

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-847

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA: 20-847

Drug: Esclim® (Estradiol Transdermal System)

Sponsor: Fournier Labs

Date of Submission: 08/07/97, 10/23/98, 10/24/97
10/27/97, and 11/14/97

Type of Submission: Original NDA and 4 amendments

Reviewer: Venkateswar R. Jarugula, Ph.D.

I. SYNOPSIS

Fournier Labs submitted NDA 20-847 for Esclim® (Estradiol Transdermal System) on 08/07/97. The proposed indications for this product are treatment of moderate to severe vasomotor symptoms associated with the menopause, treatment of vulval and vaginal atrophy, and treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. The sponsor is seeking approval for five sizes of patches, 11, 16.5, 22, 33, and 44 cm² containing 5, 7.5, 10, 15 and 20 mg of estradiol which are designed to deliver 25, 37.5, 50, 75, and 100 µg/day, respectively. The labeling indicates that the Esclim® system should be applied twice weekly (first patch for 3 days followed by second patch for 4 days in a week).

Thirteen clinical pharmacology studies were submitted to support the Clinical Pharmacology and Biopharmaceutics requirements of the NDA. In these studies, the relative bioavailability, single and multiple dose pharmacokinetics, dose proportionality, effect of site of application, influence of shelf-life on estradiol's bioavailability and the adhesion performance of the transdermal systems were investigated. In addition, blood samples for the measurement of steady-state estradiol levels were collected in the clinical trial conducted in the United States (No. C TS 17 93 01). During the early part of the drug development, four preliminary studies were conducted to determine the optimum formulation, the choice of manufacturing process and reproducibility of the manufacturing process. These four studies are not considered relevant to evaluation of the pharmacokinetics or bioavailability of Esclim because these studies were exploratory in nature.

In response to the FDA's request for additional information, on 10/23/97, 10/24/97, 10/27/97 and 11/14/97 the sponsor submitted four amendments to the NDA which

included a revised summary for Human PK and Bioavailability section of the NDA, an electronic version of the summary section, and individual study summaries.

The overall results submitted in the Human PK and Bioavailability section of the NDA showed that:

1. The bioavailability of serum estradiol following the application Esclim is very similar to the commercial patches: Estraderm[®] and Vivelle[®].
2. The pharmacokinetics of estradiol is dose proportional following application of Esclim patches with sizes: 11, 22 and 44 cm².
3. Steady-state serum estradiol and estrone levels were obtained within two weeks after the multiple dosing with Esclim.
4. The sites of application, iliac fossa, femoral triangle and upper arm were not bioequivalent to the buttock (clinical site). Application of Esclim[®] 50 patch to the abdomen resulted in 18% lower baseline corrected mean AUC while upper arm and thigh resulted in 15% and 16% higher baseline corrected mean AUC, respectively, in comparison to the buttock.
5. The adhesion performance and the skin tolerability of Esclim patches in the clinical trials were found to be comparable to the commercial patches, Estraderm and Vivelle.
6. The average transdermal delivery rates of Esclim 25, 50 and 100 calculated from the serum estradiol levels and a clearance value of 1600 L/day, are close to their nominal delivery rates while those calculated based on the residual drug concentration in the used patches are much higher.

II. RECOMMENDATION

NDA 20-847 submitted by Fournier Laboratories has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. The pharmacokinetics and bioavailability of estradiol were adequately characterized following the single and multiple dose applications of Esclim patch and from the Clinical Pharmacology and Biopharmaceutics perspective, NDA 20-847 is acceptable. However, the following deficiencies or comments are noted:

Reviewer Comments:

1. According to the agency's 80-125% bioequivalence criteria, the sites of application, iliac fossa (abdomen), femoral triangle and upper arm were not bioequivalent to the reference site, buttock. Although from the statistical perspective, the application sites were not bioequivalent to the reference site, based on estradiol plasma levels and

clinical experience for the proposed indications, the clinical division (HFD-580) decided that the upper arm, thigh and buttock sites can be approved. But the abdomen site is not acceptable.

2. In a telecon dated 6/3/98, it was conveyed to the sponsor that additional clinical data are needed to approve the abdomen as site of application. In response, the sponsor stated that they are not willing to do any additional clinical studies and hence they agreed to withdraw the abdomen site from the labeling.
3. The sponsor's request for a waiver of the requirement of the submission of bioavailability data for the approval of the two intermediate sizes, 16.5 and 33 cm² is acceptable. This decision is based on the *in vitro* comparative release data and the pharmacokinetic/clinical data bracketing the lower and higher doses.
4. The sponsor's proposed *in vitro* release method and specifications are acceptable provided the release specification are changed as follows:

minutes	%
minutes	%
minutes	%

Please convey the Recommendation and Reviewer Comments 3 and 4 to the sponsor as appropriate.

ISI 6/30/98

Venkateswar R. Jarugula, Ph.D.
Division of Pharmaceutical Evaluation II

Rough draft initialed by Angelica Dorantes, Ph.D. AD 6/22/98

Final draft initialed by Angelica Dorantes, Ph.D. ISI 6/30/98

cc: NDA 20-847, HFD-580 (Safran, Moore), HFD-870 (M.Chen, Dorantes, Jarugula), CDR (B.Murphy for Drug).

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III. BACKGROUND

Estradiol is the principal form of estrogens secreted by the granulosa cells of the developing follicle in the ovaries of ovulating women and is responsible for the development and maintenance of reproductive system and of the secondary sexual characteristics in women. After natural or surgical menopause, ovarian hormonal secretion is depleted, leading to reduced circulating estradiol levels. The decline in ovarian function at menopause is associated with several distressing clinical symptoms such as "hot flushes", night sweats, and genito-urinary atrophy. Over time, menopause increases women's susceptibility to osteoporosis.

Hormone replacement therapy with both an estrogen and progestin is recommended for most postmenopausal women with a uterus. For those women who have undergone a hysterectomy, estrogen alone is more commonly used because endometrial carcinoma is not a concern. Currently estrogen replacement therapy is achieved by oral, or transdermal administration of natural or conjugated estrogens or through percutaneous devices delivering 17 β -estradiol. Orally administered estradiol is subject to "first pass" metabolism in intestinal mucosa and liver to form estrone and glucuronide and sulfate conjugates. Transdermal administration of estradiol has the advantage of avoiding the first pass metabolism thereby maintaining the physiological ratio of estrone/estradiol and produces constant serum estradiol levels over long periods of time.

Fournier Laboratories has developed a new matrix type of transdermal delivery system for estradiol called Esclim (TS 17) with the intentions of improving skin tolerability, cosmetic appearance and adhesion. The following five transdermal systems (to be applied twice a week) were developed:

TS 17 25:	11 cm ² /5mg estradiol, delivering 25 μ g/day
TS 17 37.5:	16.5 cm ² /7.5 mg estradiol, delivering 37.5 μ g/day
TS 17 50:	22 cm ² /10 mg estradiol, delivering 50 μ g/day
TS 17 75:	33 cm ² /15 mg estradiol, delivering 75 μ g/day
TS 17 100:	44 cm ² /20 mg estradiol, delivering 100 μ g/day

I. FORMULATION

The formulation used in the clinical trials is same as the to-be marketed formulation and the manufacturing site for both formulations is the same. The composition of the final formulation used in clinical trials as well as the commercial formulation is summarized in Table 1.

Table 1. Composition of the clinical trials and to-be marketed formulations.

Component	Quantity per Batch		
	Proposed Commercial Product	Theoretical % (w/w)	Clinical Study Batches
✓ Estradiol	4.31 kg ^a	1.8	kg ^b
✓ EVA-high	kg		kg
✓ EVA-low	kg		kg
✓ Ethylcellulose	kg		kg
✓ Octyldodecanol	kg		kg
✓ Dipropylene glycol ^c	kg		kg
	kg		kg
active mass batch total	kg^a		kg

^aAdjusted according to estradiol potency.

^bAnhydrous basis.

^cReduced during drying.

^dRemoved during drying.

^eInert gas.

^fThe protective film is slightly larger than the transdermal system in order to facilitate handling.

Reviewer Comment

Since, the composition of the clinical trials formulation and to-be marketed formulation is the same and there is only 3-fold scale up in the commercial batch, no bioequivalence study is required.

V. *In Vitro* Release Testing:

The proposed dissolution method and the specifications are summarized below:

Apparatus:

Dissolution Medium:

Volume (25 and 37.5 µg/day):

Volume (50, 75 and 100 µg/day):

Temperature:

Speed of Rotation:

Sample Pull Times:
 Sample Volume:
 Units Tested:

Table 2: Proposed *In Vitro* release specifications:

Dosage Strength ($\mu\text{g}/\text{day}$)	Patch Size (cm^2)	Proposed Dissolution Specification		
		% Dissolved		
		min	min	min
25	11	% of label content	% of label content	% of label content
37.5	16.5			
50	22			
75	33			
100	44			

Table 3. Mean *in vitro* release data from clinical pharmacology and clinical trials:

%Dissolved at 30 min	% Dissolved at 180 min	% Dissolved at 480 min
29 \pm 2	75 \pm 4	96 \pm 3

The individual *in vitro* release data for these studies is included in Appendix II.

Reviewer Comments:

- Based on the mean dissolution data of batches from clinical pharmacology studies and clinical trials, it is recommended that the release specifications be changed as follows:

minutes	% of label content
minutes	% of label content
minutes	% of label content.

- It should be noted that during the early part of the development of this drug product, the sponsor used a different dissolution method with rotating paddle over disk). However, comparative dissolution data provided in the NDA) showed that the *in vitro* release of estradiol from Esclim patches is similar (data not shown) between the earlier method and the proposed method

VI. BIOWAIVER REQUEST FOR SIZES 16.5 AND 33 CM²

For the approval of the intermediate size patches, 16.5 and 33 cm², the sponsor requested a waiver for the requirement of the submission of bioavailability data for these patches. To support the biowaiver request, comparative dissolution data were submitted. Figure 1

illustrates the comparative in vitro release profiles for the 11, 16.5, 22, 33 and 44 cm² patch sizes.

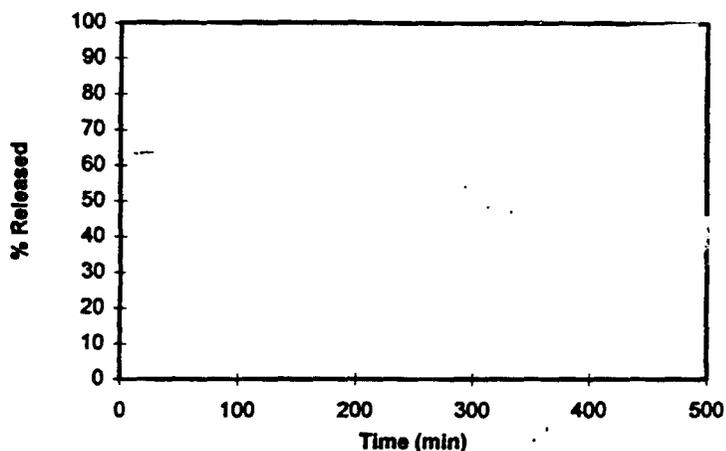


Figure 1. Comparison of in vitro release profiles for all patch sizes available.

