CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-048

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

Date: January 5, 1999

Place: PKLN 17B-43

To: HFD-580

From: Sam H. Haidar, R.Ph., Ph.D.

RE: **NDA 21-048**

Background:

NDA 21-048 for 17β-Estradiol Transdermal System (E_2III TS) was submitted on November 20, 1998. E_2III TS is a transdermal patch delivering 50, 75, and 100 μg (patch sizes of 13.5, 20, 27 cm^2, respectively) of estradiol per day. The proposed indication is treatment of moderate to severe vasomotor symptoms associated with menopause, vulval and vaginal atrophy.

Comments:

1. The sponsor conducted six studies (see Attachment) to investigate the pharmacokinetics of E_2III TS. These studies provided data on single vs. multiple dose pharmacokinetics, dose proportionality, relative bioavailability (comparing different application sites), and a relative bioavailability comparison to marketed patches.

2. The sponsor submitted *in vitro* dissolution methodology, data and proposed specifications.

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) finds the provided information appropriate to support the filing of NDA 21-048.

cc:
NDA 21-048
HFD-870 (M. Chen, A. Parekh, S. Haidar)
HFD-580 (D. Moore, P. Price)
CDR (Barbara Murphy For Drug)

Attachment

NDA 21-048

Summary Table of Human Pharmacokinetics/Bioavailability Studies

TABLE 3.6.2A. TABLE OF PHARMACOKINETIC STUDIES

Protocol No. Report No. Investigator(s) (Country) *Location in Submission*	Study Design	Diagnosis / Criteria for Inclusion	Test Product / Reference / Therapy	Dose, Route, Frequency (Duration of Treatment)	Batch/Lot Number	No. In PK Analysis	Applicant Conclusion
PHARMACOKINETIC STUDIES							
Cygnus 329-01 GMR-30414 [redacted] (US) *Vol. 1.015 / 49*	Single-dose, OL study	Healthy, postmenopausal women, pretreatment endogenous estradiol (E_2) levels < 20 pg/mL, FSH > 50 IU/L and within 20% of their ideal body weight.	20 cm^2 E_2 II TS (5 [redacted] mg E_2)	120 µg E_2/day. Transdermal, single application, (7 days)	01213A	23	Detectable levels of estradiol were produced after a single E_2 II TS application. There were no serious or unexpected treatment-emergent adverse events.
Cygnus 329-02 GMR-30415 [redacted] (US) *Vol. 1.016 / 1*	Randomized, OL, 4-way crossover, comparative study	Healthy postmenopausal women with pretreatment endogenous estradiol levels < 20 pg/mL, FSH > 50 IU/L and within 20% of their ideal body weight.	E_2 III TS [redacted] 20 cm^2 (3.90 mg); Estraderm 20 cm^2 (8 mg).	E_2 III TS: [redacted] 75 µg/day (20 cm^2); Estraderm 100 µg /day Transdermal. E_2 III TS- single application Estraderm- two consecutive 3.5 -day applications (7 days).	E_2 III TS [redacted] 00864 [redacted] 00874 [redacted] 00854 (20 cm^2). Estraderm: IF167985	24	The three patches exhibited a dose-proportional response with respect to C_{max}, AUC_{0-192}, and AUC_{0-172}. None of the patches were equivalent to Estraderm with respect to bioavailability. There were no serious or unexpected treatment-emergent adverse events.
Cygnus 329-03 GMR-30565 [redacted] (US) *Vol. 1.019 / 1*	Randomized, OL, 3-way crossover, comparative study	Healthy postmenopausal women with pretreatment endogenous estradiol levels < 20 pg/mL, FSH > 50 IU/L, and within 20% of their ideal body weight.	E_2 III TS: 13.5 cm^2 (2 [redacted] mg); 27 cm^2 (5 [redacted] mg); Estraderm 20 cm^2 (8 mg).	E_2 III TS: 50 µg E_2/day (13.5 cm^2); 100 µg E_2/day (27cm^2) Estraderm 100 µg E_2/day. Transdermal. E_2 III TS - single application. Estraderm- two consecutive 3.5 - day applications a week (7 days)	E_2 III TS: 00465 (13.5 cm^2), 00475 (27 cm^2). Estraderm: IF174559	24	The 7-day application of the 27 cm^2 E_2 III TS produced AUCs very similar to those provided by the two consecutive 3.5-day applications of Estraderm and were twice those of the 13.5 cm^2 E_2 III TS.

TABLE 3.6.2A. TABLE OF PHARMACOKINETIC STUDIES

Protocol No. Report No. Investigator(s) (Country) *Location in Submission*	Study Design	Diagnosis / Criteria for Inclusion	Test Product / Reference / Therapy	Dose, Route, Frequency (Duration of Treatment)	Batch/Lot Number	No. In PK Analysis	Applicant Conclusion
Cygnus 329-04 GMR-30566 — (US) *Vol. 1.022 / 1*	Single-dose, OL study	Healthy postmenopausal women who had completed the Cygnus 329-03 study (Wyeth GMR-30565)	25 cm^2 Climara (7.80 mg)	100 µg E_2/day. Transdermal, single application. (7 days)	P50078	20	The 7-day application of the Climara patch resulted in a mean C_{max} of 156 pg/mL, and a mean t_{max} of 22 hours. The mean AUC_{0-168} was 15,004 pg.h/mL, and the mean C_{avg} over this time interval was 91 pg/mL. Most adverse events were mild; none were severe.
0802E1-106-US GMR-30333 — (US) *Vol. 1.024 / 168*	Randomized, OL, 3-treatment, 2-period, incomplete block design.	Healthy postmenopausal women with pretreatment endogenous E_2 levels of < 73.4 pmol/L (20 pg/mL), FSH levels >50 IU/L and within 20% of their ideal body weight	E_2 III TS 13.5 cm^2 (2 — mg); 20 cm^2 (3.90 mg); 27 cm^2 (5— mg).	13.5 cm^2, 50 µg E_2/day; 20 cm^2, 75 µg E_2/day; 27 cm^2, 100 µg E_2/day. Transdermal. Once weekly. Each subject received 2 sizes of E_2 III TS, separated by a 7- to 10-day washout period. (14 days)	491858/00665 (13.5 cm^2), 491859A/00685 (20 cm^2), 491860A/00705 (27 cm^2)	28	Baseline-adjusted 17β-estradiol C_{max}, AUC_{168}, AUC_T and C_{avg} increased proportionally with increasing patch size. In general, there appeared to be little or no accumulation from week 1 to week 2 for any of the analytes.
0802E1-127-US GMR-32309 —(US) *Vol. 1.023 / 1*	Single-dose, 3-treatment (application to hip, buttock and abdomen) 3-period, randomized, crossover study.	Healthy hysterectomized postmenopausal women with FSH concentration > 50 IU/L, estradiol concentration < 20 pg/mL.	E_2 III TS 27 cm^2 (5 — ng).	100 µg E_2/day. Transdermal application to abdomen, buttock, and hip. Single application (7 days)	01346	36	Patches when applied at three different application sites were bioequivalent for all estradiol, estrone, and estradiol pharmacokinetic parameters except t_{max}, with no significant difference among any of the parameters.

SEP 17 1999

Memo to the Record

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

Date: September 17, 1999

To: HFD-580

From: Sam H. Haidar, R.Ph., Ph.D.

