 0.45-, 0.9- and 1.8-mg EA tablets in postmenopausal women (n=18)

Analyte	Parameter	Arithmetic Mean (%CV) by EA Dose		
		0.45 mg	0.9 mg	1.8 mg
Estradiol	C _{max} (dose#7)	56.7 (57)	90.1 (51)	177.3 (55)
	t _{max} (dose#7)	0.50 -	0.43 -	0.75 -
	AUC(0-τ)	565.0 (26)	1066.5 (25)	2211.3 (26)
	C _{avg}	23.5 (26)	44.4 (25)	92.1 (26)
	C _{min}	18.0 (44)	32.4 (35)	67.1 (38)
	kel ss	0.0268 (25) ^b	0.0312 (25)	0.0324 (27)
	t _{1/2}	25.9 -	22.2 -	21.4 -
	Fluctuation	169.5 (80)	132.6 (81)	124.7 (91)
	Swing	263.2 (88)	203.8 (93)	195.9 (104)
	R	1.68 (19)	1.97 (24)	2.41 (20)
Estrone ^a	C _{max} (dose#7)	155.0 (40)	313.9 (25)	680.6 (25)
	t _{max} (dose#7)	6.0 -	5.0 -	6.0 -
	AUC(0-τ)	2363.8 (34)	4980.9 (32)	11510.8 (32)
	C _{avg}	98.5 (34)	207.5 (32)	479.6 (32)
	C _{min}	68.3 (58)	135.8 (52)	330.0 (48)
	kel ss	0.0435 (22)	0.0431 (30)	0.0393 (30)
	t _{1/2}	15.9 -	16.1 -	17.6 -
	Fluctuation	90.3 (48)	94.6 (38)	78.7 (36)
	Swing	155.9 (58)	177.2 (65)	131.1 (53)
	R	1.65 (18)	1.92 (20)	2.26 (20)
Estrone Sulfate ^a	C _{max} (dose#7)	- -	- -	29547.7 (34)
	t _{max} (dose#7)	- -	- -	1.8 -
	AUC(0-τ)	- -	- -	314490.3 (41)
	C _{avg}	- -	- -	13103.8 (41)
	C _{min}	- -	- -	2273.0 (70)
	kel ss	- -	- -	0.0442 (35)
	t _{1/2}	- -	- -	15.7 -
	Fluctuation	- -	- -	228.3 (36)
	Swing	- -	- -	2062.2 (76)
	R	- -	- -	1.76 (21)
SHBG	Trough ^c	38.0 (18)	41.6 (17)	57.5 (23)

C_{max}(dose#7) : Maximum serum concentration following multiple dosing, pg/mL

t_{max}(dose#7) : Time of C_{max}(dose#7), median, h

AUC(0-τ) : AUC from time 0 to 24 hours post-dose, pg·h/mL

C_{avg} : Average serum concentration over dosing interval = AUC(0-τ)/τ, pg/mL

C_{min} : Minimum serum concentration over dosing interval, pg/mL

kel ss : Apparent elimination rate constant following multiple dosing, 1/h

t_{1/2} : Apparent elimination half-life. Harmonic mean values are reported (0.693 / mean kel ss value), h

Fluctuation : $100 \times (C_{max}(dose\#7) - C_{min}(dose\#7)) / C_{avg}$

Swing : $100 \times (C_{max}(dose\#7) - C_{min}(dose\#7)) / C_{min}(dose\#7)$

R : Accumulation Factor = AUC(0-τ) / AUC(0-24)

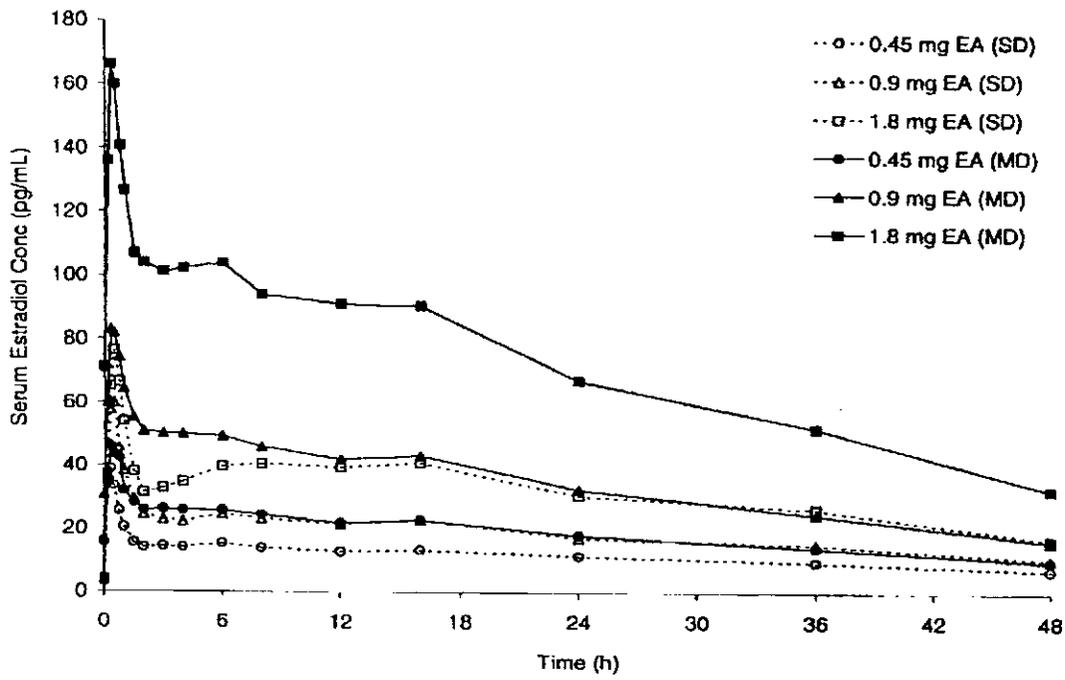
^a Pharmacokinetic parameters have been calculated from baseline-adjusted concentrations