Reviewer Comment:

In vitro release data for the intermediate sizes (16.5 and 30 cm²) are similar to that obtained for the sizes (11, 22 and 44 cm²) used in clinical studies. Therefore, the sponsor's request for a waiver for the submission of bioequivalence data for the 16.5 and 30 cm² can be granted.

VII. *In Vitro* Skin Permeation:

No studies were conducted to evaluate *in vitro* skin permeation of the Esclim[®] transdermal system due to the sponsor's inability to obtain sufficient human cadaver skin. Sponsor stated that a recent agreement with a new supplier should enable them to conduct *in vitro* skin permeation studies and when these studies are completed, the data would be submitted to the agency.

VIII. ANALYTICAL METHODOLOGY

Reviewer Comment:

The assay validation data for the measurement of serum estradiol, estrone and estrone sulfate appears to be appropriate and are acceptable.

IX. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Table 7 includes a list of the clinical pharmacology and biopharmaceutic studies submitted to support the NDA.

Table 7. List of pharmacokinetic studies submitted.

Study No.	Study Design	Objective	#enrolled/ completed
Preliminary studies			
K VP005 90 01	open-label randomized, two application for 7 days, four-way crossover	compare plasma levels of 3 prototype formulation with estraderm	8/8
K VP005 90 02	open-label randomized, two applications for 7 days, four-way crossover	optimum loading dose in the formulation in comparison to Estraderm	8/8
K TS 17 91 01	randomized crossover, single application	choice of manufacturing process	13/12
Pivotal studies			
K TS 91 02	randomized crossover, single application	Effect of scale-up on bioavailability	9/9
K POE 91 01	Randomized, single application, four-way crossover	Dose proportionality of three patch sizes 10, 20 and 40 cm ²) and comparison with Estraderm 50	25/24
KH TS 17 92 01	Randomized crossover, single application for 3 days	Effect of site of application on the bioavailability of estradiol	12/12
KH TS 17 92 02	Randomized crossover, single application for 4 days	Effect of age of batch on the bioavailability	6/6
K TS 17 93 01	Randomized two-way crossover, single application for 7 days	Relative bioavailability of Esclim 50 with System [®] 50	12/12
K TS 17 93 02	Multiple dose, two application per week for 3 weeks	Steady-state PK of Esclim 50	19/18
K TS 17 94 02	Randomized two-way crossover, single application for 4 days	Relative BA of Esclim 25 with System 50	19/18
K TS 17 95 01	Multiple dose, two application per week for 3 weeks	Steady-state PK of Esclim 25	12/12
K TS 17 96 02	Randomized 3-way crossover, single application for 4 days	Relative BA of Esclim 50 and 100 with Vivel [®] 50	24/24
K TS 17 96 03	Randomized crossover, multiple dose for 3 weeks	Multiple dose PK of Esclim 25 in comparison with Estraderm 25	12/12
Clinical studies			
C TS 17 93 01	Randomized, placebo-controlled double-blind, parallel group for 12 weeks	Phase III safety and efficacy of Esclim 25, 50 and 100, one blood sample at weeks 5, 9 and 12	199/196

Preliminary Studies: K VP005 90 01, K VP005 90 02, K TS 17 91 01 and K TS 17 91 02 were conducted during the early part of the drug development process. The results of these 4 preliminary studies helped the sponsor in the selection of final formulation and manufacturing conditions.

A. Bioavailability

The bioavailability of the Esclim patches was determined in comparison to the commercial patches Vivelle[®], Estraderm[®] and System[®] in studies K TS 17 96 02, K TS 17 96 03, and K TS 17 93 01, respectively.

Esclim[®] Vs. Vivelle[®]: In study K TS 17 96 02, the bioavailability of Esclim[®]-50 and Esclim[®]-100 were compared with that of Vivelle[®]-50, a commercial matrix patch marketed by Ciba Geigy, in 24 postmenopausal women following single application of each patch for 4-days. The serum E₂ levels and the pharmacokinetic parameters are given in Figure 2 and Table 8, respectively.

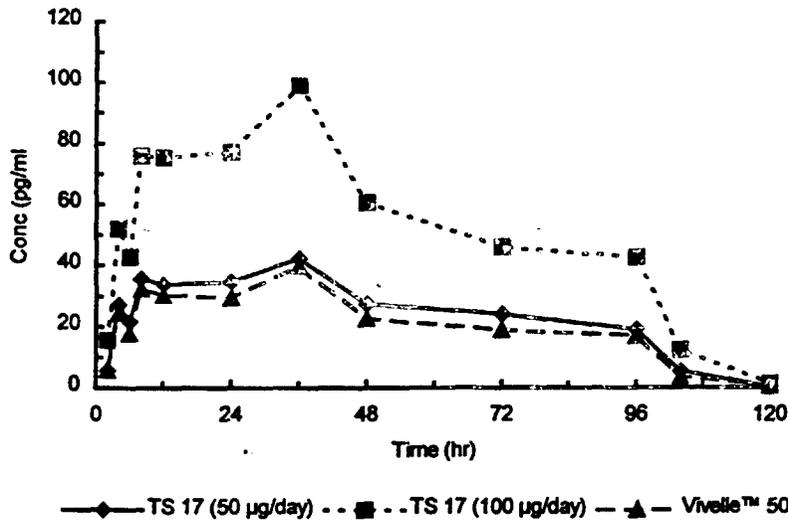


Figure 2. Mean baseline corrected serum estradiol concentration Vs time profiles following single application for 4 days each of Esclim[®] 50, Esclim[®] 100 and Vivelle™ 50.

Table 8. Mean pharmacokinetic parameters of serum estradiol following single application for 4 days each of Esclim[®]-50, Esclim[®]-100 and Vivelle[™]-50.

Parameter	Esclim (50 µg/day)	Esclim (100 µg/day)	Vivelle (50 µg/day)
Baseline unadjusted:			
C _{max} (pg/ml)	61.6 ± 33.0	124 ± 66.4	56.3 ± 35.9
T _{max} (hr)	27.5 ± 15.6	27.0 ± 12.7	30.1 ± 18.5
AUC ₍₀₋₁₂₀₎ (pg.hr/ml)	3707 ± 1966	7106 ± 4148	3247 ± 1763
Baseline adjusted:			
C _{max} (pg/ml)	55.0 ± 32.7	116.8 ± 66.1	49.4 ± 35.7
T _{max} (hr)	27.5 ± 15.6	27.0 ± 12.7	30.1 ± 18.5
AUC ₍₀₋₁₂₀₎ (pg.hr/ml)	2982 ± 1903	6342 ± 4082	2535 ± 1691

Esclim[®] Vs. Estraderm[®]: In Study K TS 17 96 03, the bioavailability of Esclim[®]-25 was evaluated in comparison to that of Estraderm[®]-25 in 12 healthy postmenopausal women following three week multiple application. Each week, two successive patches were applied to the buttocks, one for 3 days, and second patch for 4 days (second patch was applied immediately following the removal of first patch). Serum E₂ levels were measured at baseline and at fixed time intervals during the third week of each treatment. The mean serum E₂ levels and the mean pharmacokinetic parameters are listed in Figure 3 and Table 9.

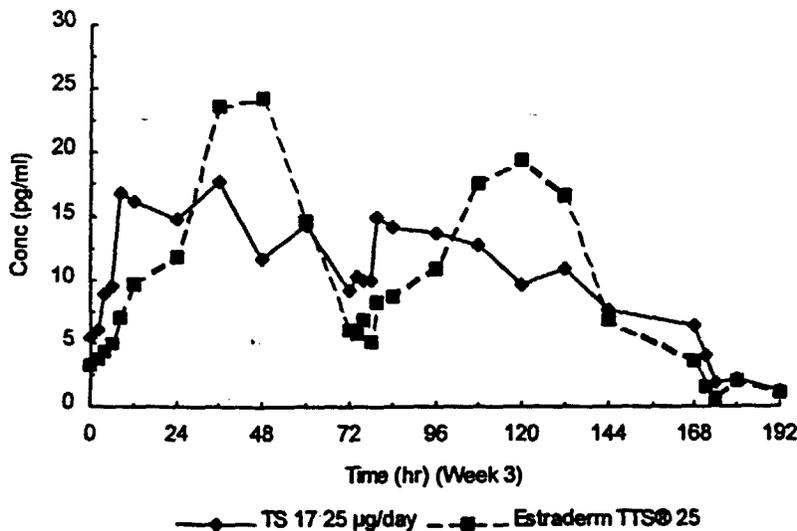


Fig 3. Mean serum estradiol levels (baseline corrected) during third week following multiple application of Esclim[®]-25 and Estraderm[®]-25.

Table 9. Mean pharmacokinetic parameters derived from baseline corrected serum estradiol during third week following multiple application of Esclim[®] and Estraderm[®]

Parameter	Esclim (25µg/day)	Estraderm (25µg/day)
C _{max} (pg/ml)	24.1 ± 11.5	29.3 ± 9.7
C _{avg} (pg/ml)	11.8 ± 5.0	13.4 ± 4.2
T _{max} (h)	16.0 ± 11.8	44.4 ± 8.1
AUC _(0-168h) (pg.h/ml)	1983 ± 836	2256 ± 711
%Fluctuation	174 ± 35.3	202 ± 23.2

Reviewer Comments:

- The relative bioavailability of Esclim[®]-50 is 1.17 when compared to Vivelle and serum levels are very similar to those of Vivelle[™]-50.
- The bioavailability of Esclim[®]-25 is also comparable to that of Estraderm[®]-25 with a relative bioavailability of 0.88.
- It appears that the serum levels of E₂ are relatively constant with less fluctuation from Esclim application when compared to those from Estraderm application.

B. Bioequivalence:

Bioequivalence studies were not conducted since the formulation used in clinical trials was the to-be-marketed formulation.

C. Sites of Application

In study KH TS 17 92 01, the bioavailability of estradiol from Esclim[®]-50 patch applied to four different body sites was investigated in 12 healthy post menopausal volunteers. A 10 mg/22 cm² patch designed to deliver 50 µg/day was applied to iliac fossa (abdomen), femoral triangle (thigh), the external part of the upper arm, and the upper outer quadrant of the buttock, the site used in the clinical trials. The pharmacokinetic parameters obtained from the study are listed in Table 10 and the serum concentration profiles are illustrated in Figure 4.

Table 10. Mean pharmacokinetic parameters of estradiol following the single application of Esclim[®] 50 for 3 days to different body sites.