RE: **NDA 21-048**

The labeling changes submitted by the sponsor in a fax dated September 16, 1999 (see Attachment) are acceptable. Additionally, the revised *in vitro* release specification submitted by the sponsor in a fax dated August 9, 1999 is acceptable. The revised specification is given below:

Time	Estradiol release (Percent of label claim)
1 hour	
3 hour	
6 hour	

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

9/17/99

cc:
NDA 21-048
HFD-870 (M. Chen, A. Parekh, J. Hunt, S. Haidar)
HFD-580 (D. Spell-LeSane, P. Price)
CDR (Barbara Murphy For Drug)

96 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA: 21-048

Compound: Estradiol Transdermal Delivery System (E_2III TS) SEP 17 1999

Sponsor: Wyeth-Ayerst

Type of Submission: Original NDA and amendments

Date of Submission: November 20, 1998

Reviewer: Sam H. Haidar, R.Ph., Ph.D.

I. Synopsis:

NDA 21-048 for 17β-Estradiol Transdermal System (E_2III TS) was submitted on November 20, 1998. E_2III TS is a matrix transdermal patch delivering 50, 75, and 100 μg (patch sizes of 13.5, 20, 27 cm^2, respectively) of estradiol per day, over 7 days. The proposed indication for E_2III TS is treatment of moderate to severe vasomotor symptoms associated with menopause, vulval and vaginal atrophy

In support of NDA 21-048, the sponsor has submitted the following definitive pharmacokinetic and bioavailability studies:

1. Cygnus 329-03, evaluated the relative bioavailability of E_2III TS 13.5 cm^2 and 27 cm^2 patches to the marketed product Estraderm®,

2. 0802E1-127-US, evaluated the bioavailability of E_2III TS 27 cm^2 patch when applied to three different body sites: abdomen, hip and buttock,

3. 0802E1-106-US, evaluated the dose-proportionality of E_2III TS 13.5 cm^2, 20 cm^2 and 27 cm^2 patches.

In addition to the above studies, the sponsor submitted two preliminary studies which were conducted to determine the final formulation and patch size for clinical development. The formulation used in clinical testing is the same as the to-be-marketed formulation.

II. Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 21-048, submitted on November 20, 1998. Based on the review of the pharmacokinetic and biopharmaceutics studies submitted, OCPB/DPEII finds this NDA acceptable. However, the reviewer has the following comments:

1. The proposed *in vitro* release specifications for estradiol are not acceptable, the recommended specifications are as follows:

   1.0 hours [redacted]
   3.0 hours [redacted]
   6.0 hours [redacted]

2. Labeling should be modified as outlined in section IX, **Labeling Comments**, page 14.

Comments 1 and 2 and recommendation should be communicated to the sponsor as appropriate.

Sam H. Haidar

Sam H. Haidar, R.Ph., Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD initialed by John Hunt, Deputy Director JH 8/17/99
FT signed by John Hunt, Deputy Director 9/17/99

cc:
NDA 21-048
HFD-870 (M. Chen, A. Parekh, J. Hunt, S. Haidar)
HFD-850 (L. Lesko)
HFD-340 (C.T. Viswanathan)
HFD-580 (D. Moore, P. Price)
CDR (Barbara Murphy for Drug)

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III. Background:

Estradiol is the most active of the naturally occurring estrogens, which are formed by the ovarian follicles under the influence of the pituitary gland. Estrogens control the development and maintenance of the female sex organs, the secondary sex characteristics and the mammary glands. In women between the ages of 40 and 50, the ovarian function declines resulting in the cessation of menstruation (menopause). During the time leading to menopause, the decline in estrogen levels produces various symptoms in a large percentage of women. Those symptoms include hot flushes, inappropriate sweating, vaginal dryness, and atrophy of the breasts. Additionally, the long-term deficiency in estrogen has been associated with osteoporosis.

Hormone replacement therapy (HRT) involves the administration of an estrogen (alone or in combination with a progestin) to ameliorate vasomotor and other symptoms associated with menopause, and the prevention of osteoporosis. Currently, HRT is administered mainly by the oral route or through the skin using transdermal delivery systems (TDS). Regardless of the route of administration, estradiol is cleared rapidly from the plasma. It has a terminal half-life of about 2 - 4 hours.

This NDA is for a transdermal patch delivering 50, 75, and 100 µg (patch sizes of 13.5, 20, 27 cm^2, respectively) of estradiol per day. It is designed to provide systemic estrogen replacement therapy by releasing 17β-estradiol (E2) through the skin.

IV. Formulation

E_2III TS is a solid matrix transdermal patch. Three sizes of the patch are intended to be marketed; a 13.5 cm^2 size which delivers 50 µg/day E2, a 20 cm^2 size which delivers 75 µg/day E2, and a 27 cm^2 size which delivers 100 µg/day E2. The patches are round and translucent, with a removable, pre-cut liner. Release of estradiol from the system is controlled mainly by the adhesive. Figure 1 illustrates E_2III TS patch and components.

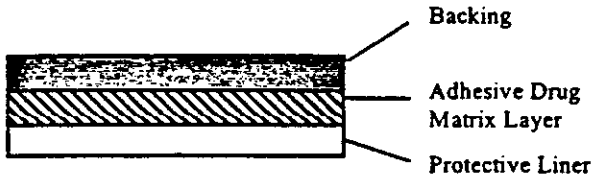


Figure 1. Schematic representation of E_2III TS patch and its components.

Reviewer Comment

1. The clinically tested formulation and the "to be marketed" formulation are the same and they were manufactured at the same site.

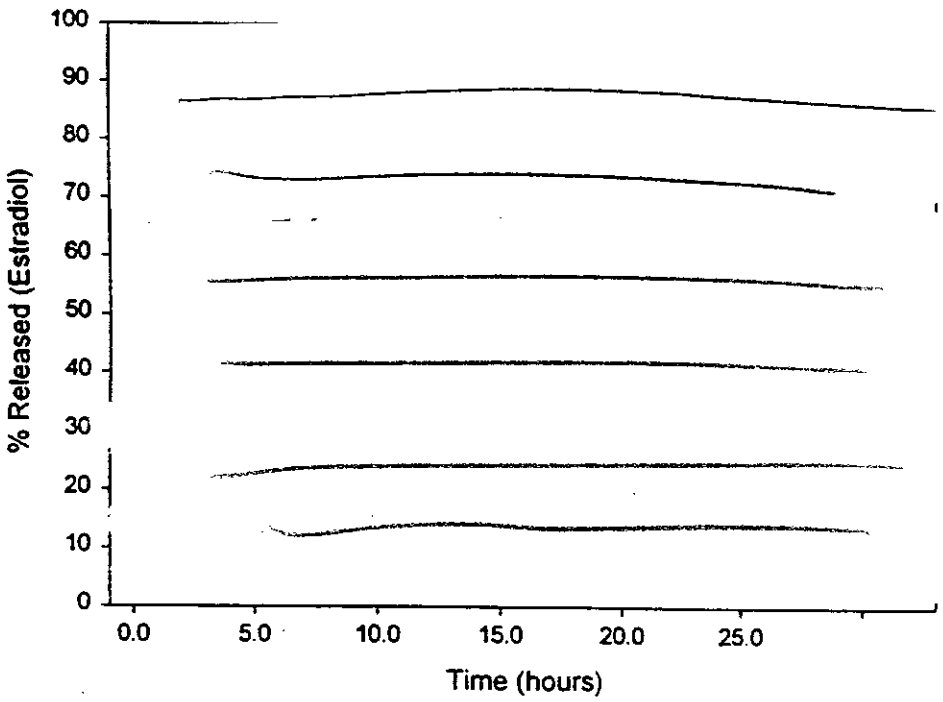


Figure 2. *In Vitro* cumulative release (estradiol) over time of clinically tested batches.