^b n=16; parameters could not be calculated for all subjects

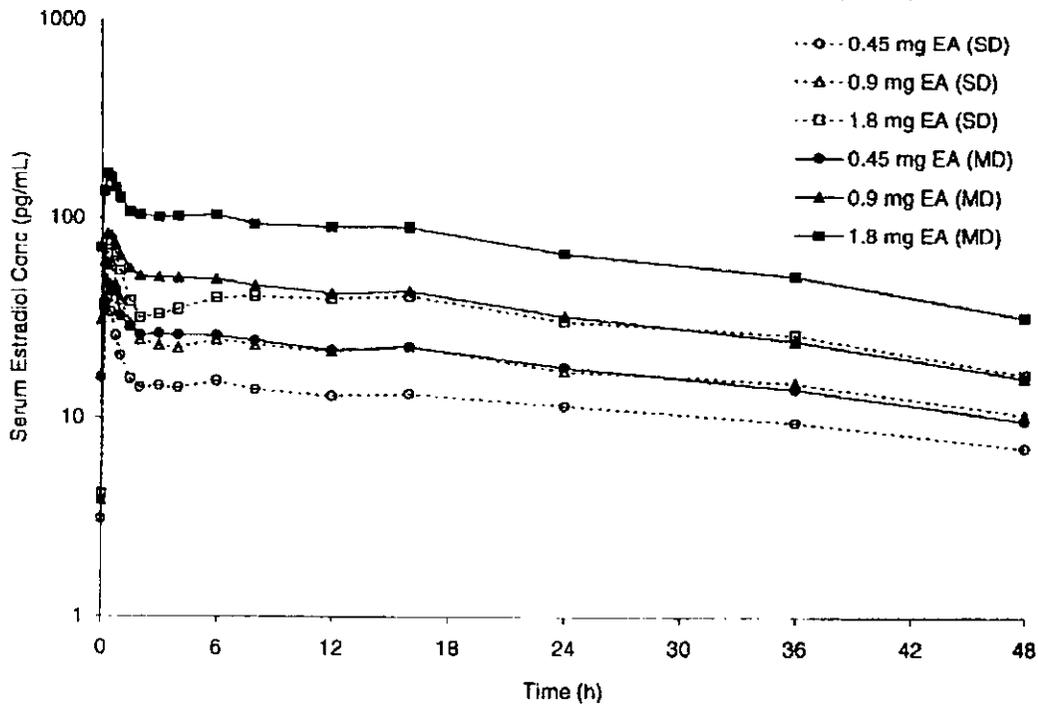
^c Trough = Concentration at end of 24-h dosing interval for Dose #7, nmol/L

Serum E2 concentrations following administration of single-dose and multiple-dose regimens are compared in the following figures.

Mean Serum E2 Concentrations (Linear Scale) Following Single-Dose (SD) and Multiple-Dose (MD) Administration of EA Tablets (n=18)



Mean Serum E2 Concentrations (Log Scale) Following Single-Dose (SD) and Multiple-Dose (MD) Administration of EA Tablets (n=18)

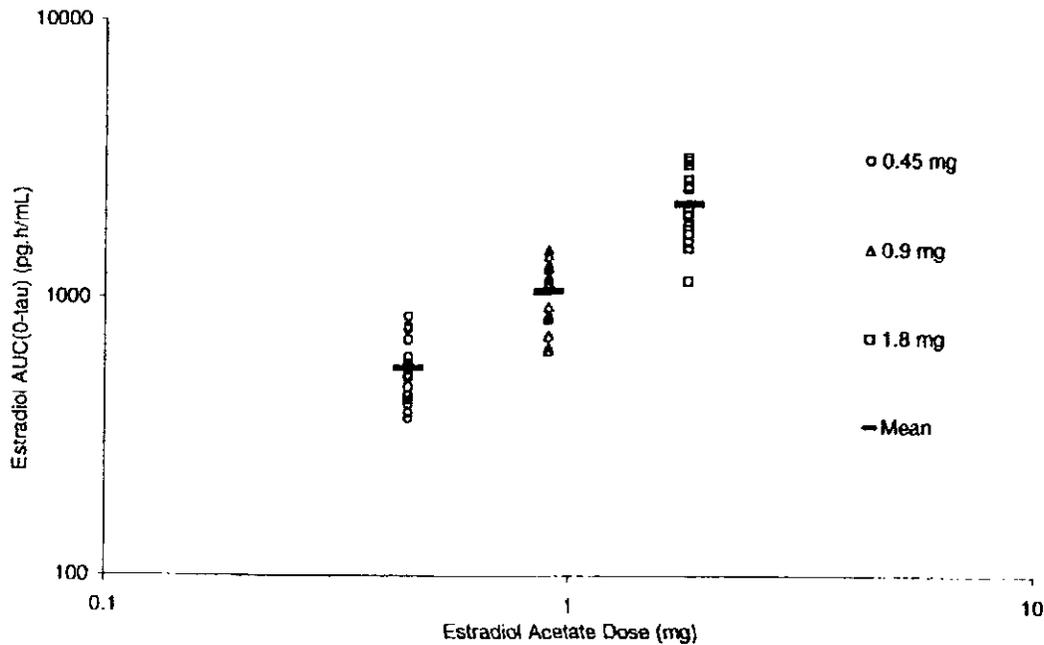


Following administration of EA tablets, serum E2 concentrations increased rapidly (median t_{max} < 1 hour) and then decreased rapidly to relatively constant E2 concentrations from 6 to 48 hours post-dose. Baseline-adjusted serum E1 concentrations increased gradually until 4-8 hours post-dose (median t_{max} = 6.0 hours for all doses). Thereafter, serum E1 concentrations decreased mono-exponentially. Following administration of the 1.8-mg EA tablet, baseline-adjusted serum E1S concentrations increased gradually until 3-4 hours post-dose (median t_{max} = 3.0 hours). Thereafter, baseline-adjusted serum E1S concentrations decreased mono-exponentially until 48 hours post-dose.