Treatment	C _{max} (pg/ml)	T _{max} (h)	C _{avg(0-72)} (pg/ml)	AUC _(0-72h) (pg/h/ml)	AUC _(0-96h) (pg/h/ml)
Baseline uncorrected					
Iliac fossa	57.3 (27.7)	17.0 (9.0)	34.2 (16.1)	2890 (1312)	3311 (1477)
Femoral	80.1 (34.8)	21.7 (11.6)	49.0 (24.6)	4106 (1826)	4578 (1938)
Upper arm	80.2 (44.1)	16.7 (7.9)	47.4 (24.3)	3825 (1897)	4306 (1925)
Buttock	72.6 (36.2)	16.3 (10.0)	42.8 (20.7)	3477 (1530)	3885 (1622)
Baseline Corrected					
Iliac fossa	49.3 (27.9)	17.0 (9.0)	26.2 (16.4)	2313 (1334)	2542 (1509)
Femoral	69.5 (34.3)	21.7 (11.6)	38.6 (24.5)	3348 (1825)	3611 (1954)
Upper arm	72.6 (43.6)	16.7 (7.9)	39.8 (24.1)	3293 (1875)	3579 (1915)
Buttock	64.5 (36.4)	16.3 (10.0)	34.7 (20.8)	2894 (1537)	3107 (1632)

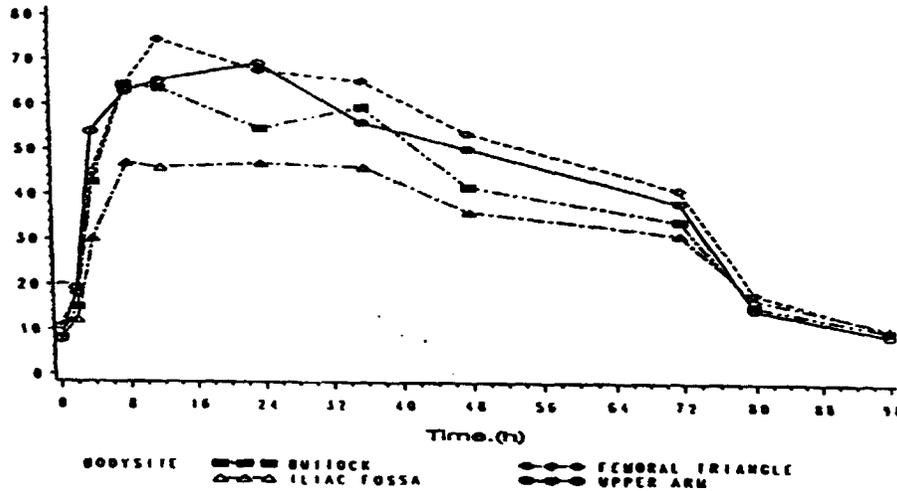


Figure 4. Mean unadjusted serum estradiol levels following the single application of Esclim[®] 50 to different body sites.

Confidence Intervals using Dunnett's and two one-sided t-tests for pharmacokinetic parameters of Esclim 50 patch applied to four different body sites:

Parameter	Treatment	Ratio	95% CI (Dunnett's t-test)	90% CI (two one-sided t-test)
C_{max}	B vs D	115.4	81.4 - 163.4	90.8 - 146.5
C_{max}	C vs D	108.1	76.3 - 153.1	85.1 - 137.3
C_{max}	A vs D	76.8	54.2 - 108.9	60.5 - 97.5
AUC_{0-72}	B vs D	122.4	84.9 - 176.3	95.3 - 157.1
AUC_{0-72}	C vs D	107.3	74.4 - 154.5	83.5 - 137.8
AUC_{0-72}	A vs D	79.9	55.5 - 115.1	62.2 - 102.6
CAV_{72}	B vs D	119.2	80.2 - 177.5	90.8 - 156.7
CAV_{72}	C vs D	108.8	73.1 - 161.9	82.8 - 142.9
CAV_{72}	A vs D	76.5	51.4 - 113.9	58.2 - 100.5

A: Iliac Fossa, B: Femoral Triangle C: Upper arm, D: Buttock (reference site)

Reviewer Comments

- Since, the confidence intervals (using both Dunnett's and two one-sided t-tests) as shown in the table are outside of equivalency criteria (80 to 125%) for all the pharmacokinetic parameters, the application sites are not considered bioequivalent.
- The number of subjects used in the study (n=12) is too small to provide enough power for this kind of study. Therefore, the results of this study are not conclusive to demonstrate bioequivalence.
- Application of Esclim[®]-50 patch to the abdomen resulted in lower baseline corrected mean AUC_{0-96h} (18%) while upper arm and thigh resulted in higher baseline corrected mean AUC_{0-96h} (15% and 16%, respectively) in comparison to the buttock.

- Although from the Agency's BE criteria, the application sites are not bioequivalent to the reference site, based on therapeutic range of estradiol for the proposed indications, the clinical division (HFD-580) has decided that the upper arm, thigh and buttock sites can be approved but the abdomen is not acceptable due to the following reasons:

1. lack of clinical efficacy data for abdomen site
2. low serum estradiol levels predicted with lower dose 25 at the abdomen site
3. approximately 30% change in AUC when application sites are rotated from thigh and upper arm to abdomen.

D. Dose Proportionality

Single dose

The dose proportionality of estradiol transdermal systems was investigated in a dose ranging study (protocol K POE 91 01) in 24 postmenopausal women. In this study, the transdermal absorption of estradiol from three different sizes of Esclim patch (10, 20 and 40 cm²) in comparison to a reference patch (Estraderm TTS[®] 50, Ciba-Geigy) was studied. The mean serum estradiol concentration-time profiles are illustrated in Figure 5 and the mean pharmacokinetic parameters are listed in Table 11.

Table 11. Mean pharmacokinetic parameters of baseline corrected serum estradiol for different doses of Esclim.

Patch size	C _{max} (pg/ml)	C _{av} (pg/ml)	T _{max} (h)	AUC ₍₀₋₇₂₎ pg.hr/ml	AUC ₍₀₋₉₆₎ pg.hr/ml
10cm ² patch	19.40 (14)	9.90 (9)	33.50 (22.28)	891 (742)	972 (784)
20cm ² patch	42.88 (35)	21.35 (17)	22.67 (16.79)	1829 (1275)	1997 (1359)
40cm ² patch	82.82 (50)	41.70 (27)	18.83 (10.52)	3705 (2217)	3957 (2324)

Figure 1a

MEAN SERUM ESTRADIOL LEVELS AFTER A SINGLE APPLICATION OF DIFFERENT ESTRADIOL PATCH SIZES TO 24 POSTMENOPAUSAL WOMEN

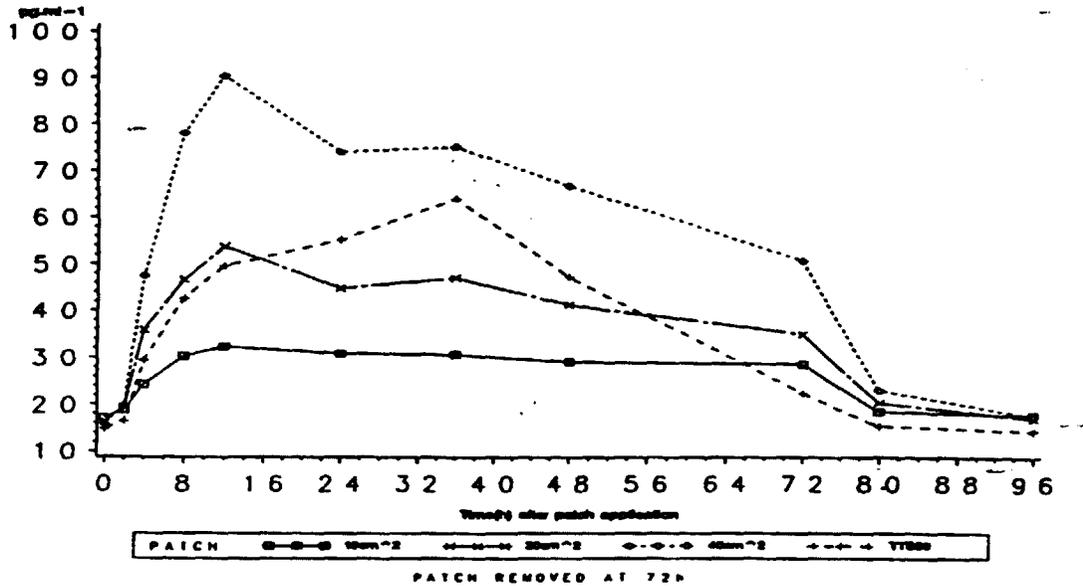


Figure 5: Mean uncorrected serum estradiol levels following single application of different sizes of Esclim.

There was no statistically significant difference among the three different patches in the dose normalized C_{max} , $AUC_{(0-72)}$, and $AUC_{(0-96)}$ values. Furthermore, a linear relationship exists between the surface area of the patch (10 to 40 cm²) and baseline corrected $AUC_{(0-96)}$ and C_{max} values

Multiple dose

The dose proportionality of Esclim was also investigated at steady state in a double-blind, parallel-group design, safety and efficacy study (C TS 17 93 01) following 12 weeks of treatment with three dosage strengths of TS 17 (25, 50 and 100 µg/day). A blood sample for measurement of steady state serum E₂, estrone (E₁) and estrone sulfate (E₁S) and FSH concentrations was collected between 24 and 72 hours after application of the last patch at Visits 1 (Week 5), 2 (Week 9) and 3 (Week 13). The mean steady-state serum levels of E₂, E₁, E₁S and FSH are presented in Table 12 and the relationship between serum concentration of E₂, E₁ and E₁S Vs nominal delivery rate are illustrated in Figure 6.

Table 12: Steady-state serum levels of estrogens at week 13 following multiple dosing.

Patch	Steady State Serum Concentration			
	Estradiol (pg/mL)	Estrone (pg/mL)	Estrone Sulfate (ng/dL)	FSH (mIU/mL)
Placebo	19.6±14.0 ^a 31 ^b	29.7±11.7 31	42.9±24.0 30	113.6±39.6 32
25 µg/day	48.2±27.4 22	38.7±21.5 22	152.6±129.7 22	75.6±28.8 22
50 µg/day	102.8±63.6 24	49.0 ± 28.0 24	236.1±147.1 22	34.4±19.8 26
100 µg/day	165±116 28	64.9±31.7 28	373.6±272.0 28	19.2±15.0 28

^aMean ± SD

^bNo. of subjects

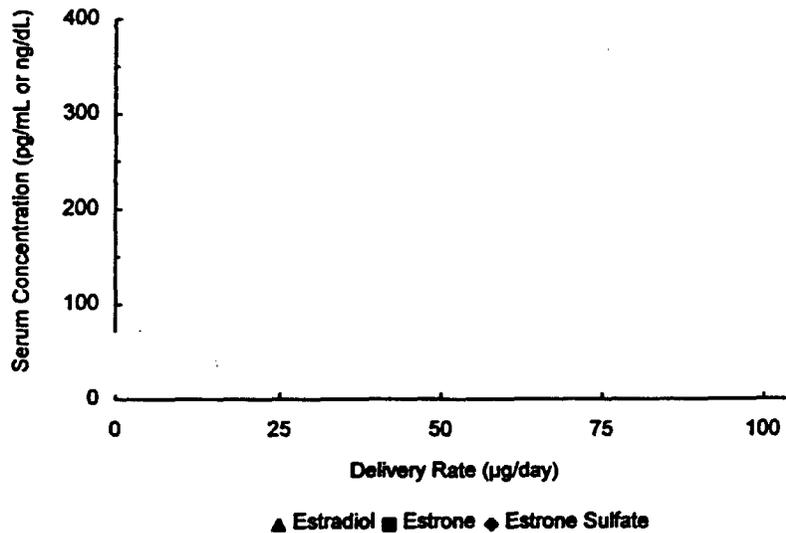


Figure 6. Relationship between serum levels of hormones and the nominal delivery rate

Cross-study comparison:

Dose proportionality of the Esclim patches was also demonstrated in a cross study comparison between studies K TS 17 9402 and K TS 17 96 02. The plasma estradiol levels from these two studies are illustrated in Figure 7 and the PK parameters are listed in Table 13 below.