Reviewer Comments

2. The proposed *in vitro* dissolution method is acceptable.

3. The proposed *in vitro* release specifications for estradiol are not acceptable, the recommended specifications are as follows:

1.0 hours
3.0 hours
6.0 hours

VI. Analytical Methodology

A radioimmunoassay (RIA) was used in the studies to determine estradiol, estrone, and estrone sulfate concentrations in serum. Sample preparation prior to assay included organic solvent extraction. The serum extract was further purified by chromatography to separate potential interfering endogenous steroids from the analytes of interest. Assay validation data for estradiol, estrone, and estrone sulfate are presented in Tables III, IV and V.

Table III. Estradiol assay validation.

	Nominal Estradiol Concentrations (pg/mL)		
Mean			
Accuracy (%)			
Intra-assay Precision (%CV)			
Inter-assay Precision (%CV)			

The lower limit of quantitation was .

Table IV. Estrone assay validation.

	Nominal Estrone Concentrations (pg/mL)		
Mean			
Accuracy (%)			
Intra-assay Precision (%CV)			
Inter-assay Precision (%CV)			

The lower limit of quantitation was

Table V. Estrone sulfate assay validation.

	Nominal Estrone Sulfate Concentrations (pg/mL)		
Mean			
Accuracy (%)			
Intra-assay Precision (%CV)			
Inter-assay Precision (%CV)			

The lower limit of quantitation was

Reviewer Comment

1. The analytical methods and validation for the estimation of estradiol, estrone and estrone sulfate concentrations in serum are acceptable.

VII. Clinical Pharmacology and Biopharmaceutics Studies

Table VI. Summary of clinical studies.

Study No./Lot No.	Study Design	Dosage Form	No. of Subjects
Pivotal Pharmacokinetic Studies			
Cygnus 329-03/ 00465 (13.5cm^2) 00475 (27cm^2)	Open label, 3 way crossover, single-dose relative bioavailability comparison with Estraderm 20 cm^2.	E_2III TS 50 µg/day (13.5 cm^2), 100 µg/day (27 cm^2), Estraderm	24
0802E1-106-US/ 00665 (13.5cm^2) 00685 (20cm^2) 00705 (27cm^2)	Open label, 3-treatment, 2-period dose-proportionality.	E_2III TS 50 µg/day (13.5 cm^2), 75 µg/day (20 cm^2), 100 µg/day (27 cm^2),	28
0802E1-127-US/ 01436	Open label, 3-way crossover, single-dose relative bioavailability, comparing application sites: hip, abdomen and buttock.	E_2III TS 100 µg/day (27 cm^2)	36

1. Pharmacokinetics:

a) *Single/Multiple Dose and Dose Proportionality*

Study 0802E1-106-US evaluated the single and multiple dose pharmacokinetics of estradiol, estrone and estrone sulfate following the administration of E_2III TS 13.5 cm^2, 20 cm^2 and 27 cm^2 patches in healthy postmenopausal women. Dose proportionality between the different patches was also examined in the same study. The results are listed in Table VII (Week 1) and Table VIII (Week 2). Table IX provides the ratios of the pharmacokinetic parameters for estradiol, estrone and estrone sulfate, comparing Week 1 to Week 2 of each treatment. The mean proportionality ratios for estradiol $AUC_{0\text{-}168}$ at Week 1 was 1.0:1.5:2.2 and, for Week 2, 1.0:1.4:2.2. These are comparable to the expected ratios of 1.0:1.5:2.0 for the 2.53, 3.90, and 5.27 mg 17β-estradiol E_2III TS patches, demonstrating linear dose proportionality.

Table VII. Summary of pharmacokinetic parameters (mean ± SD), corrected and uncorrected for baseline, for estradiol, estrone and estrone sulfate after a single (7 day) application of E_2III TS 13.5 cm^2, 20 cm^2 or 27 cm^2 patch to the lower abdomen.

Analyte Treatment Size (E_2 content/TS)	n	Unadjusted for Baseline[a] C_{max} (pg/mL)	t_{max} (h)	AUC_t[b] (pg·h/mL)	C_{avg} (pg/mL)	Baseline Adjusted[a] C_{max} (pg/mL)	t_{max} (h)	AUC_t[b] (pg·h/mL)	C_{avg} (pg/mL)
		Single Application (Week 1)							
Estradiol									
E_2III TS									
13.5 cm^2 (2 [illegible] g)	18	57 ± 36	34 ± 24 (12 - 96)	6504 ± 3773 (2739 - 15784)	39 ± 23 (16 - 94)	47 ± 29	34 ± 24 (12 - 96)	4893 ± 3136 1717 - 12645)	29 ± 19 (10 - 75)
20 cm^2 (3.90 mg)	19	72 ± 42	33 ± 20 (12 - 96)	8456 ± 4816 (4409 - 25252)	50 ± 29 (28 - 150)	66 ± 43	33 ± 20 (12 - 96)	7367 ± 4940 (3256 - 24578)	44 ± 29 (19 - 146)
27 cm^2 (5. [illegible])	19	91 ± 32	40 ± 31 (12 - 144)	10466 ± 2274 (6885 - 16182)	62 ± 14 (41 - 96)	85 ± 32	40 ± 31 (12 - 144)	9531 ± 2454 (5452 - 15587)	57 ± 15 (33 - 93)
Estrone									
E_2III TS									
13.5 cm^2 (2.63 mg)	18	43 ± 17	72 ± 44 (24 - 168)	5589 ± 2465 (2594 - 12992)	33 ± 15 (15 - 77)	nd[c]	nd	nd	nd
20 cm^2 (3.90 mg)	19	55 ± 23	61 ± 38 (24 - 168)	6968 ± 2718 (4036 - 13806)	41 ± 16 (24 - 82)	nd	nd	nd	nd
27 cm^2 (5. [illegible])	19	60 ± 18	75 ± 33 (24 - 144)	7782 ± 2172 (4675 - 11638)	46 ± 13 (28 - 69)	nd	nd	nd	nd
Estrone Sulfate									
E_2III TS									
13.5 cm^2 (2 [illegible])	18	692 ± 535	63 ± 41 (0 - 144)	79575 ± 62278 (13062 - 198143)	474 ± 371 (78 - 1179)	nd	nd	nd	nd
20 cm^2 (3.90 mg)	19	944 ± 547	81 ± 33 (48 - 168)	109739 ± 62358 (24681 - 253238)	653 ± 371 (147 - 1507)	nd	nd	nd	nd
27 cm^2 (5. [illegible] g)	19	1092 ± 557	82 ± 37 (24 - 144)	12,8043 ± 69579 (30546 - 275774)	762 ± 414 (182 - 1642)	nd	nd	nd	nd

a: Mean ±S.D. (range)
b: $AUC_{0\text{-}168}$ hr
c: nd = not determined

Table VIII. Summary of pharmacokinetic parameters (mean ± SD), corrected and uncorrected for baseline, for estradiol, estrone and estrone sulfate after two (7 day) applications of E_2III TS 13.5 cm^2, 20 cm^2 or 27 cm^2 patches to the lower abdomen.