Relatively low median t_{max} values for E2 and E1 indicated that E2 was rapidly absorbed following single- and multiple-dose administration of 0.45-, 0.9- and 1.8-mg EA tablets. Estrone t_{max} values were higher than those for E2. Examination of E2 and baseline adjusted E1 C_{max} and AUC values following multiple-dose EA administration revealed that extent of E2 absorption increased linearly with EA dose.

Following multiple-dose administration of EA tablets, 95% confidence interval for E2 AUC(0- τ) slope included 1.0 (95% CI= 0.9245 to 1.0426), indicating that E2 AUC(0- τ) values increased proportionally with increasing dose, as seen in the following figure.

Serum E2 AUC(0-tau) Values following Multiple-Dose Administration of EA Tablets versus EA Dose (n=18)



The 95% confidence interval for slope for E2 C_{max} values approached 1.0 (95% CI= 0.7031 to 0.9741), indicating slightly lower than dose proportional increase in C_{max} with increasing dose.

For E1 C_{max} , the 95% confidence interval for slope included 1.0, indicating that baseline - adjusted E1 single- and multiple-dose C_{max} values increased proportionally with increasing dose. The confidence intervals for E1 AUC values did not include 1.0 (95% CI= 1.0706 to 1.2209).

Dose-proportionality was confirmed statistically for E2 AUC(0- τ) and E1 single- and multiple-dose C_{max} . The corresponding E2 C_{avg} values increased dose-proportionally with increasing EA dose; E2 C_{avg} values were 23.5, 44.4, and 92.1 pg/mL for the 0.45, 0.90 and 1.8mg tablets, respectively. Pharmacokinetic linearity was demonstrated for E2 for the 1.8-mg EA dose only. For E1, linearity was demonstrated for the 0.45-mg EA dose only. The 90% confidence interval for the ratio of least-squares means where ratio = AUC(0-t)/AUC(0-inf) was within the 80-125% range for the 1.8-mg dose and 0.45-mg dose for E2 and baseline-adjusted E1, respectively. For E1S, the 90% confidence interval was not within the 80-125% range for the 1.8-mg EA dose.

Lack of significant difference between Dose 6 and Dose 7 trough values for E2 and E1S confirmed that steady state was achieved for E2 and E1S. The Dose 7 baseline-adjusted E1 trough value was only 6% higher than that for Dose 6. By Dose 7 of multiple-dose administration of EA tablets, steady state was achieved.

SHBG concentrations did not change significantly from pre-dose SHBG concentration following single- and multiple-dose administration of 0.45-mg EA tablets. Following administration of the 0.9- and 1.8-mg EA tablets, there was a trend of increasing SHBG concentrations with increasing dose. SHBG concentration following 0.9-mg EA tablet administration increased 6.1% from pre-dose to dose 7. Following administration of 1.8-mg EA tablets, SHBG concentrations increased 73.2% from pre-dose to dose 7, but Dose 7 SHBG concentration was only 9% higher than dose 6 SHBG concentration, suggesting that the 7 day trial was sufficient to closely approach effect (altered SHBG concentration) steady-state.

Approximately 1.3% of E2 circulates unbound; about 40% of the bound fraction is bound to SHBG, while the remaining E2 is bound to albumin. Literature reports indicate that increases in SHBG by oral estrogen administration are dose-dependent. Low estrogen doses are not sufficient to increase SHBG concentration, but literature reports show that following oral E2 doses of 2-mg/day for 13 days, E2 increases SHBG concentration by 76%. These reports further justify the sponsor's assertion that steady state was closely approximated by day 7 of the previously mentioned trial.

E2 was extensively metabolized to the less active E2 metabolites, E1 and E1S. Baseline-adjusted serum E1 concentrations were 4 to 5 times higher than serum E2 concentrations. Baseline-adjusted serum E1S concentrations were approximately 140 times higher than serum E2 concentrations.

As expected with compounds which undergo extensive enterohepatic circulation, pharmacokinetic linearity could not be demonstrated at all doses of EA tablets; following single- and multiple-administration of the 1.8-mg EA dose only, E2 AUCinf and AUC(0-t) values were not statistically different. For E1, linearity was demonstrated for the 0.45-mg EA dose only. Estradiol, E1 and E1S apparent elimination half-life values were independent of dose. Estradiol

apparent elimination half-life values of 21 to 26 hours were about 50% longer than those for E1 (15.9 to 17.6 hours) and E1S, reflecting enterohepatic circulation of E2.

Reviewers comments:

- Estradiol was rapidly absorbed following oral administration of EA tablets. Estradiol and E1 exposure increased dose-proportionally with increasing dose; the corresponding E2 C_{avg} values were 23.5, 44.4, and 92.1 pg/mL.
- Increase in SHBG concentration depended on EA dose; SHBG concentration was not significantly changed by 0.45- and 0.9-mg tablet single- or multiple-dose administration, but multiple-dose administration of 1.8-mg EA tablets resulted in a 73.2% increase in SHBG concentration. This increase can be assumed to closely approximate the effect on SHBG at steady state.
- Estradiol was extensively metabolized to the less active metabolites E1 and E1S; baseline-adjusted serum E1 and E1S concentrations were 4-5 times and approximately 140 times higher than serum E2 concentrations, respectively.
- Estradiol apparent elimination half-life values were 21 to 26 hours.
- The 3 doses of EA tablets (0.45, 0.9 and 1.8 mg EA) administered in single- and multiple-dose regimens were generally well tolerated; the spectrum of adverse events was similar to what would be expected from oral estrogen.