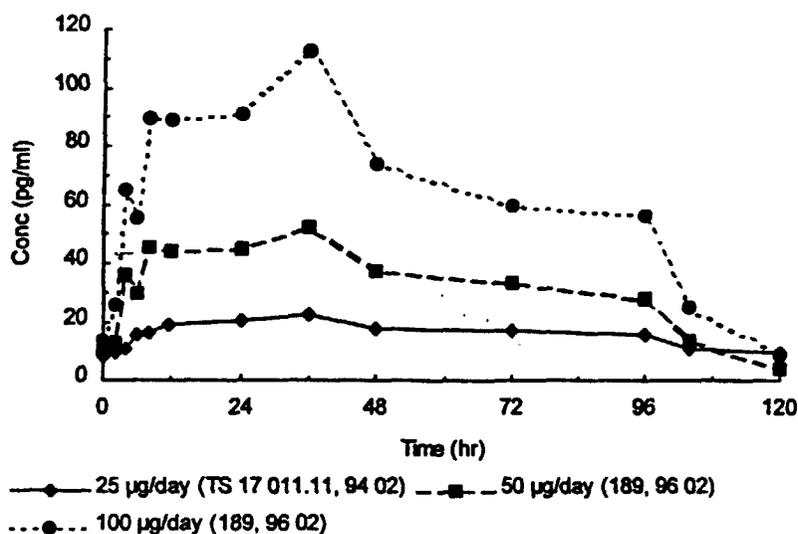


Figure 7. Mean Uncorrected Serum Concentrations of Total Estradiol after Administration of TS 17 Patches of Different Release Rates (Studies K TS 17 94 02 and 96 02).

Table 13. Baseline corrected mean bioavailability parameters after administration of Esclim patches (Studies K POE 91 01, K TS 94 02 and K TS 96 02).

Study	Release Rate (µg/day)	C _{max} (pg/mL)	AUC (hrxpg/mL)
K POE 91 01	22.5	19.4 ± 14.9	972 ± 785
K TS 17 94 02	25	16.3 ± 10.7	920 ± 644
K POE 91 01	45	42.9 ± 35.1	1997 ± 1359
K TS 17 96 02	50	55.0 ± 32.7	2982 ± 1903
K POE 91 01	90	82.8 ± 50.8	3957 ± 2325
K TS 17 96 02	100	116.8 ± 66.1	6342 ± 4082

Reviewer Comments

- The results observed in study K POE 91 01 conclusively show that the pharmacokinetics of estradiol following application of Esclim patches (10, 20 and 40 cm²) are dose proportional.
- Dose proportionality of Esclim patches (25, 50 and 100 µg/day) at steady state was shown in study C TS 17 93 01.
- It should be noted that dose proportionality was also shown for Esclim 25, 50 and 100 patches in Studies K TS 17 94 02 and K TS 17 96 02.

E. Multiple Dose/Steady State PK

The pharmacokinetics of estradiol, estrone and estrone sulfate following multiple application of Esclim 50 over 3 weeks was determined in study K TS 17 93 02 in 18 healthy postmenopausal women. The mean baseline corrected serum estradiol and estrone levels following application of Esclim 50 for three weeks are included in Table 14.

Table 14. Baseline corrected mean (\pm SD) trough concentrations of estradiol and estrone following multiple application of Esclim 50.

Time	Mean \pm SD Trough Concentration (pg/mL)	
	Estradiol	Estrone
3-day applications		
Day 3	33.0 \pm 14.7	15.5 \pm 10.1
Day 10	30.4 \pm 16.5	10.7 \pm 10.1
Day 17	34.7 \pm 19.8	23.7 \pm 17.2
4-day applications		
Day 7	27.4 \pm 15.2	6.6 \pm 8.1
Day 14	28.4 \pm 15.4	16.9 \pm 13.5
Day 21	27.5 \pm 16.7	6.3 \pm 6.4
Week	Mean \pm SD AUC ₍₀₋₁₆₈₎ (pg•hr/mL)	
1	7776 \pm 3804	2785 \pm 2123
2	8923 \pm 4784	3730 \pm 2184
3	9081 \pm 4444	3906 \pm 2488

Reviewer Comments:

- Based on the consistent values for C_{min} values observed in this study, it can be concluded that the serum levels of estradiol and estrone reached steady-state by the second week of treatment with Esclim. However, it should be noted that the trough values for estrone are variable.
- Based on the AUC₍₀₋₁₆₈₎ values for both estradiol and estrone, it appears that there is no appreciable accumulation following the multiple application of Esclim patch to the buttocks.

Multiple dose PK was also determined in Study K TS 17 95 01 during a 3 week period in 12 postmenopausal healthy women. Each week, two patches (5 mg/11 cm², 22 μ g/day) were applied to the outer quadrant of the buttock, one for 3 days and the second for 4 days. The mean baseline unadjusted serum concentrations of estradiol, estrone and estrone sulfate are illustrated in Figure 8.

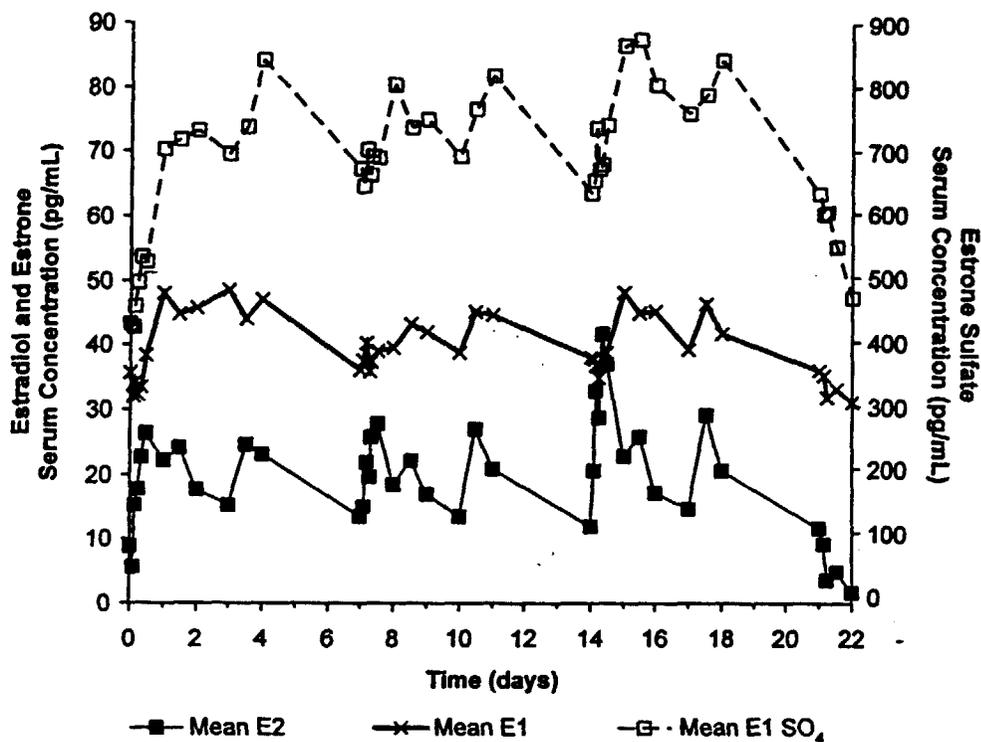


Figure 8. Mean uncorrected serum hormone levels following multiple application Esclim 25.

Reviewer Comments

- Similar to study K TS 17 93 02, the results of this study showed that steady state concentrations for estradiol and estrone were attained by the second week .
- The ratio of uncorrected serum estradiol to estrone was approximately 0.45 throughout the 3 -week treatment period.

F. SPECIAL POPULATIONS

Elderly Subjects

No studies were performed to evaluate the pharmacokinetics of estradiol from Esclim patches in elderly versus young females. However, the sponsor did a reanalysis of seven of the pharmacokinetic studies and concluded that there was no difference in pharmacokinetics between the subjects of age >65 years and <65 years. This conclusion is not fully supported because there were only nine (out of 83 total) subjects of age >65 years across seven pharmacokinetic studies analyzed for this purpose.

G. DRUG-DRUG INTERACTIONS

Specific drug-drug interaction studies have not been performed with Esclim.

H. PK/PD CORRELATION

In clinical trial C TS 17 9301, a double-blind, parallel-group, placebo-controlled study, a single blood sample for the measurement of steady state serum estradiol, estrone, estrone sulfate and FSH concentrations was collected between 24 and 72 hours post application at weeks 5, 9 and 13. The dose-response relationship between the percentage (%) patients with complete relief of vasomotor symptoms and serum estradiol levels at week 5 is illustrated in Figure 9.

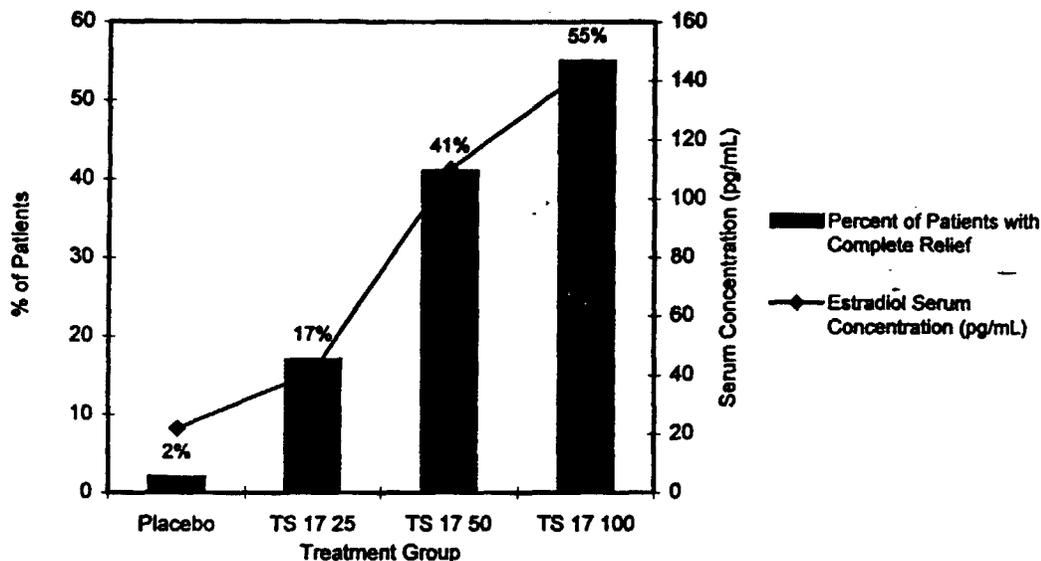


Figure 9. Relationship between mean serum estradiol levels and relief from vasomotor symptoms.