Analyte Treatment Size (E_2 content/TS)	n	Unadjusted for Baseline[a] C_{max} (pg/mL)	Unadjusted for Baseline[a] t_{max} (h)	Unadjusted for Baseline[a] AUC_t[b] (pg·h/mL)	Unadjusted for Baseline[a] C_{avg} (pg/mL)	Baseline Adjusted[a] C_{max} (pg/mL)	Baseline Adjusted[a] t_{max} (h)	Baseline Adjusted[a] AUC_t[b] (pg·h/mL)	Baseline Adjusted[a] C_{avg} (pg/mL)
		Second Application (Week 2)							
Estradiol									
E_2III TS									
13.5 cm^2 (2 — mg)	18	56 ± 35	20 ± 16 (12 - 72)	6279 ± 4839 (2384 - 22462)	37 ± 29 (14 - 134)	47 ± 26	20 ± 16 (12 - 72)	4649 ± 2844 *1878 - 13270)	28 ± 17 (11 - 79)
20 cm^2 (3.90 mg)	19	87 ± 76	20 ± 21 (12 - 96)	6,963 ± 3,423 (2285 - 16632)	41 ± 20 (14 - 99)	81 ± 77	20 ± 21 (12 - 96)	5927 ± 3696 (794 - 15952)	35 ± 22 (5 - 95)
27 cm^2 (5. — mg)	19	103 ± 40	30 ± 36 (12 - 168)	10115 ± 4630 (6079 - 25242)	60 ± 28 (36 - 150)	98 ± 40	30 ± 36 (12 - 168)	9180 ± 4802 (3264 - 24318)	55 ± 29 19 - 145
Estrone									
E_2III TS									
13.5 cm^2 (2 — mg)	18	43 ± 26	66 ± 42 (12 - 168)	5679 ± 3070 (2914 - 16150)	34 ± 18 (17 - 96)	nd	nd	nd	nd
20 cm^2 (3.90 mg)	19	55 ± 27	44 ± 29 (12 - 120)	6503 ± 2300 (3596 - 11378)	39 ± 14 (21 - 68)	nd	nd	nd	nd
27 cm^2 (5. — mg)	19	63 ± 22	55 ± 42 (0 - 174)	7963 ± 3129 (4152 - 16758)	47 ± 19 (25 - 100)	nd	nd	nd	nd
Estrone Sulfate									
E_2III TS									
13.5 cm^2 (2 — mg)	18	725 ± 507	59 ± 56 (0 - 172)	8222 ± 62515 (14750 - 208693)	466 ± 372 (88 - 1242)	nd	nd	nd	nd
20 cm^2 (3.90 mg)	19	999 ± 725	44 ± 39 (12 - 172)	99863 ± 67554 (27053 - 231325)	594 ± 402 (161 - 1377)	nd	nd	nd	nd
27 cm^2 (5 — mg)	19	1088 ± 693	73 ± 58 (12 - 174)	123,030 ± 78,132 (21360 - 305368)	732 ± 465 (127 - 1818)	nd	nd	nd	nd

a: Mean ± SD (range).
b: $AUC_{0\text{-last h}}$.
c: nd = not determined.

Table IX. Mean ratios of pharmacokinetic parameters for estradiol, estrone and estrone sulfate after two (7 day) applications of E_2III TS 2.6 mg, 3.90 mg or 5. mg patch to the lower abdomen.

Analyte	Treatment Group (E_2 III TS Size)	Ratio (week 1 vs 2) C_{max}	AUC_{168}	AUC_T	C_{av}
Baseline-Adjusted Estradiol	2.6 mg, 13.5 cm^2	1.06	1.10	1.13	1.10
	3.90 mg, 20 cm^2	1.17	0.83	0.85	0.83
	5 mg, 27 cm^2	1.18	0.94	0.96	0.94
Estradiol	2.6 mg, 13.5 cm^2	1.04	0.94	0.99	0.94
	3.90 mg, 20 cm^2	1.16	0.86	0.90	0.86
	5 mg, 27 cm^2	1.17	0.95	0.99	0.95
Estrone	2.6 mg, 13.5 cm^2	0.96	1.00	1.11	1.00
	3.90 mg, 20 cm^2	0.99	0.96	1.05	0.96
	5 mg, 27 cm^2	1.04	1.01	1.10	1.01
Estrone Sulfate	2.6 mg, 13.5 cm^2	1.23	0.99	1.08	0.99
	3.90 mg, 20 cm^2	1.03	0.89	0.97	0.89
	5 mg, 27 cm^2	1.05	0.95	1.03	0.95

AUC_T = area truncated at the last measurable serum concentration at time T.

Reviewer Comments:

1. Steady state levels were achieved for estradiol, estrone and estrone sulfate following a single application of E_2III TS 13.5 cm^2, 20 cm^2 or 27 cm^2 transdermal systems.

2. Repeat dosing (x2) of E_2III TS 13.5 cm^2, 20 cm^2 or 27 cm^2 transdermal systems resulted in no accumulation of estradiol.

3. Increasing patch size (i.e., dose) resulted in a linear and proportional increase in blood exposure, demonstrating dose-proportionality.

2. Protein Binding

No protein binding studies were done for this NDA; however, published literature indicates that estradiol is primarily bound to sex hormone binding globulin (SHBG), and to a lesser extent, to albumin.

3. Bioavailability/Bioequivalence:

a) Absolute/Relative Bioavailability

The absolute bioavailability of estradiol was not determined for this NDA. The relative bioavailability of E_2III TS patches and the marketed product Estraderm was evaluated in 24 healthy postmenopausal women in Study Cygnus 329-03. In this Study, three patches (E_2III TS 5 mg, E_2III TS 2.6 mg and Estraderm) were applied to each subject in a

single dose, 3-way cross-over design. The results are listed in Table X. Additionally, the relative bioavailability of E_2III TS 5 [redacted] mg patches was determined following a single 7 day application to different body sites: abdomen, buttock, and hip in 36 postmenopausal women (Study 0802E1-127). The results are listed in Table XI. Figure 3 illustrates concentration vs. time profiles for estradiol following application of E_2III TS 5 [redacted] mg patches to three body sites.

Table X. Mean estradiol and estrone pharmacokinetic parameters (corrected and uncorrected for baseline) following a single dose application to the lower abdomen of E_2III TS 2.6 mg and 5 [redacted] mg patches and Estraderm.

Analyte / Treatment / Size (E_2 content/TS)	n	Unadjusted for Baseline[a] C_{max} (pg/mL)	Unadjusted for Baseline[a] t_{max} (h)	Unadjusted for Baseline[a] AUC_t[b] (pg·h/mL)	Unadjusted for Baseline[a] C_{avg} (pg/mL)	Baseline Adjusted[a] C_{max} (pg/mL)	Baseline Adjusted[a] t_{max} (h)	Baseline Adjusted[a] AUC_t[b] (pg·h/mL)	Baseline Adjusted[a] C_{avg} (pg/mL)
Estradiol									
E_2III TS									
13.5 cm^2 (2.6 mg)	24	75 ± 38 [redacted]	43 ± 44 (8 - 192)	7,734 ± 3,809 (2,98 - 18,166)	46 ± 23 (14 - 108)	69 ± 37 [redacted]	43 ± 44 (8 - 192)	6,802 ± 3,643 (1,855 - 16,990)	41 ± 22 (11.0 - 101.1)
27 cm^2 (5 [redacted] mg)	24	119 ± 78 [redacted]	42 ± 27 (6 - 108)	11,869 ± 5,534 (4,698 - 26,265)	71 ± 33 (28 - 156)	113 ± 76 [redacted]	42 ± 27 (6 - 108)	10,806 ± 5,181 (3,973 - 22,541)	64 ± 31 (23.6 - 134.2)
Estraderm									
20 cm^2 (8 mg)[c]	24	147 ± 91 [redacted]	72 ± 47 (4 - 144)	13,522 ± 7,986 (3,893 - 45,466)	80 ± 48 (23 - 271)	134 ± 68 [redacted]	72 ± 47 (4 - 144)	11,427 ± 4,471 (3,782 - 22,590)	68 ± 27 (22.5 - 134.5)
Climara[d]									
25 cm^2 (7.8 mg)	20	nd[e]	nd	nd	nd	156 ± 82 [redacted]	22 ± 14 (6 - 60)	15,004 ± 7,004 (5,007 - 36,045)	91 ± 42 (29.8 - 214.6)
Estrone									
E_2 III TS									
13.5 cm^2 (2.6 mg)	24	60 ± 22 [redacted]	77 ± 51 (24 - 192)	6,623 ± 1,901 (3,787 - 13,275)	39 ± 11 (23 - 79	37 ± 22 [redacted]	77 ± 51 (24 - 192)	2,141 ± 1,678 (635 - 8,238)	16 ± 10 (3.8 - 49.0)
27 cm^2 (5 [redacted] mg)	24	79 ± 29 [redacted]	66 ± 39 (24 - 168)	9,110 ± 3,002 (3,775 - 14,757)	54 ± 18 (22 - 88)	55 ± 30 [redacted]	66 ± 39 (24 - 168)	5,120 ± 2,852 (38 - 10,625)	31 ± 17 (0.2 - 63.2)
Estraderm									
20 cm^2 (8 mg)[c]	24	87 ± 25	92 ± 46 (36 - 156)	9,979 ± 2,847 (4,745 - 18,195)	59 ± 17 (28 - 108)	61 ± 21 [redacted]	92 ± 46 (36 - 156)	5,723 ± 3,347 (1,429 - 9,552)	34 ± 13 (8.5 - 56.9)