2. Exposure-Response Information (from Medical Review)

The sponsor performed two Phase 3 studies in support of this submission. Study PR 00501 was conducted at 44 study sites in the U.S. 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

Study PR 01502 was conducted at 40 sites in the U.S. 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

VMS Results-Frequency

Mean change from baseline in the numbers of moderate to severe hot flashes 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).

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

Study Visit	EA 0.9 mg (n=100)	EA 1.8 mg (n=95)	Placebo (n=94)	p-values*		
				Overall	EA 0.9 vs. PBO	EA 1.8 mg vs. PBO
Baseline						
Mean Number	78.5	82.4	86.1	0.414	0.188	0.596
Week 4						
Mean Number	24.3	21.9	51.5			
Mean Change	-54.2	-60.5	-34.6	<0.001	<0.001	<0.001
Week 8						
Mean Number	19.2	9.3	46.1			
Mean Change	-59.3	-73.1	-40.0	<0.001	<0.001	<0.001
Week 12						
Mean Number	17.5	7.3	46.8			
Mean Change	-61.0	-75.0	-39.3	<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.

LOCF = last observation carried forward

ITT = intent-to-treat

PBO = placebo

* p-values are from a 2-way ANOVA interaction with treatment as the factor.

The mean change from baseline at Weeks 4, 8, and 12 in the number of moderate to severe hot flashes using LOCF for the ITT* Population are presented in the following table. The mean changes from baseline in the numbers of moderate to severe hot flashes 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 flashes in the EA 0.45 mg group first achieved statistical significance compared to placebo at Week 6 ($p=0.042$).

Mean Change from Baseline to Weeks 4, 8, and 12 in the Number of Moderate-to-Severe Hot Flashes Per Week During Therapy Using LOCF (ITT*Population) for Study PR 01502.

Study Visit	EA 0.45 mg (n=113)	Placebo (n=108)	p-values*
Baseline			
Mean Number	86.2	85.8	0.691
Week 4			
Mean Number	44.1	51.5	
Mean Change	-42.1	-34.3	0.113
Week 6			
Mean Number	38.7	49.0	

Mean Change	-47.5	-36.8	0.042
Week 8			
Mean Number	35.9	45.7	
Mean Change	-50.4	-40.1	0.048
Week 12			
Mean Number	34.1	43.1	
Mean Change	-52.2	-42.8	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

^a p-values are from a 2-way ANOVA interaction with treatment as the factor.

VMS Results-Severity

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).

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

Study Visit	EA 0.9 mg (n=100)	EA 1.8 mg (n=95)	Placebo (n=94)	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	1.8	1.9	2.3		
Mean Change	-0.7	-0.7	-0.2	<0.003	<0.004
Week 8					
Mean Severity	1.5	1.2	2.2		
Mean Change	-1.0	-1.3	-0.3	<0.001	<0.001
Week 12					
Mean Severity	1.4	1.0	2.2		
Mean Change	-1.1	-1.5	-0.3	<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 as the factor.

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, $p<0.001$).

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 01502

Study Visit	EA 0.45 mg (n=113)	Placebo (n=108)	p-values ^a
Baseline Mean Severity	2.5	2.6	0.621
Week 4 Mean Severity	2.3	2.4	
Mean Change	-0.3	-0.2	0.259
Week 5 Mean Severity	2.2	2.4	
Mean Change	-0.3	-0.1	0.010
Week 8 Mean Severity	2.1	2.4	
Mean Change	-0.5	-0.2	<0.001
Week 12 Mean Severity	1.9	2.3	
Mean Change	-0.7	-0.3	<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

^ap-values are from a 2-way ANOVA interaction with treatment as the factor.

VVA Results

3 Page(s) Withheld



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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

[

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C. Intrinsic Factors (renal, hepatic)

All studies to characterize the pharmacokinetics of LA tablets were conducted in the target population, postmenopausal women. No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

D. Extrinsic Factors (DDI)

The sponsor did not perform any drug interaction studies. However, the following is the language used in all estrogen-containing labels (and is proposed by sponsor for this label):

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 decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma [] concentrations of estrogens and may result in side effects.

E. General Biopharmaceutics

1. Formulation

The clinical batch size was pilot scale [] tablets) and was increased by a factor of ten times to give the commercial batch size [] tablets). The clinical batch formula and the commercial formulations are identical for the 0.9 mg and 1.8 mg tablets. In the commercial formulation for the 0.45 mg tablet, [] , and

This resulted in [] for the 0.45 mg tablet [] in the formulation.

This constitutes a Level 1 change according to the SUPAC IR guidance and as such, requires no further dissolution testing or bioequivalence study. The equipment used to produce the clinical batches is of the same design and operating principles as that used to produce commercial batches.

These minor changes to the formulation of the to-be-marketed 0.45 mg tablet do not warrant bridging studies. The following table lists the formulation of the to-be-marketed EA tablets (the 1.152 mg tablet is not intended for market).

Composition of Estradiol Acetate Tablets

Component	Amount Per Tablet (mg)			
	1.152 mg Tablet	0.45 mg Tablet	0.9 mg Tablet	1.8 mg Tablet
Estradiol acetate ^a				
Iron Oxide Color (Yellow)				
Povidone				
Lactose Monohydrate,				
Microcrystalline Cellulose				
Croscarmellose Sodium				
Silicon Dioxide				
Magnesium Stearate				
Acetic Acid				
Purified Water ^b				
Total	90.0	90.0	90.0	90.0

2. Bioavailability

The bioavailability study (PR-05000) was reviewed in the pharmacokinetics portion of this review, page 10. The study summary is presented under Reviewers comments on page 14.