From the Figure 9, it appears that there is an apparent relationship between the steady-state estradiol levels and the % of patients with complete relief from vasomotor symptoms. However, no attempt was made by the sponsor to model the PK/PD relationship between the concentration and the response.

X. *IN VIVO* TRANSDERMAL DELIVERY RATE

In vivo transdermal delivery rate (TDR) of estradiol from Esclim was determined in two ways.

Residual Analysis:

The transdermal delivery rate of estradiol from Esclim patches was determined by assaying the residual drug content of used transdermal systems in Study K TS 17 95 01 containing 5 mg estradiol and delivering 25 µg/day. The assayed estradiol content of used transdermal systems was corrected by the following correction factor to account for loss in adhesive content:

$$\text{Correction factor (cf)} = \frac{\text{Average adhesive weight of 5 unused transdermal systems}}{\text{Adhesive weight of the used transdermal system}}$$

The corrected estradiol content = assayed estradiol content x cf

The delivery rate was calculated from the difference in estradiol content between unused and used transdermal systems. The average delivery rate calculated by this method 55 µg/day with a 95% confidence interval of 41 to 69 µg/day. This is approximately twice the nominal delivery rate. The reasons for this high estimated delivery rate may be because the total amount delivered over 4 days is only 2% of the total loading dose in the system and also because of analytical errors.

From average serum estradiol levels:

The *in vivo* delivery rate of estradiol from Esclim patch was also calculated from the average serum estradiol concentrations and estradiol clearance as follows:

$$TDR = CL \times \delta C_{avg}$$

where CL is total clearance and δC_{avg} is the mean basal corrected average serum estradiol concentration. CL is assumed to be independent of δC_{avg} and is taken from literature as 1600 L/day. The estimated TDR for Esclim and other patches used in pharmacokinetic studies was summarized in Table 15.

Table 15. Estimated *in vivo* transdermal delivery rates of estradiol

Transdermal System	Nominal Delivery Rate (µg/day)	Estimated <i>In Vivo</i> Delivery Rate (µg/day)
TS 17 25	25	19.9
TS 17 50	50	51.2
TS 17 100	100	101.1
Estraderm TTS® 25	25	21.4
Estraderm TTS® 50	50	52.1
Vivelle™ 50	50	42.3

Reviewer Comment

- The estimated *in vivo* transdermal delivery rates based on average serum estradiol levels and clearance are close the nominal delivery rates for the different strengths. However, the delivery rates estimated from residual concentrations of estradiol in the used patches are much higher. Due to the low amount of estradiol delivered from the patch (<2%), the *in vivo* method of estimation is more appropriate than the residual analysis method.

XI. ADHESION

The adhesion performance of Esclim transdermal systems was evaluated in 11 clinical pharmacology studies and 5 clinical trials. The adhesion data collected during the clinical development of Esclim is summarized in Tables 16 and 17.

Table 16. Adhesion data from pharmacokinetic studies:

Study Number	Number of Subjects	Number of Applications	Number of Detachments	Number of Partial Detachments
KH TS 17 92 02	6	12	0	0
K TS 17 96 03	12	72	2	4*
K TS 17 93 02	18	108	1	0
K TS 17 91 02	9	18	0	0
K TS 17 91 01	12	49	0	0
K POE 91 01	24	72	2	0
K TS 17 93 01	12	12	0	0
K TS 17 95 01	12	72	3	1
K TS 17 96 02	24	48	1	3
K TS 17 94 02	18	18	0	0
KH TS 17 92 01	12	48	0	0
TOTALS	159	529	9	8
PERCENT		100%	1.7%	1.5%

Out of the 529 patch applications evaluated in the above listed studies, there was a low incidence of approximately 3.2% of either partially or completely detached patches.

Table 17. Adhesion data collected in clinical trails

Study	Dose of patch	Total No. of applications	No.(%) of applications detached	No. (%) of patients with ≥ 1 detachment
Study 9301 (U.S.)	TS 17 25	1194	66 (5.5)	26 (54.2)
	TS 17 50	1197	56 (4.3)	20 (42.6)
	TS 17 100	1207	57 (4.7)	22 (46.8)
Study 9102 (France)	TS 17 50	831	23 (2.8)	10 (31.3)
Study 9104 (Multinational)	TS 17 50	3706	224 (6.0)	86 (60.1)
	Estraderm 50	3406	384 (11.3)	93 (67.4)
Study 9103	TS 17*	17702	770 (4.4)	135 (60.8)
Study 9201	TS 17*	67901	2631 (3.9)	220 (53.5)

*adjustable doses were used in the uncontrolled studies

In the three controlled studies (9301, 9102 and 9104), which included approximately 8135 patch applications, approximately 5% of the patches required replacement due to inadequate adhesion. From the study 9104, it appears that Esclim 50 patch has shown better adhesion performance than Estraderm, although the difference is not statistically significant.

Reviewer Comment:

- In general, the adhesive performance of Esclim patch appears to be adequate (2.8% - 6%) and acceptable.

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XII. LABELING

The Clinical Pharmacology section of the proposed labeling should be replaced with the following:

Redacted 3

pages of trade

secret and/or

confidential

commercial

information

Special Populations

No specific studies have been conducted using Esclim® in any special population.

Drug Interactions

No specific drug interaction studies have been conducted using Esclim®.

Adhesion

Adhesion is a critical factor related to efficacy. The extent of estradiol absorption from Esclim® transdermal systems is related to the surface area in contact with the skin. Therefore, patch lifting and detachment have pharmacokinetic and therapeutic implications related to the reduced surface area that is in contact with the skin under these conditions.

The adhesivity of the Esclim® transdermal systems was prospectively evaluated in three separate controlled clinical trials. In these trials, which included approximately 8135 patch applications (twice-weekly applications), approximately 5% of the patches required replacement due to inadequate adhesion. In a placebo-controlled study evaluating the efficacy and safety of Esclim® 25, 50, and 100, no difference in the frequency of detachment was observed among the three different patch sizes. In a 4-month clinical trial comparing the safety and efficacy of the Estraderm TTS® 0.05 mg/day estradiol transdermal system to the Esclim® 50 system, 6.0% of the Esclim® systems required replacement, compared with 11.3% of the Estraderm TTS® systems.

The adhesivity of the Esclim® transdermal systems was evaluated in eleven separate clinical pharmacokinetic studies. In these studies, which included approximately 529 patch applications (single applications or twice-weekly applications), approximately 2% of the patches required replacement due to inadequate adhesion and an additional 1.5% of the patches became partially detached.

1. Summary of Study K POE 91 01

Title: "A Comparative Estradiol Patch Dose-Ranging Study in 24 Postmenopausal Females".

Objectives: To measure the concentration of estradiol in serum after application of three different sizes Esclim patch and Estraderm.

To monitor the volunteers for adverse events during the study.

Study Design:

Balanced, randomized, single dose, crossover study comparing the pharmacokinetics of three different patch sizes and Estraderm in 24 postmenopausal women who have serum estradiol levels less than 25 pg/ml.

The subjects who met the selection criteria received the following treatments according to their randomization schedule:

- A. Patch LF 10cm², Batch No. 483 VP
- B. Patch LF 20cm², Batch No. 484 VP
- C. Patch LF 40cm², Batch No. 482 VP
- D. Estraderm TTS 50 Ciba, Batch No. B133100.

The patch was worn for 3 days during each study period with a 4 four day washout period between the removal of the previous patch and the application of next patch. The site of application was buttocks for all the patches.

Sample Collection:

Blood samples were collected immediately before patch application and at 2, 4, 8, 12, 24, 36, 48, 72, 80 and 96 h following patch application.

Assay Method:

Results:

Pharmacokinetic parameters of estradiol:

Patch size	C _{max} (pg/ml)	C _{av} (pg/ml)	T _{max} (h)	AUC ₍₀₋₇₂₎ pg.hr/ml	AUC ₍₀₋₉₆₎ pg.hr/ml
Not corrected for endogenous estradiol					
10cm ² patch	36.35 (14.80)	26.79 (9.26)	33.50 (22.28)	2108 (747)	2587 (811)
20cm ² patch	59.10 (34.34)	37.73 (16.62)	22.67 (16.79)	2990 (1207)	3557 (1275)
40cm ² patch	98.46 (50.13)	57.86 (27.79)	18.83 (10.52)	4870 (2138)	5494 (2222)
Estraderm	70.15 (21.30)	37.91 (9.27)	31.0 (13.20)	3250 (832)	3639 (885)
Corrected for endogenous estradiol					
10cm ² patch	19.40 (14)	9.90 (9)	33.50 (22.28)	891 (742)	972 (784)
20cm ² patch	42.88 (35)	21.35 (17)	22.67 (16.79)	1829 (1275)	1997 (1359)
40cm ² patch	82.82 (50)	41.70 (27)	18.83 (10.52)	3705 (2217)	3957 (2324)
Estraderm	55.55 (21)	23.42 (9)	31.0 (13.20)	2201 (830)	2249 (838)