a. Mean ± SD (range).
b. $AUC_{t=168}$.
c. Two consecutive 3.5-day patches.
d. Study 329-04 used the same protocol as 329-03 and included 20 of the subjects from study 329-03 making it, essentially, a fourth non-randomized treatment group; only baseline-adjusted estradiol parameters were determined for Climara.
e. nd = not determined.

Table XI. Mean estradiol pharmacokinetic parameters (corrected for baseline) and relative bioavailability of E_2III TS 5.[illegible] mg patches following application to the lower abdomen, hip and buttock.

Treatment		C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{168} (pg•h/mL)	AUC_T (pg•h/mL)	AUC (pg•h/mL)	C_{avg} (pg/mL)
Applied to abdomen	Mean ±SD	100 ± 45	43 ± 30	7.8 ± 2.8	11033 ± 4103	11349 ± 4167	11406 ± 4175	68 ± 25
	CV, %	45.4	68.8	36.0	37.2	36.7	36.6	36.6
	Geometric Mean	91	34	7.4	10289	10659	10659	63
	Range	[illegible]	(12 - 144)	(3.6 - 19.0)	(5293 - 22664)	(5498 - 23283)	(5643 - 23385)	(34 - 139)
Applied to buttock	Mean ±SD	106 ± 51	34 ± 21	9.0 ± 4.9	10605 ± 4707	10855 ± 4788	10904 ± 4783	65 ± 28
	CV, %	48.2	60.3	54.8	44.4	44.1	43.9	43.9
	Geometric Mean	95	28	8.1	9564	9801	9856	59
	Range	[illegible]	(8 - 72)	(7.1 - 33.4)	(4211 - 21123)	(4410 - 21741)	(4577 - 21842)	(27 - 130)
Applied to hip	Mean ±SD	95 ± 40	41 ± 21	8.7 ± 2.9	10245 ± 4284	10514 ± 4353	10570 ± 4354	63 ± 26
	CV, %	41.9	50.6	33.7	41.8	41.4	41.2	41.2
	Geometric Mean	87	36	8.3	9399	9661	9720	58
	Range	[illegible]	(8 - 96)	(4.3 - 27.7)	(4770 - 20809)	(4984 - 21374)	(5260 - 21507)	(31 - 128)
p-Values from log-transformed analysis of variance for a three-period crossover design								
Sequence		.07	.57	-	.22	.23	.23	.28
Subject within Sequence		.001	.03	-	.001	.001	.001	.001
Treatment		.35	.19	-	.20	.18	.18	.18
Period		.53	.15	-	.11	.11	.10	.10
Statistical Power		.84	.27	-	.92	.92	.92	.92
Buttock vs. Abdomen								
Least Squares Mean Ratio (%)		105	83	-	93	92	92	92
90% CI		95-116	66-103	-	85-102	85-101	85-101	85-101
Hip vs. Abdomen								
Least Squares Mean Ratio (%)		96	104	-	91	91	91	91
90% CI		87-106	83-130	-	84-100	83-100	83-100	83-100

a: C_{max} = peak concentration; t_{max} = time peak concentration occurs; $t_{1/2}$ = terminal-phase elimination half-life; AUC = area under the concentration-time curve; C_{avg} = average concentration

AUC_T = area truncated at the last measurable serum concentration at time T.

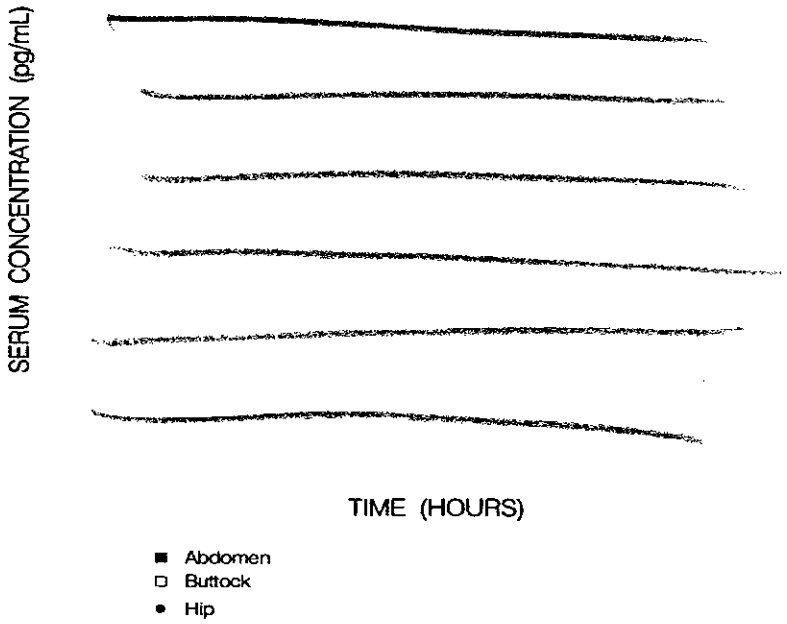


Figure 3. Serum estradiol concentration vs. time profiles following application of E_2III TS 5.26 mg patches to the lower abdomen, buttock and hip.

Reviewer Comments:

1. The bioavailability of estradiol in E_2III TS 5— mg appears to be similar (differences not statistically significant) to that of the Estraderm® patch. The bioavailability of E_2III TS 5 — mg patch is about 95% relative to the Estraderm® 8 mg patch (2 consecutive, 3.5 day applications).

2. The bioavailability of estradiol when the E_2III TS 5 — mg patch is applied to the lower abdomen is equivalent relative to the buttock and the hip as alternate application sites.

4. Estimation of Delivery Rate

Delivery rate was estimated by a combination of two methods: measuring the residual amount of estradiol in the patches following application to postmenopausal women, and by using a clearance rate of 1128 L/day for E_2 (literature value) in conjunction with the observed AUC. The residual analysis yielded an average E_2 daily delivery rate ±SD of 57 ± 21, 86 ± 29, and 114 ± 36 µg/day for the 13.5 cm^2, 20 cm^2 and 27 cm^2 patches, respectively. When an assumed E_2 clearance of 1128 L/24 hours (literature value) was used, the daily delivery rates calculated were 47 and 74 µg/day for the 13.5 cm^2 and 27 cm^2 patches, respectively. According to the sponsor, combining the two methods resulted in an estimated daily E_2 delivery rate of 50, 75, and 100 µg /day for the 13.5 cm^2, 20 cm^2 and 27 cm^2 patches, respectively. The residual analysis method is appropriate here because the total amount of estradiol delivered is > 13% of the amount of estradiol in unused patches.

5. Special Populations

No studies were performed in Special Populations.

6. Metabolism

The metabolism of estradiol is well defined and no new studies were needed.

7. Drug Interactions

No studies were done to evaluate drug interactions.