3. Food Effect

The objective of study PR-09601 was to assess the effect of food on E2 bioavailability following oral administration of a single dose of EA. Briefly, this single-center, randomized, balanced, single-dose, two-treatment, two-period, two-sequence crossover study was conducted in 18 healthy postmenopausal female volunteers. All subjects received one 1.8-mg EA tablet with 240 mL of water in each of two treatment periods. In period 1, half the subjects received treatment following an overnight fast of at least ten hours and did not receive food for at least 4 hours post-dose (fasted treatment). The other half of the subjects received treatment within 5 minutes of

consuming a high-fat, high-calorie, test meal over a 30-minute period (fed treatment) following an overnight fast of at least ten hours. After a two-week washout, each subject received the alternative treatment. Serum E2 and E1 were determined by a validated ${}^3\text{H}$ assay.

All sixteen (16) subjects completed the study. Pharmacokinetic data from only 14 subjects was evaluable. The subjects had a median (range) age of 65.5 (47-75) years, median (range) weight of 66.6 (58.4-82.0) kg, and a median (range) height of 160.0 (152.4-175.3) cm. Fifteen subjects were Caucasian; one was Hispanic.

Following administration of a 1.8-mg EA tablet with a high fat, high calorie breakfast, lower E2 C_{max} values and higher t_{max} values indicated a decreased rate of E2 absorption. Similar AUC values between the two treatment groups indicated that the systemic exposure to E2 was unchanged, as seen in the following table and figures. Serum E1 mean C_{max} , AUC, and apparent terminal elimination rate constant values were comparable for the two treatment groups.

Summary of E2 and E1 Pharmacokinetic Parameter Values Following Oral Administration of One 1.8-mg EA Tablet in the Fed or Fasted State (n=14)

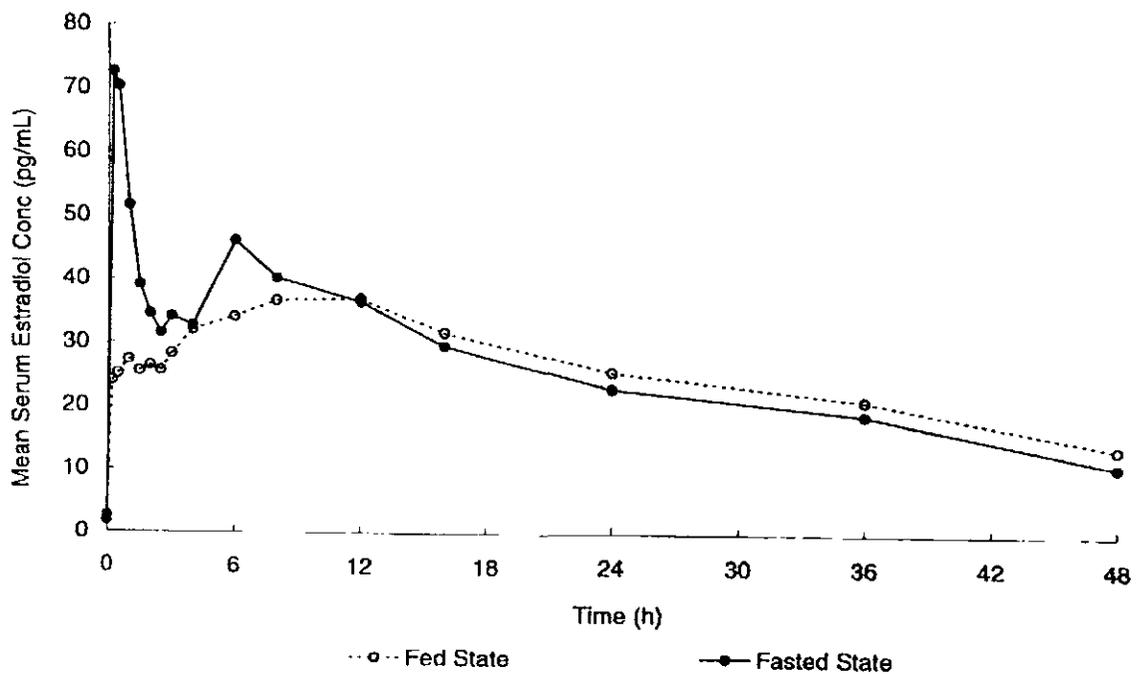
Analyte	Parameter	Geometric Mean		Ratio	90% Confidence Interval
		Fasted	Fed		
Estradiol	C_{max}	69.62	44.29	63.61	53.14 - 76.15
	AUC(0-t _{ldc})	1128.10	1143.13	101.33	94.62 - 108.52
	AUC _{inf}	1609.84	1628.51	101.16	91.23 - 112.17
	$t_{\text{max}}^{\text{a}}$	2.40	8.30	397.16	-
Estrone	C_{max}	367.61	379.53	103.24	93.45 - 114.06
	AUC(0-t _{ldc})	7366.45	7857.64	106.67	99.45 - 114.41
	AUC _{inf}	9278.57	10096.13	108.81	101.31 - 116.87
	$t_{\text{max}}^{\text{a}}$	5.83	6.86	117.72	-

C_{max} = Maximum serum concentration (pg/mL); AUC(0-t_{ldc}) = Area under serum concentration-time curve from 0 to t_{ldc}, the time of last determinable concentration (pg/mL·h); AUC_{inf} = Area under the serum concentration-time curve from 0 to infinity (AUC_{inf} is calculated as the sum of AUC(0-t_{ldc}) plus the ratio of the last measurable serum concentration to the elimination rate constant) (pg/mL·h); t_{max} = time of C_{max} (h)