Figure 1a

MEAN SERUM ESTRADIOL LEVELS AFTER A SINGLE APPLICATION OF DIFFERENT ESTRADIOL PATCH SIZES TO 24 POSTMENOPAUSAL WOMEN

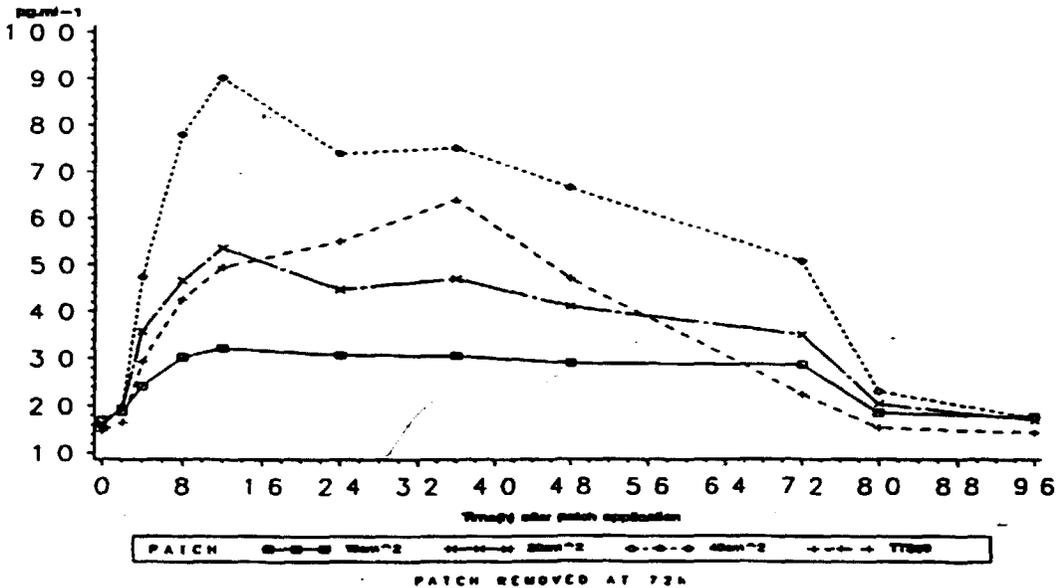
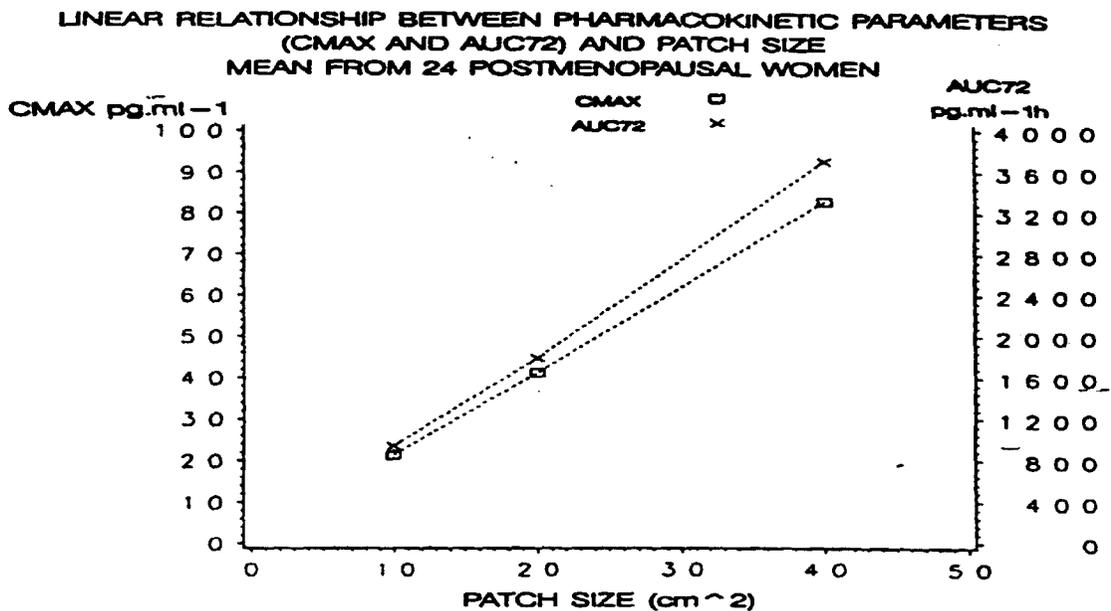


Figure 1b



Reviewer Comments:

1. The C_{max} and AUC of serum estradiol corrected for endogenous levels are found to be dose proportional with respect to the patch size.
2. It should be noted that no data are available for dose proportionality of serum estrone and estrone sulfate levels in this study. However, other multiple dose studies address this issue.

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2. STUDY KH TS 17 92 01

Title: "Transdermal Absorption of Estradiol From an Estradiol Transdermal System, TS 17, After Application to Four Different Body Sites."

Objectives: To investigate the transdermal absorption profile of estradiol after single application of TS 17 to four different body sites (iliac fossa, femoral triangle, external part of the upper arm and upper quadrant of the buttock).

To monitor the volunteers for adverse events, local skin tolerability and patch adhesiveness during the study.

Study Site:

Study Design:

This was an open label, single dose, randomized four-way cross over study in 12 postmenopausal female volunteers who according a randomization schedule received the following treatments:

Treatment A: TS 17 0.05 transdermal system applied to iliac fossa
(Batch No. ARR 1159)

Treatment B: TS 17 0.05 transdermal system applied to femoral triangle
(Batch No. ARR 1159)

Treatment C: TS 17 0.05 transdermal system applied to external part of upper arm
(Batch No. ARR 1159)

Treatment D: TS 17 0.05 transdermal system applied to outer quadrant of buttock
(Batch No. ARR 1159)

Each transdermal system was applied for 3 days with a 4-day drug free washout period between the applications.

Sample Collection:

Blood samples (5 ml) for serum were collected before each application and at 2, 4, 8, 12, 24, 36, 48, 72, 80 and 96 h following the application.

The subject's skin was assessed prior to application and a daily visual inspection of patch was carried out. Any loss of adhesion and irritation at the application site following the removal of the patch at 72 h were noted on the subjects case record file.

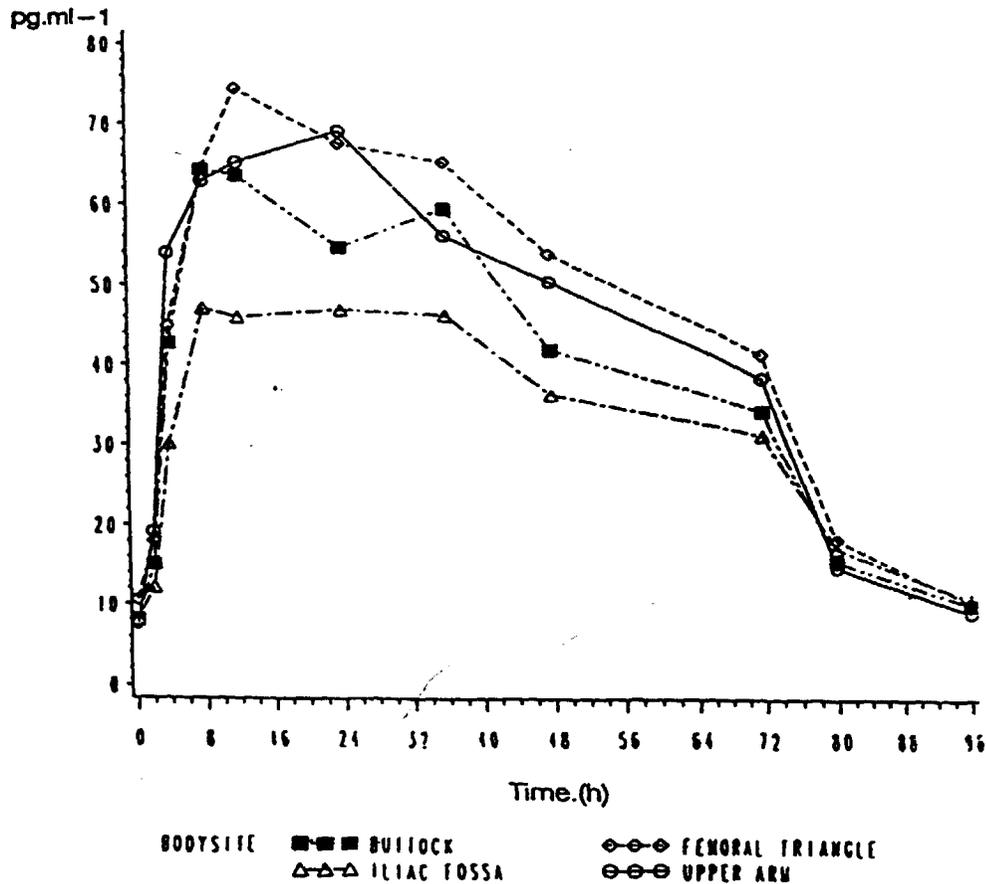
Assay Methodology:

Results:

Mean pharmacokinetic parameters

Treatment	C _{max} (pg/ml)	T _{max} (h)	C _{ave(0-72)} (pg/ml)	AUC _(0-72h) (pg/h/ml)	AUC _(0-96h) (pg/h/ml)
Baseline uncorrected					
Iliac fossa	57.3 (27.7)	17.0 (9.0)	34.2 (16.1)	2890 (1312)	3311 (1477)
Femoral	80.1 (34.8)	21.7 (11.6)	49.0 (24.6)	4106 (1826)	4578 (1938)
Upper arm	80.2 (44.1)	16.7 (7.9)	47.4 (24.3)	3825 (1897)	4306 (1925)
Buttock	72.6 (36.2)	16.3 (10.0)	42.8 (20.7)	3477 (1530)	3885 (1622)
Baseline Corrected					
Iliac fossa	49.3 (27.9)	17.0 (9.0)	26.2 (16.4)	2313 (1334)	2542 (1509)
Femoral	69.5 (34.3)	21.7 (11.6)	38.6 (24.5)	3348 (1825)	3611 (1954)
Upper arm	72.6 (43.6)	16.7 (7.9)	39.8 (24.1)	3293 (1875)	3579 (1915)
Buttock	64.5 (36.4)	16.3 (10.0)	34.7 (20.8)	2894 (1537)	3107 (1632)

SERUM CONCENTRATION LEVELS OF ESTRADIOL AFTER APPLICATION OF LF TS17 TRANSDERMAL SYSTEMS TO FOUR DIFFERENT BODY SITES
 -----MEAN-----



Sponsor's Conclusions:

1. The transdermal system was well tolerated when applied to the four tested body sites.
2. Based on the ANOVA of the log transformed PK parameters corrected for baseline, no significant difference in estradiol bioavailability from TS 17 0.05 applied to four different sites was observed except for C_{max} ($p < 0.05$). When the same analysis was performed without log transformation, there was no significant difference in C_{max} .
3. The transdermal patch (TS17 0.05) usually applied to the buttock, could be applied to either iliac fossa or femoral triangle or upper arm without any change in estradiol absorption.

Reviewer Comments:

1. The number subjects used ($n=12$) in the study is not adequate in power to demonstrate bioequivalence.
2. Although, there was no statistically significant difference in pharmacokinetic parameters of E_2 , following patch application to different sites, the application sites are not bioequivalent because the estimated 95% confidence intervals for each of the test application sites (abdomen, upper arm, thigh) in comparison to the reference site (buttock) are outside the 80 - 125% range.
3. The measured plasma levels of E_2 following patch application to iliac fossa are lower than those after buttock while the plasma E_2 levels for upper arm and thigh are higher than those for buttock.
4. Application of Esclim[®] 50 patch to the abdomen resulted in lower AUC (18%) while upper arm and thigh resulted in higher AUC (15% and 16%, respectively) in comparison to the buttock.
5. Although from the agency's criteria, the application sites are not bioequivalent to the reference site, based on therapeutic range of estradiol for the proposed indications, the clinical division (HFD-580) has decided that the upper arm, thigh and buttock sites can be approved but the abdomen is not acceptable due to the following reasons:
 - lack of clinical efficacy data for abdomen site
 - lower serum estradiol levels predicted with lower dose 25 at the abdomen site
 - approximately 30% change in AUC when application sites are rotated from thigh and upper arm to abdomen.

3. Study Report K TS 17 96 02

Title: "Comparative Pharmacokinetic Study of Estradiol After 4-day Application of Three Different Estradiol Transdermal Systems (Esclim[®] 50, Esclim[®] 100 and Vivelle[®] 50) in 24 healthy post-menopausal women."

Objective: To evaluate the pharmacokinetics of estradiol after a 4-day application of 3 different estradiol transdermal systems (Esclim[®] 50, Esclim[®] 100 and Vivelle[®] 50) in 24 healthy post-menopausal women.