8. PK/PD Relationships and Population Pharmacokinetics

No formal population pharmacokinetic studies were done in this NDA. The sponsor did collect blood samples during Phase III studies, but only summary statistics of the blood levels of E_2, E_1 and E_1 sulfate were presented. Additionally, the sponsor evaluated the

relationship between E_2 levels and various covariates, i.e., weight, age, number of cigarettes smoked per day, and race. The sponsor's conclusion was that there was no correlation between serum E_2 levels and any of the covariates listed above.

Reviewer Comments:

1. The sponsor's conclusion with regard to lack of correlation between E_2 levels and weight is inconsistent with the results of previous studies. A likely explanation of the inconsistency lies in the fact that the sponsor excluded in the clinical trials all women who were beyond 30% of their ideal body weight. This resulted in a study population with a narrow range of body weight, which made it difficult to discern the effect of this covariate on E_2 levels.

VIII. Adhesion

Adherence of E_2III TS patches (13.5 cm^2, 20 cm^2, and 27 cm^2) was evaluated at the end of each cycle during the pivotal Phase III Clinical Trials. Adhesion was scored using a 4-point scale: 0 = no adhesion (patch fell off), 1 = 1% to 49% adhered, 2 = 50% to 89%, and 3 = 90% to 100% adhered. Of 1284 systems evaluated, 89% had adhesion of 90% to 100%. Less than 3% of the patients had a score of 0, where the patch fell off.

Reviewer Comments:

1. E_2III TS patches (13.5 cm^2, 20 cm^2, and 27 cm^2) appear to have acceptable adhesion properties.

IX. Labeling

The sponsor's proposed labeling is included in Attachment A.

Reviewer comment:

The recommended labeling changes are based in part on the Division's (DRUDP) draft guidance for estrogen labeling. The changes are listed below:

1. The **Clinical Pharmacology** section should be written according to following:

CLINICAL PHARMACOLOGY

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 500 μg 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.

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

Pharmacokinetics

TRADENAME produces mean serum concentrations of estradiol comparable with those produced by premenopausal women in the early follicular phase of the ovulatory cycle. The pharmacokinetics of TRADENAME were evaluated in more than 100 healthy postmenopausal women in six clinical pharmacokinetic studies.

Absorption

Transdermal administration of estradiol produces therapeutic serum concentrations of estradiol with lower circulating concentrations of estrone and estrone conjugates and requires smaller total doses than does oral estradiol therapy.

The average daily dose absorbed from TRADENAME was 4.3 ± 1.5 μg of estradiol per cm^2 active surface area, based on analyses of the residual estradiol content in TRADENAME systems worn over a continuous 7-day interval in postmenopausal women. The 13.5 cm^2, 20 cm^2, and 27 cm^2 TRADENAME systems deliver approximately 0.050mg, 0.075mg, and 0.10mg of estradiol per day.

In a multiple-dose, randomized, crossover study, 28 postmenopausal women were treated for 2 weeks with two of the three doses of TRADENAME (0.050mg, 0.075mg, or 0.10mg). Each transdermal system was worn for 1 week (2 applications), with a 7- to 10-day washout period between doses. TRADENAME was applied to two sites on the abdomen. The pharmacokinetic parameters of serum estradiol are shown in Table 1 (unadjusted for baseline).

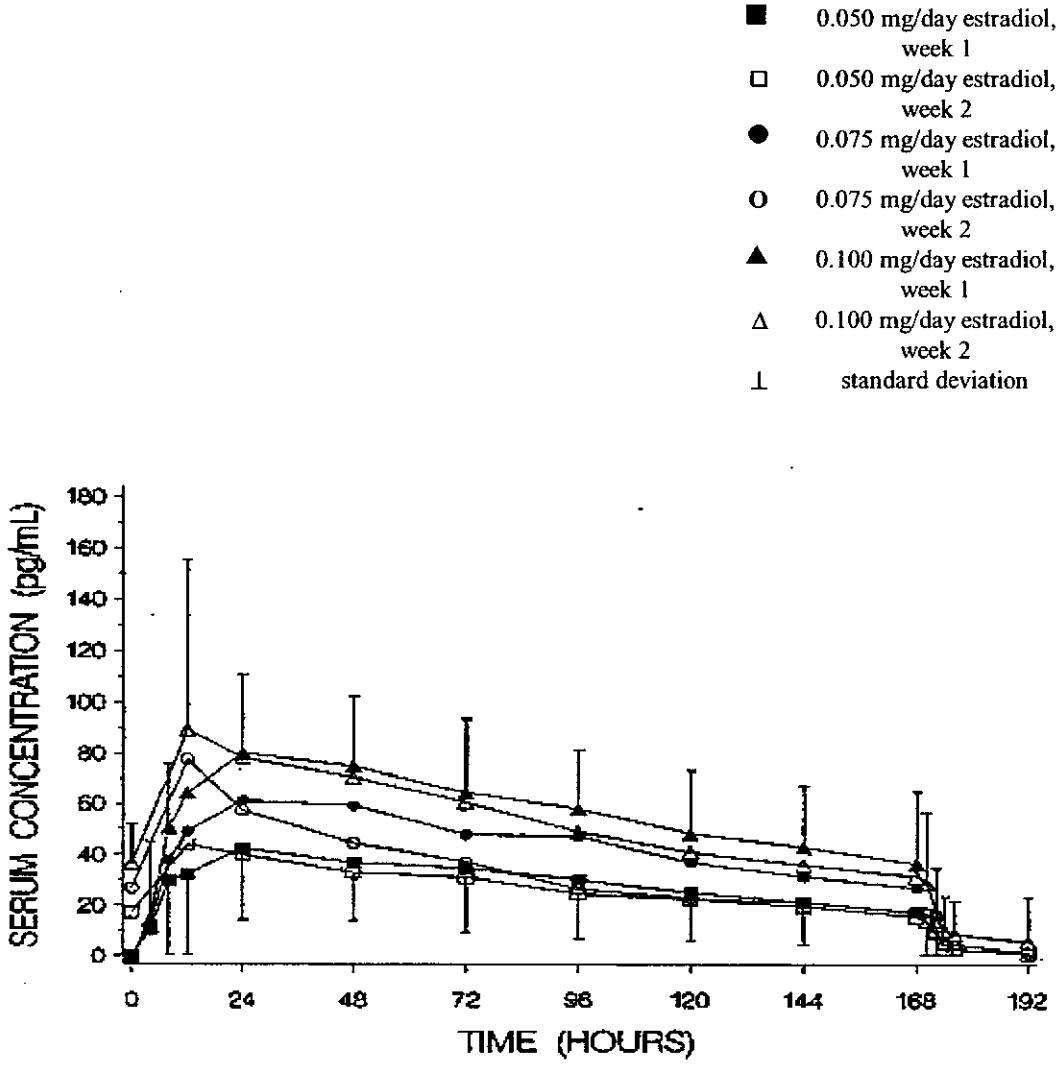
Table 1. PHARMACOKINETIC PARAMETERS OF TRADENAME, SERUM ESTRADIOL UNADJUSTED FOR BASELINE (MEAN ± SD)

Treatment (mg/day)	Application Site	Week	C_{max} (pg/mL)	C_{avg} (pg/mL)	C_{min}[a] (pg/mL)
0.050	Abdomen	1	57 ±36	39 ± 23	26 ± 15
		2	56 ±34	37 ± 29	25 ± 24
0.075	Abdomen	1	72 ±42	50 ± 29	33 ± 16
		2	87 ±76	41 ± 20	23 ± 11
0.100	Abdomen	1	91 ±32	62 ± 14	42 ± 13
		2	103 ±40	60 ± 28	37 ± 33
0.100	Abdomen	1	105 ±45	75 ± 25	-
	Hip	1	100 ±40	70 ± 26	-
	Buttocks	1	112 ±51	72 ± 28	-

a: C_{min} = concentration at time of TRADENAME removal.