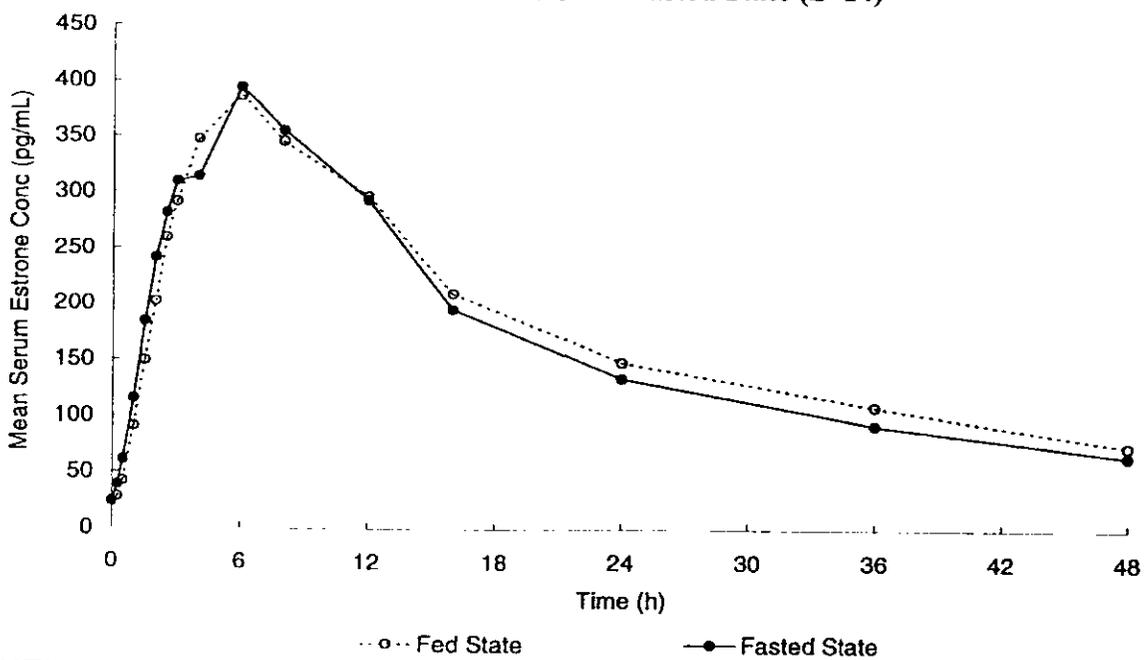
^a the arithmetic means are reported for t_{max} values

Mean Serum E2 Concentration-Time Profile Following Oral Administration of One 1.8-mg EA Tablet in the Fed or Fasted State (n=14)

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Mean Serum E1 Concentration-Time Profile Following Oral Administration of One 1.8-mg EA Tablet in the Fed or Fasted State (n=14)



Reviewers comments:

- Administration of a 1.8-mg EA tablet with food decreased the rate but not the extent of E2 bioavailability.
- Estradiol acetate tablets (1.8 mg) were generally well tolerated.

4. In Vitro Dissolution

Dissolution method development experiments were performed on estradiol acetate 0.45 mg, 0.9 mg, and 1.8mg tablets using various combinations of paddle speed, dissolution media composition and media volume. Based on the method development results, 500 mL sodium lauryl sulfate (SLS) and a paddle speed of 75 rpm was selected by the sponsor. Additional dissolution profiles were generated in deionized water and in buffers at pH 1.2, 3.6, 4.5, and 6.8 with and without 0.5% sodium lauryl sulfate (SLS) and with different concentrations of SLS.

The following two tables list the results of numerous dissolution tests performed by the sponsor at assorted SLS concentrations and paddle speeds.

**Effect of SLS concentration on Dissolution of EA 0.9 mg Tablets
(500 mL of medium at 75 rpm)**

		Amount Dissolved (% Label Claim) by Sample Time (minutes)								
% SLS	Time (mins.)	5	10	15	30	45	60	90	120	
0.5%	Average	17.2	36.6	45.7	57.9	66.6	67.3	76.5	75.0	
	%RSD	13.87	6.07	6.37	7.45	7.76	8.92	5.61	16.82	
	Min									
	Max									
1%	Average	14.3	32.4	38.5	54.2	61.4	67.5	73.0	78.1	
	%RSD	32.56	5.75	15.92	1.76	2.22	2.16	3.29	3.34	
	Min									
	Max									
2%	Average	55.1	76.6	80.1	83.9	88.0	91.3	92.7	94.1	
	%RSD	5.34	4.00	3.60	3.10	3.00	4.49	4.09	3.91	
	Min									
	Max									
3%	Average	64.7	88.9	92.9	94.2	93.5	95.7	96.0	98.6	
	%RSD	13.28	4.91	4.82	5.27	4.72	3.0	3.07	3.26	
	Min									
	Max									

Reference: Galen Laboratory Notebook (NB): NB 727, Pgs 001-010, 019-024, 062-070, 089-093

**Effect of SLS concentration on Dissolution of EA 0.9 mg Tablets
(500 mL of medium at 75 rpm)**

		Amount Dissolved (% Label Claim) by Sample Time (minutes)							
% SLS	Time (mins.)	5	10	15	30	45	60	90	120
—	Average	26.0	39.9	49.4	62.4	71.8	73.6	77.4	78.7
	%RSD	8.30	2.73	1.14	5.01	2.69	3.90	1.54	1.68
	Min								
	Max								
—	Average	24.1	39.7	54.7	63.2	67.3	73.4	72.3	79.6
	%RSD	11.01	2.95	19.26	6.07	4.73	4.40	7.00	4.76
	Min								
	Max								
—	Average	35.5	56.3	66.5	79.5	86.3	88.5	90.7	92.0
	%RSD	4.43	2.19	1.19	0.70	1.38	0.92	0.59	0.68
	Min								
	Max								
—	Average	37.7	65.6	74.4	88.3	90.8	93.8	93.9	95.9
	%RSD	5.33	3.72	5.50	2.80	4.91	2.79	4.27	4.71
	Min								
	Max								
—	Average	69.1	95.7	97.1	97.3	96.3	95.6	98.2	98.0
	%RSD	5.15	1.45	1.55	1.67	2.24	1.43	2.23	1.38
	Min								
	Max								
—	Average	76.8	97.9	102.7	102.8	102.9	102.7	103.0	103.5
	%RSD	9.51	2.15	0.84	1.25	1.33	1.23	2.30	2.01
	Min								
	Max								