Investigator:

Study Center:

Study Design:

This was a randomized, 3-way crossover study in 24 healthy post-menopausal women with serum E₂ less than 25 pg/ml and FSH greater than 20 IU/l. The subjects were randomly assigned to receive the following in three periods:

Treatment A: Esclim[®] 50 (22cm²) patch containing 10 mg of E₂ with a delivery of 50 µg/24 h.

Treatment B: Esclim[®] 100 (44cm²) patch containing 20 mg of E₂ with a delivery of 100 µg/24 h.

Treatment C: Vivelle[®] 50 patch containing 4.33 mg E₂ with a delivery of 50 µg/24 h.

Each system was applied for 4 days on upper outer quadrant of the buttock with three day washout period between the removal of the first patch and the application of the second one.

Sample Collection:

Blood samples for assessment of serum E₂ levels were collected at 0, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 104 and 120 hours after application.

In addition, local skin tolerability, patch adhesion was examined by the investigator and patients at each visit.

Analytical Methods:

Results:

The mean base-line corrected serum estradiol profiles are illustrated in Fig 1 and the mean pharmacokinetic parameters are listed in Table 1

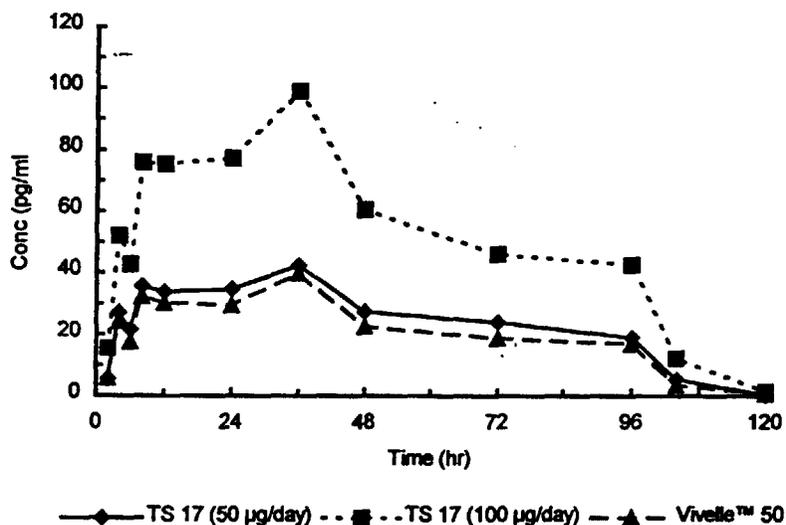


Fig 1. Mean base-line corrected serum estradiol concentration profiles following application of Esclim (50 and 100 µg/day) and Vivelle™

Table 1. Mean bioavailability parameters of serum estradiol

Parameter ^a	TS 17 (50 µg/day)	TS 17 (100 µg/day)	Vivelle™ 50 (50 µg/day)
Uncorrected			
C _{max} (pg/mL)	61.6±33.0	124±66.4	56.3±35.9
T _{max} (hr)	27.5±15.6	27.0±12.7	30.1±18.5
AUC (0-120) (pg•hr/mL)	3707±1966	7106±4148	3247±1763
Basal-corrected			
C _{max} (pg/mL)	55.0±32.7	116.8±66.1	49.4±35.7
T _{max} (hr)	27.5±15.6	27.0±12.7	30.1±18.5
AUC (0-120) (pg•hr/mL)	2982±1903	6342±4082	2535±1691

^aOne woman was excluded from the analysis due to ovarian reviviscence during the study.

Sponsors' Conclusions:

- Esclim 50 patch produced baseline corrected serum estradiol concentrations that are very similar to those produced by Vivelle™ 50 patch.
- Esclim, 50 and 100 µg/day patches were shown to be dose proportional in terms of their C_{max} and AUC values.

Reviewer Comment:

Sponsor's conclusions of the study are appropriate and acceptable.

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4. Summary of Study K TS 17 96 03

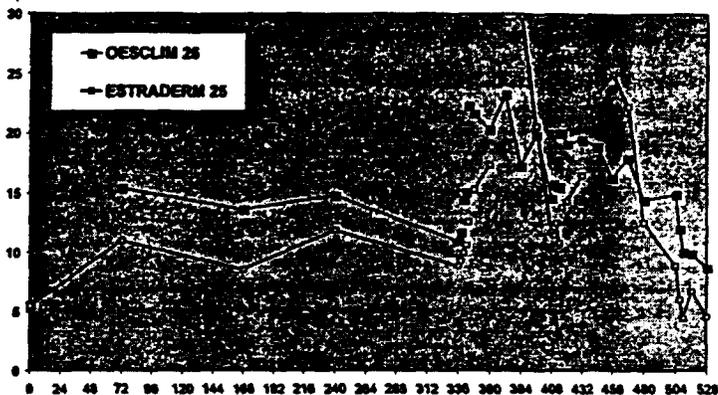
NAME OF STUDIED PRODUCT	OESCLIM [®] 25 (Laboratoires FOURNIER SCA) and ESTRADERM TTS [®] 25 (CIBA-GEIGY) estradiol transdermal systems (E2 TS).
TITLE OF THE STUDY	Comparative pharmacokinetic study of estradiol following 3-week multiple applications of two different estradiol transdermal systems (OESCLIM [®] 25 versus ESTRADERM TTS [®] 25) in 12 healthy post-menopausal women
PRINCIPLE INVESTIGATOR	
STUDY LOCATION	
START AND END OF STUDY	Start: July 16, 1996 End: September 4, 1996
STUDY AIM	To compare the E2 pharmacokinetic profiles obtained from two different E2 TS during the last week of a continuous 3 week application
CLINICAL PHASE	I
EXPERIMENTAL DESIGN	<p style="text-align: center;"> 3-day application patch application 4-day application patch removal </p> <p>An additional 12-day final course of progestogen was to be performed at the discretion of the clinical gynaecologist if double endometrial lining was larger than 6 mm on the day of the follow-up visit.</p>
NUMBER OF SUBJECTS TO BE INCLUDED	12
INCLUSION CRITERIA	<p>Healthy post-menopausal women (30-70 years old) confirmed by:</p> <ol style="list-style-type: none"> amenorrhea for at least 12 months <u>or</u> bilateral ovariectomy more than 3 months before the study, serum FSH level of greater than 20 IU/L, serum estradiol level of less than 25 pg/ml. <p>Additional tests were performed in order to ensure the normality of target organs, in particular an endometrial ultrasonography, mammography and cervical smear.</p>
FORMULATIONS, ROUTE OF ADMINISTRATION, DOSAGE	OESCLIM [®] 25 (11 cm ² total surface area) containing 5 mg of E2 with delivery of approximately 25 µg/24 h (treatment A).
TREATMENT DURATION	2 periods of continuous wearing over 3 weeks separated by a 1-week wash-out period (6 weeks of E2 treatment per subject).

EVALUATION CRITERIA	<p>Principal criteria</p> <p>1. E2 serum levels determined by</p> <p><u>On week 1 and week 5:</u> at time 0 before the first application.</p> <p><u>On weeks 1, 2, 5 and 6:</u> just before removal of each TS.</p> <p><u>On weeks 3, 4 (period I) and weeks 7, 8 (period II):</u> For each 3-day application: 0, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 h. For each 4-day application: 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, 99, 102, 108 and 120 h.</p> <p>2. Pharmacokinetic parameters (uncorrected and corrected for endogenous values).</p> <p><u>On weeks 3, 4 (period I) and weeks 7, 8 (period II):</u></p> <p>AUC₀₋₇₂, AUC₇₂₋₁₆₈, AUC₀₋₁₉₂, C₇₂, C₁₆₈, C_{min}^{ss}, C_{max}^{ss}, t_{max}^{ss} C_{av}^{ss}, % PTF.</p> <p>Secondary criteria Safety, local skin tolerability and adhesiveness of the transdermal systems.</p>
STATISTICAL METHOD	Descriptive and statistical analysis (analysis of variance)
REFERENCE TREATMENT, DOSAGE	ESTRADERM TTS® 25 (5 cm ² delivery surface) transdermal system containing 2 mg of E2 with delivery of approximately 25 µg/24 h (treatment B)
RESULTS	
CHARACTERISTICS OF SUBJECTS ENTERED	Twelve healthy post-menopausal females were enrolled, all of them completed the study. Their body weight was between 54 and 82 kg (mean 66.9 kg), their height was between 151 and 176 cm (mean 164.3 cm) and their age was between 51 and 66 years (mean 57.3 years).
SAFETY	Both preparations were well tolerated. Adverse events were of minor degree. Mastalgia, depressive mood and vaginal discharge were the adverse events observed which were classified as probably related to estradiol. Mastalgia was slightly more prevalent with the ESTRADERM TTS® 25. No serious adverse events were reported. Upon discharge all subjects were in a state of good health.
TRANSDERMAL SYSTEM ADHESIVENESS AND LOCAL SKIN TOLERABILITY	The adhesiveness of both transdermal systems was comparable. The local skin tolerability of both treatment was very good.

PHARMACOKINETIC ANALYSIS

The extent of estradiol absorption is not statistically different following OESCLIM[®] 25 and ESTRADERM TTS[®] 25. The 90% confidence interval on log-transformed AUC₀₋₁₉₂ was 68.8: 112.3; The C_{av} were 17.4 and 18.9 pg/ml, respectively. The C_{ssmin} following OESCLIM[®] 25 was systematically higher than following ESTRADERM TTS[®] 25 (9.1 versus 7.7 pg/ml). The rate of estradiol absorption was faster with OESCLIM[®] 25 (t_{max} 16 h versus 44 h).

E2 levels (pg/ml)



CONCLUSIONS

OESCLIM[®] 25 and ESTRADERM TTS[®] 25, applied as 3+4 days per week over 3 weeks were well tolerated. The most frequently reported adverse events were hot flushes. However, most of the subjects who were suffering from hot flushes had experienced these symptoms before treatment at a higher frequency. Therefore, the relation to the test preparations was classified as doubtful.

The patch adhesiveness of both transdermal systems was comparable.

Both patches were well tolerated on the skin. Skin reactions (itching) of a minor degree were observed following ESTRADERM TTS[®] 25.

The treatments exhibited significant differences concerning the rate of absorption (shorter t_{max} following OESCLIM[®] 25) but no significant differences with respect to the extent of absorption. The peak-trough fluctuation after OESCLIM[®] 25 was about 20% lower than that following ESTRADERM TTS[®] 25. This difference, which was significant (p<0.05), was consistent with lower C_{max} and higher C_{min} as well as with generally higher trough levels after OESCLIM[®] 25.

It must, however, be regarded that the post-absorptive E2 levels were relatively low in relation to the endogenous basal levels, due to the low dose of exogenous E2.

The lower fluctuation after OESCLIM[®] 25 appears to be an advantage from a clinical point of view.

Reviewer Comment:

Sponsor's conclusions of this study are appropriate and acceptable.