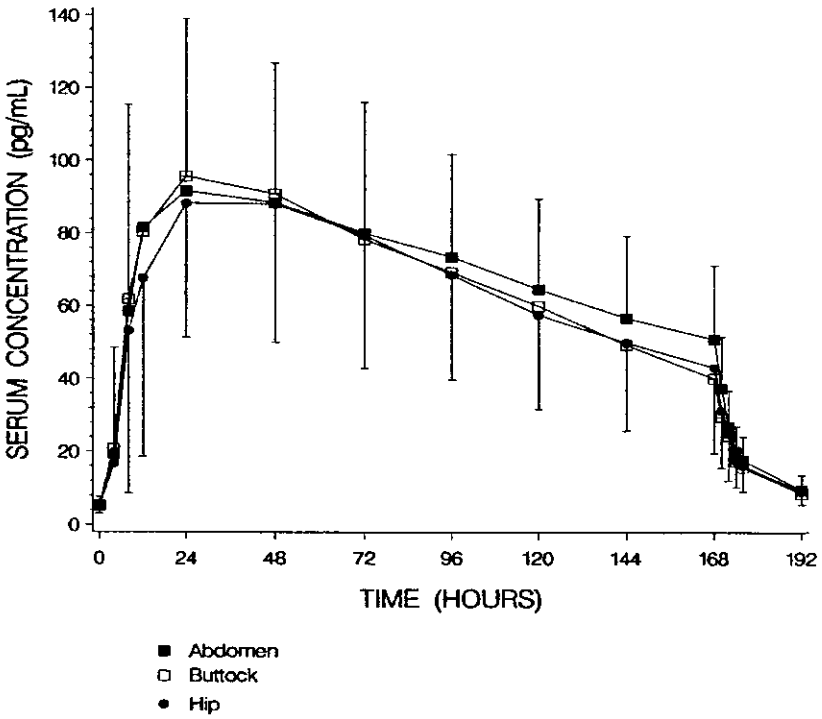
The mean steady state serum estradiol concentration profiles with the application of TRADENAME patches delivering 0.050, 0.075, and 0.100 mg/day are shown in Figure 1.

Figure 1. MEAN SERUM ESTRADIOL CONCENTRATIONS ADJUSTED FOR BASELINE LEVELS IN 28 HEALTHY POSTMENOPAUSAL WOMEN RECEIVING TRADENAME



The relative bioavailability of TRADENAME at three different application sites was examined in a single-dose (0.100 mg/day) study with 36 healthy, hysterectomized, postmenopausal women. In this randomized, crossover study, patches were applied to the lower abdomen, the outer aspect of the hip, and the upper quadrant of the buttock. The pharmacokinetic parameters of serum estradiol (unadjusted for baseline levels) are shown in Table 1 and the mean serum concentration profiles are shown in Figure 2. There were no significant differences in pharmacokinetic parameters among the three application sites.

Figure 2. MEAN SERUM ESTRADIOL CONCENTRATIONS IN 36 HEALTHY POSTMENOPAUSAL WOMEN RECEIVING ONE 7-DAY APPLICATION OF TRADENAME (0.100 mg/day) APPLIED TO ABDOMEN, HIP, OR BUTTOCK



Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone-binding globulin (SHBG), and to a lesser degree to albumin.

Metabolism

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 estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation 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 estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Because transdermally absorbed estradiol is not subject to first-pass liver metabolism, the ratio of serum concentrations of estradiol to either of its major metabolites, estrone or estrone sulfate, is significantly greater than that seen for the oral route of administration. The mean ratio of estradiol to estrone was 1.3 for TRADENAME. The clinical relevance of the estradiol to estrone ratio is unknown.

The serum concentrations of estradiol and its metabolites were measured after 12 weeks of therapy (Table 2).

Table 2. SERUM CONCENTRATIONS OF ESTRADIOL AND ITS METABOLITES AFTER 12 WEEKS OF THERAPY WITH TRADENAME (pg/mL)

	0.050 mg/day		0.075 mg/day		0.100 mg/day	
Hormone	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Estradiol	58	41 ± 26	66	47 ± 36	70	67 ± 55
Estrone	58	41 ± 32	65	44 ± 19	69	52 ± 32
Estrone sulfate	58	592 ± 597	65	740 ± 523	69	850 ± 725

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Because estradiol has a short elimination half-life, transdermal administration of estradiol allows for rapid decline in blood levels after TRADENAME is removed.

Special Populations

TRADENAME has been studied only in postmenopausal women.

Race: No formal studies were done to evaluate the effect of race on the disposition of TRADENAME

Hepatic Insufficiency: No formal studies were done to evaluate the effect of hepatic disease on the disposition of TRADENAME.

Renal Insufficiency: No formal studies were done to evaluate the effect of renal disease on the disposition of TRADENAME.

Drug-Drug Interactions: No specific drug interaction studies have been conducted using TRADENAME.

Adhesion

In two 12-week, double-blind, placebo-controlled studies, a total of 442 patients received 0.050, 0.075, or 0.100 mg/day TRADENAME. The percent adhesion of the patch at weeks 4, 8, and 12 was assessed. Among the TRADENAME recipients, 88% to 90% of the patches observed were 90 to 100% adherent. One patient in the X mg Tradename arm discontinued therapy during these clinical trials because of adhesion failure. In these trials, 4.1% (71/1730), 3.9% (74/1883) and 4.6% (83/1814) of the 0.050, 0.075 and 0.100 mg patches, respectively, required replacement due to inadequate adhesion.

Attachment A

NDA 21-048

Proposed Labeling

24 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Attachment B

NDA 21-048

Study Summaries

SYNOPSIS

TITLE: A SINGLE-DOSE, RELATIVE BIOAVAILABILITY STUDY OF A 7-DAY 17ß-ESTRADIOL TRANSDERMAL DELIVERY SYSTEM (E_2 III TS) AT THREE DIFFERENT APPLICATION SITES IN HEALTHY, HYSTERECTOMIZED, POSTMENOPAUSAL WOMEN

Protocol No.: 0802E1-127-US

INVESTIGATORS: [redacted]

STUDY CENTERS: [redacted]

STUDY PERIOD : CLINICAL PHASE: 1
(DATE OF FIRST ENROLLMENT) September 1997
(DATE OF LAST COMPLETION) November 1997

OBJECTIVES: The primary objective was to determine the relative bioavailability of 17ß-estradiol delivered transdermally from three different sites on healthy, hysterectomized, postmenopausal women. A secondary objective was to evaluate any evidence of topical irritation in the area surrounding the transdermal delivery system (TS) application site.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Generally healthy, hysterectomized, postmenopausal women or hysterectomized women who had had a bilateral oophorectomy performed because of benign pathologic findings at least 6 months before the study start were eligible for the study if they were between the ages of 35 and 65, inclusive. Subjects without a postoperative report of hysterectomy must have had the absence of uterus and cervix verified by examination by a board-certified gynecologist. The serum follicle stimulating hormone (FSH) concentration had to be greater than 50 IU/L and estradiol concentration had to be less than 73 pmol/L.

NUMBER OF SUBJECTS (PLANNED, ENROLLED, COMPLETED, ANALYZED): 36 planned, 36 enrolled, 36 completed, 36 analyzed.

DURATION OF TREATMENT: Subjects were to participate for a total of approximately 33 days, including three 2½-day 2-night inpatient stays, three 1½-day 1-night inpatient stays, and 21 outpatient visits. Seven-day treatment periods were to be separated by 7 to 10-day washout intervals.