Reference: Galen Laboratory Notebooks (NB): NB 718, Pgs 062-071; NB 727, Pgs 025-047, 058-061, 071-075, 081-088

Incomplete EA dissolution was observed at SLS concentrations below the critical micelle concentration C_{MC} ; whereas dissolution media containing C_{MC} SLS and higher consistently yielded C_{MC} dissolved at 30 minutes and later for all tablet strengths.

The sponsor studied the effect of tablet strength, at different paddle speeds, on the dissolution rate of estradiol acetate. The following tables list the results of these tests.

Effect of Tablet Strength on Amount of EA Dissolved (as % of Label Claim) in 500 mL of — SLS (Paddle Speed — rpm)

		Amount Dissolved (% Label Claim) by Sample Time (minutes)							
Dose (mg)	Time (mins.)	5	10	15	30	45	60	90	120
0.9	Average	37.7	65.6	74.4	88.3	90.8	93.8	93.9	95.9
	%RSD	5.33	3.72	5.50	2.80	4.91	2.79	4.27	4.71
	Min								
	Max								
1.8	Average	26.2	48.9	61.8	77.9	85.6	91.1	94.7	96.9
	%RSD	58.11	1.27	1.85	0.60	1.15	0.74	1.16	0.58
	Min								
	Max								

Reference: Galen Laboratory Notebooks (NB): NB 727, Pgs 081-088; NB 741, Pgs 001-011

Effect of Tablet Strength on Amount of EA Dissolved (as % of Label Claim) in 500 mL of — SLS (Paddle Speed : — rpm)

		Amount Dissolved (% Label Claim) by Sample Time (minutes)							
Dose (mg)	Time (mins.)	5	10	15	30	45	60	90	120
0.45	Average	38.8	68.8	77.3	89.5	95.1	98.2	99.8	100.6
	%RSD	32.69	8.75	7.56	6.80	5.62	5.60	1.88	2.40
	Min								
	Max								
0.9	Average	55.1	76.6	80.1	83.9	88.0	91.3	92.7	94.1
	%RSD	5.34	4.00	3.60	3.10	3.00	4.49	4.09	3.91
	Min								
	Max								
1.8	Average	32.2	64.2	74.6	83.4	90.3	93.7	100.4	101.8
	%RSD	17.09	5.37	3.10	3.07	8.07	7.73	5.70	5.35
	Min								
	Max								

Reference: Galen Laboratory Notebooks (NB): NB 727, Pgs 089-100; NB 741, Pgs 001-011

Effect of Tablet Strength on Amount of EA Dissolved (as % of Label Claim) in 500 mL of — SLS (Paddle Speed ~ rpm)

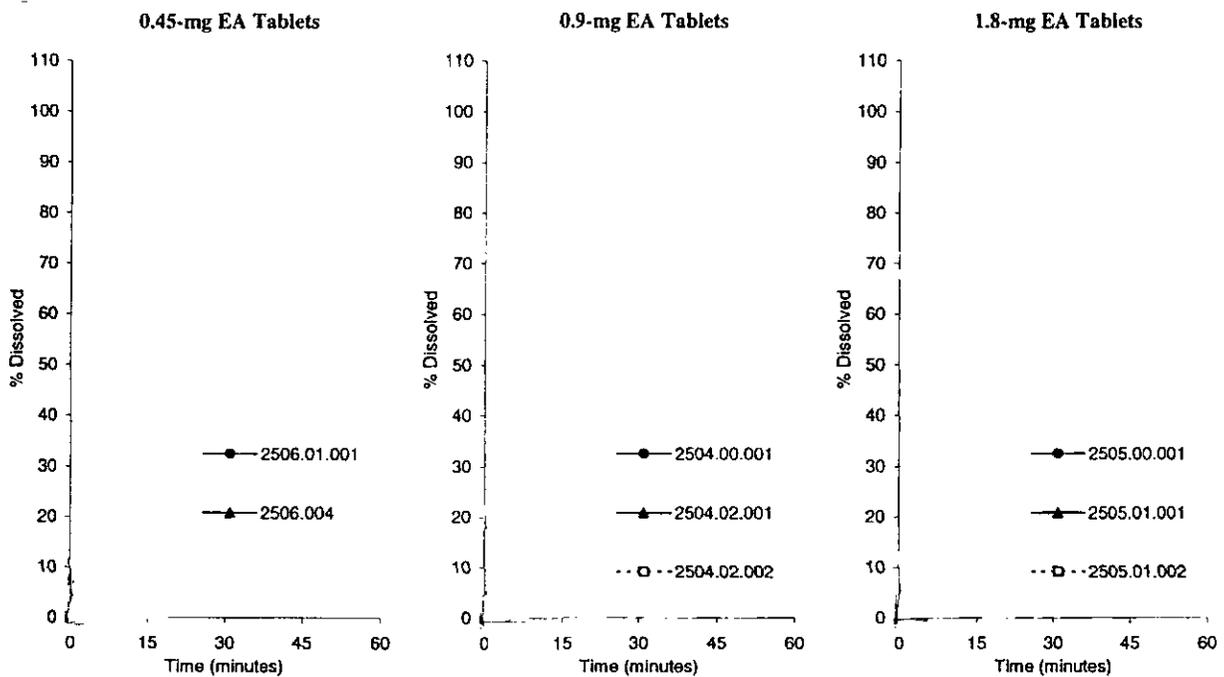
		Amount Dissolved (% Label Claim) by Sample Time (minutes)							
Dose (mg)	Time (mins.)	5	10	15	30	45	60	90	120
0.45	Average	ND	ND	94.9	98.6	98.4	100.1	98.7	ND
	%RSD	ND	ND	3.60	2.00	0.88	1.74	1.78	ND
	Min								
	Max								
0.9	Average	69.1	95.7	97.1	97.3	96.3	95.6	98.2	98.0
	%RSD	5.15	1.45	1.55	1.67	2.24	1.43	2.23	1.38
	Min								
	Max								
1.8	Average	ND	ND	90.3	99.8	100.2	100.7	100.5	ND
	%RSD	ND	ND	1.65	1.35	1.80	1.48	3.01	ND
	Min								
	Max								

Reference: Galen Laboratory Notebooks (NB): NB 727, Pgs 058-061, 071-075; NB 741, Pgs 012-022
 ND = Not Determined

The dissolution rate of estradiol acetate tablets was independent of tablet strength and increased with increasing paddle rotational speed. Additionally, the sponsor tested dissolution rates under different volumes of dissolution medium. These tests showed greater dissolution rates at higher dissolution volumes.

The results of the dissolution tests under the proposed specifications can be seen graphically in the following figure.

Dissolution Profiles of 0.45-, 0.9- and 1.8-mg EA Tablets in — SLS (—RPM, 500mL)



Dissolution data in buffered media indicated that there was no pH effect on the *in-vitro* dissolution of EA tablets. Dissolution rates were significantly higher in media containing SLS than in each medium alone and were equivalent for all SLS containing media (water and buffers). Insignificant amounts of estradiol were detected when SLS was used as dissolution medium, indicating the stability of EA in the medium.

Dissolution profiles using the proposed parameters (500 mL of SLS, rpm paddle speed) were comparable within the same batch and among batches of the same strength. Dissolution data were also similar among all EA tablet strengths and compared well with the data for the same batches generated using SLS and rpm paddle speed. All the data sets demonstrated rapid dissolution of the drug substance from EA tablets.

Reviewers comment:

- At the 15 and 30 minute points, the average % released over all strengths is 94.1 and 98.5%, respectively. For this reason, the proposed dissolution specifications do not appear to be very discriminating. **As such, this reviewer recommends a dissolution specification of Q = [], at 20 minutes, leaving all else the same.** The chemistry reviewer concurs with this recommendation.

F. Analytical Section

Overall, all analytical assays are acceptable. Serum estradiol and estrone concentrations were determined in studies PR-05000, PR-09601 and PR-00102. The concentrations of the two analytes were determined simultaneously using a validated [] method. The analytes were []

After

]

The minimum quantification limits for E2 and E1 were 0.1 pg/mL and 0.1 pg/mL, respectively.

Serum estrone sulfate concentrations were determined in study PR-00102.1 using a validated method. Serum samples were first treated to remove free E1. The remaining serum sample was hydrolyzed under selective conditions, and the free E1 was analyzed using the E1 EIA. The minimum quantification limit for E1S was 0.1 pg/mL.

The determination of sex-hormone binding globulin was performed with a commercially available kit based on 96-well tubes with 2 capture antibodies directed against distinct epitopes of the molecule of SHBG. Addition of the third antibody labeled with ¹²⁵I-iodine completed the system, allowing the formation of a bridge between the coated antibodies and the labeled antibody. After washing, the remaining radioactivity bound to the tubes was directly related to the concentration of SHBG. The minimum quantification limit for SHBG was 0.1 nmol/L.

Serum estradiol acetate concentrations were determined in Study RR-06703 using a validated method. Study samples were thawed at room temperature and 100 µL aliquots were pipetted into 96-well tubes, and 100 µL of internal standard solution were added. After addition of 100 µL internal standard solution the samples were centrifuged. Samples were then centrifuged. Samples were reconstituted with 100 µL of internal standard solution. The minimum quantification limit for EA was 0.1 pg/mL.

4 Draft Label

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20 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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5 Appendices

A. Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics <i>New Drug Application Filing and Review Form</i>			
General Information About the Submission			
	Information		Information
<i>NDA Number</i>	21-633	<i>Brand Name</i>	FEMTRACE
<i>OCPB Division (I, II, III)</i>	DPE II (HFD 870)	<i>Generic Name</i>	Estradiol acetate
<i>Medical Division</i>	DRUDP (HFD 580)	<i>Drug Class</i>	Female Hormone Replacement Therapy
<i>OCPB Reviewer</i>	Stephan R. Ortiz, R.Ph., Ph.D.	<i>Indication(s)</i>	Post menopausal syndrome
<i>OCPB Team Leader</i>	Ameeta Parekh, Ph.D.	<i>Dosage Form</i>	IR Tablets
<i>Date of Submission</i>	10/20/2003	<i>Dosing Regimen</i>	Once daily

<i>Estimated Due Date of OCPB Review</i>	7/15/2004	<i>Route of Administration</i>	Oral
<i>PDUFA Due Date</i>	8/20/2004	<i>Sponsor</i>	Galen
<i>Division Due Date</i>	7/31/2004	<i>Priority Classification</i>	3S

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	3		
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) - <i>Healthy Volunteers-</i>				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
body wt.				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:				
(IVVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		
<i>Filability and QBR comments</i>				

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	"X" if yes	
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Stephan Ortiz
7/27/04 02:01:54 PM
BIOPHARMACEUTICS

Ameeta Parekh
7/30/04 02:00:41 PM
BIOPHARMACEUTICS