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: Each subject received three treatments with 17β-estradiol (5 — mg delivered by a 27 cm^2 TS; E_2 III TS) applied to different sites according to a predetermined randomization schedule. Treatment A was applied to the lower abdomen, treatment B to the upper quadrant of the buttock, and treatment C to the outer aspect of the hip. The batch number was 01346.

PHARMACOKINETIC/PHARMACODYNAMIC AND STATISTICAL METHODS: For each subject, the serum concentration-time profile was analyzed by using the model-independent method. Statistical comparisons of the data were made by using a three-treatment, three-period crossover analysis of variance (ANOVA). Log-transformed data were used for statistical comparisons.

SAFETY ASSESSMENT METHODS: Safety assessments were based on reports of adverse events and results of routine physical examinations and laboratory determinations. The routine physical examinations included recording of body weight, blood pressure, and heart rate.

PHARMACOKINETIC RESULTS: The following table summarizes the pharmacokinetic profile of 17β-estradiol in serum unadjusted for baseline levels following single applications of the TSs at three different application sites.

PHARMACOKINETIC PROFILE OF SERUM 17β-ESTRADIOL

Treatment[a]	C_{max}[b] (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{144} (pg•h/mL)	AUC (pg•h/mL)	C_{avg} (pg/mL)
A	105 ± 45	43 ± 30	11.8 ± 5.1	11904 ± 4152	12527 ± 4250	75 ± 25
	96	34	10.8	11207	11835	70
B	112 ± 51	34 ± 21	13.1 ± 5.8	11506 ± 4704	12059 ± 4787	72 ± 28
	101	28	12.1	10557	11120	66
C	100 ± 40	41 ± 21	13.1 ± 5.6	11127 ± 4299	11707 ± 4368	70 ± 26
	92	36	12.1	10342	10935	65
Buttock vs. Abdomen						
Geometric Mean Ratio (%)	105	83	-	94	94	94
90% confidence interval	95-116	66-103	-	87-102	87-102	87-102
Hip vs. Abdomen						
Geometric Mean Ratio (%)	96	104	-	92	92	92
90% confidence interval.	87-106	83-130	-	85-100	85-100	85-100

a : A = Applied to lower abdomen
B = Applied to upper quadrant of the buttock
C = Applied to outer aspect of the hip

b: Mean ± SD
Geometric Mean

CONCLUSION: The TSs, when applied to the lower abdomen, the upper quadrant of the buttock, and the outer aspect of the hip, were bioequivalent for all estradiol, estrone, and baseline-adjusted estradiol pharmacokinetic parameters except time to peak concentration, with no statistically significant difference among any of the parameters.

DATE OF THE REPORT: 15 Sep 1998

Reviewer's Comments:

1. Reviewer is in agreement with the sponsor's conclusions.

SYNOPSIS

TITLE: A MULTIPLE-DOSE, DOSE PROPORTIONALITY STUDY OF A 17β-ESTRADIOL TRANSDERMAL SYSTEM IN HEALTHY POSTMENOPAUSAL WOMEN: FINAL REPORT

Protocol No.: 0802E1-106-US

INVESTIGATORS: [redacted] (10605)

STUDY PERIOD : 7/96 to 9/96

CLINICAL PHASE: I

OBJECTIVE: The objective of this open-label, inpatient and outpatient, three-treatment, two-period, balanced, randomized, incomplete block design study was to examine the steady-state pharmacokinetics of three different sizes of the 17β-estradiol transdermal system (E_2 III TS) in healthy postmenopausal women.

MAIN CRITERIA FOR INCLUSION: Healthy, ambulatory, postmenopausal women between the ages of 45 and 65 years of age, and within 20% of the ideal weight for their height were eligible for the study. They could be naturally postmenopausal or could have undergone a bilateral oophorectomy. Subjects were to have endogenous 17β-estradiol levels less than 73.4 pmol/L (20 pg/mL) and follicle-stimulating hormone levels greater than 50 IU/L. Subjects were to have no significant findings at the pretreatment physical examination and a high probability for compliance and completion of the study.

NUMBER OF SUBJECTS (PLANNED, ENROLLED, ANALYZED):
24 planned, 30 enrolled, 28 completed, 28 analyzed.

DURATION OF TREATMENT: Each subject participated in the study for approximately 44 days, which included two 17-day study periods separated by a washout period of 7 to 10 days. Each study period consisted of two 1½-day inpatient stays and 14 outpatient visits over 17 days.

STUDY DRUG, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER: 17β-estradiol, transdermal system (TS), 13.5, 20, and 27 cm^2 containing 2 [redacted] 3.9, and 5.[redacted] mg of 17β-estradiol, respectively. Lot numbers for the three TS sizes listed above were 491858/00665, 491859A/00685, and 491860A/00705, respectively.

PHARMACOKINETIC AND STATISTICAL METHODS: Serum concentrations of 17β-estradiol, estrone, and estrone sulfate were determined by radioimmunoassay. Estimates of pharmacokinetic parameters were obtained by using model-independent methods, and the three treatment groups were compared by using a two-period balanced incomplete block design ANOVA.

PHARMACOKINETIC RESULTS: The following table summarizes the pharmacokinetic parameters of baseline-adjusted 17β-estradiol in serum following single and multiple applications of three sizes of a E_2 III TS.

Treatment	Week 1		Week 2	
	C_{max} (pg/mL)	C_{avg} (pg/mL)	C_{max} (pg/mL)	C_{avg} (pg/mL)
A[a]	47 ± 29[b]	29 ± 19	47 ± 26	28 ± 17
	(19 - 128)	(10 - 75)	(24 - 137)	(11 - 79)
B	66 ± 43	44 ± 29	81 ± 77	35 ± 22
	(34 - 218)	(19 - 146)	(27 - 370)	(5 - 95)
C	85 ± 32	57 ± 15	98 ± 40	55 ± 29
	(49 - 186)	(33 - 93)	(57 - 183)	(19 - 145)

a: A = 17β-Estradiol (2.6 g), 13.5 cm^2
B = 17β-Estradiol (3.90 mg), 20 cm^2
C = 17β-Estradiol (5.— mg), 27 cm^2
b: Values are mean ± SD and (range)

The mean proportionality ratios for peak concentration (C_{max}) at week 1 (1.0: 1.5: 2.1) and week 2 (1.0: 1.5: 2.0) and for AUC_{168} at week 1 (1.0: 1.5: 2.2) and week 2 (1.0: 1.4: 2.2) were very similar to the expected ratios of 1.0: 1.5: 2.0 for the 2.6 , 3.90-, and 5 ~ mg 17β-estradiol doses, respectively, demonstrating linear dose proportionality. Without adjustment of serum 17β-estradiol for baseline levels, the TSs produced week 2 C_{max} values of 56 ± 32, 87 ± 76, and 103 ± 40 pg/mL and week 2 average concentration (C_{avg}) values of 37 ± 29, 41 ± 20, and 60 ± 28 pg/mL for the 13.5, 20, and 27 cm^2 TSs, respectively. In general, there appeared to be little accumulation from week 1 to week 2 for 17β-estradiol, estrone, or estrone sulfate. Residual analysis in the TS determined a daily delivery rate of 57 ± 21, 86 ± 29, and 114 ± 36 µg/day for the 13.5, 20, and 27 cm^2 TS, respectively.

CONCLUSION: Baseline-adjusted 17β-estradiol C_{max}, AUC_{168}, AUC_T and C_{avg} increased proportionally with increasing TS size. In general, there appeared to be little or no accumulation from week 1 to week 2 for any of the analytes.

DATE OF THE REPORT: 20 Jan 1998

Reviewer's Comments:

2. Reviewer is in agreement with the sponsor's conclusions.