5. Summary of Study K TS 17 95 01

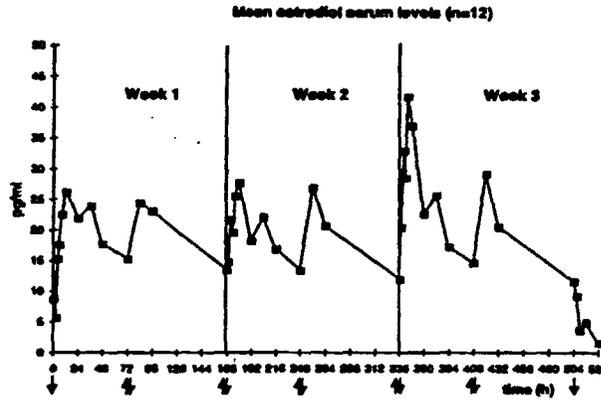
NAME OF STUDIED PRODUCT	OESCLIM® 25: estradiol transdermal system
TITLE OF THE STUDY	Pharmacokinetic study of estradiol during 3-week multiple applications of an estradiol transdermal system (OESCLIM® 25) in 12 healthy post menopausal women
PRINCIPAL INVESTIGATOR	
STUDY LOCATION	
START AND END OF STUDY	Start of study: 16 October 1995 Final patch removal from the final subject: 5 February 1996
STUDY AIM	To evaluate the estradiol pharmacokinetics during continuous wearing of LF estradiol transdermal systems (OESCLIM® 25) over 3 weeks.
CLINICAL PHASE	I
EXPERIMENTAL DESIGN	Multiple applications for each woman. Open.
NUMBER OF SUBJECTS INCLUDED	12
INCLUSION CRITERIA	Healthy post-menopausal women (30-65 years old) confirmed by: a. amenorrhea for at least 12 months or bilateral ovariectomy more than 3 months before the study, b. serum FSH level of greater than 9.6 IU/l, c. serum estradiol level of less than 25 pg/ml.
TREATMENT	Estradiol Transdermal System OESCLIM® 25. Percutaneous route. Approximate delivery rate 25 µg per 24 h.
TREATMENT DURATION	Multiple applications over 3 weeks (2 OESCLIM® 25 per week: a 3-day application immediately followed by a 4-day application).
EVALUATION CRITERIA	Estradiol, estrone and estrone sulphate serum levels determined by n = 41 blood samples corresponding to a blood volume of 328 ml per subject) <u>For weeks 1, 2 and 3:</u> - during the 3-day application: at 0 (before application), 2, 4, 6, 8, 12, 24, 36, 48 and 72 h after the 1st, 3rd and 5th applications. - during the 4-day application: at 12, 24 and 96 h after the 2nd, 4th and 6th applications. <u>Following week 3:</u> Four (4) additional blood samples were collected at 99, 102, 108 and 120 h after the last (6th) 4-day application: Pharmacokinetic parameters uncorrected and corrected for basal value (for each week): AUC ₀₋₇₂ , AUC ₀₋₉₆ , AUC _{week} , C _{min72} , C _{min96} , C _{max} , t _{max} , Cav ₀₋₇₂ , Cav ₀₋₉₆ and Cav _{week} .
STATISTICAL METHOD	Descriptive statistics.

RESULTS	
CHARACTERISTICS OF SUBJECTS ENTERED	Twelve (12) healthy post-menopausal women were enrolled into this study. Their mean age was 57.6 years (SD 6.8), their mean height was 1.58 m (SD 0.07) and their mean weight was 63.5 kg (SD 10.1).
SAFETY	<p>Adverse events</p> <p>There was a total of sixteen (16) adverse events reported in 8 subjects. Three of these events were considered to be "probably", and 6 "possibly" related to the study drug. Of the probable group, 2 adverse events were breast tenderness and 1 was a headache. Of the possible group there were 2 episodes of itch at the dose site, 2 episodes of rash at the dose site, a single episode of headache and a single episode of lightheadedness.</p>
LOCAL SKIN TOLERABILITY	There were no significant problems with local skin tolerability. Two subjects had redness and itching at the patch site on study day 18.
PATCH ADHESIVENESS	There were 4 occasions when the patch became detached (one partial and 3 complete). They were all reapplied and taped to secure them in position.
ANALYTICAL METHODS FOR ESTRADIOL FOR ESTRONE FOR ESTRONE SULPHATE	

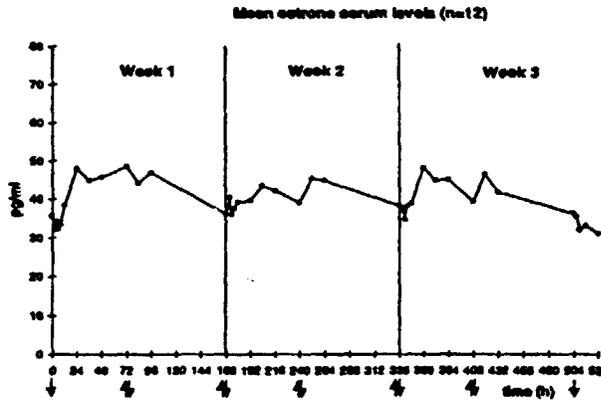
SERUM LEVELS

The E2, E1 and E1S serum levels obtained following multiple applications over 3 weeks (2 per ~~OSCLIM 085~~ application immediately followed by a 4-day application) are presented hereafter, in the following graphs:

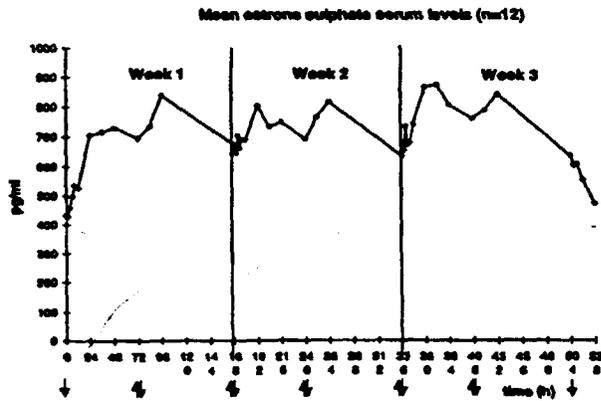
ESTRADIOL serum levels



ESTRONE serum levels



ESTRONE SULPHATE serum levels



**PHARMACOKINETIC
PARAMETERS**

ESTRADIOL pharmacokinetics (Mean ± SD)

	Week 1	Week 2	Week 3
AUC₀₋₂₄ (pg/mL.h)	1866	1685	2007
C_{av} (pg/mL)	19	18	20
C_{max} for 3-day application (pg/mL)	28	31	47
C_{max} for 4-day application (pg/mL)	10	13	33
t_{max} for 3-day application (h)	23	18	13
t_{max} for 4-day application (h)	12	14	11
C_{min} 72h* (pg/mL)	15	13	15
C_{min} 96h** (pg/mL)	6	5	6
	14	12	12
	7	6	6

ESTRONE pharmacokinetics (Mean ± SD)

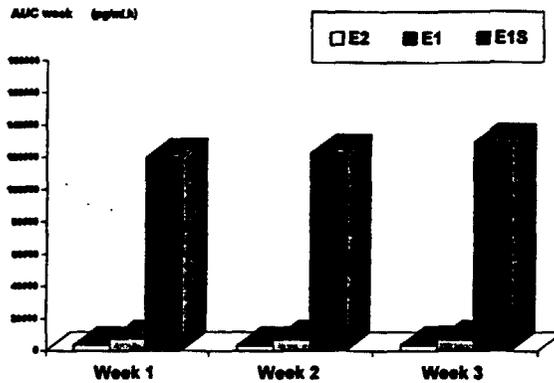
	Week 1	Week 2	Week 3
AUC₀₋₂₄ (pg/mL.h)	1444	1205	1365
C_{av} (pg/mL)	675	818	990
C_{av} (pg/mL)	43	41	41
C_{max} for 3-day application (pg/mL)	9	9	9
C_{max} for 3-day application (pg/mL)	53	49	52
C_{max} for 4-day application (pg/mL)	12	11	11
C_{max} for 4-day application (pg/mL)	51	48	48
C_{max} for 4-day application (pg/mL)	11	12	11
t_{max} for 3-day application (h)	50	31	37
t_{max} for 3-day application (h)	24	26	17
t_{max} for 4-day application (h)	8	23	18
t_{max} for 4-day application (h)	12	24	26
C_{min} 72h* (pg/mL)	48	39	39
C_{min} 72h* (pg/mL)	9	7	10
C_{min} 96h** (pg/mL)	36	38	36
C_{min} 96h** (pg/mL)	8	8	8

ESTRONE SULPHATE pharmacokinetics (Mean ± SD)

	Week 1	Week 2	Week 3
AUC₀₋₂₄ (pg/mL.h)	47802	50903	58037
AUC₀₋₂₄ (pg/mL.h)	22241	29266	37472
C_{av} (pg/mL)	715	734	772
C_{av} (pg/mL)	100	175	208
C_{max} for 3-day application (pg/mL)	783	877	952
C_{max} for 3-day application (pg/mL)	117	211	267
C_{max} for 4-day application (pg/mL)	880	880	912
C_{max} for 4-day application (pg/mL)	122	252	237
t_{max} for 3-day application (h)	41	25	39
t_{max} for 3-day application (h)	22	21	16
t_{max} for 4-day application (h)	28	22	14
t_{max} for 4-day application (h)	23	26	10
C_{min} 72h* (pg/mL)	696	693	782
C_{min} 72h* (pg/mL)	86	148	211
C_{min} 96h** (pg/mL)	674	637	637
C_{min} 96h** (pg/mL)	159	192	152

* at removal of a 3-day application
** at removal of a 4-day application

The AUC values for E2, E1 and E1S were stable over the 3 weeks as indicated in the following figure :



The AUC ratio between E2 and E1 for each of the 3 weeks was stable:

AUC	Week1	Week 2	Week 3
Ratio E2/E1	0.47	0.45	0.49

CONCLUSION

Continuous wearing of the OESCLIM[®] 25 transdermal systems was well tolerated. There were a total of 16 adverse events, none serious. Of these, 3 were considered to be “probably” related and 6 “possibly” related to the study drug. Two of the “probably” related events were breast tenderness, and the third a headache. There were no significant problems with local skin tolerability. There were 4 occasions of transdermal system detachment, one partial and 3 complete, all of which were immediately reapplied.

Multiple application for 3 weeks of OESCLIM[®] 25 produced consistent average serum concentrations of approximately 19 pg/ml for estradiol, 42 pg/ml for estrone and 740 pg/ml for estrone sulphate. No accumulation occurred following the 3-week application. The E2 to E1 ratio was maintained throughout the 3-week period at approximately 0.45.

The OESCLIM[®] 25 transdermal system would appear to be appropriate to be worn for at least the duration of this study and to deliver therapeutic doses of estradiol for the relief of menopausal symptoms.

Reviewer Comment:

Sponsor's conclusions are appropriate and acceptable.

6. Summary of Study K TS 17 93 02

Title: "Pharmacokinetic Study of Estradiol From a LF Estradiol Transdermal System, Esclim® 50, After Multiple Applications Over 3 Weeks, in 18 Healthy Post-menopausal Females."

Objectives: To evaluate the accumulation of estradiol during continuous wearing of Esclim 50 patch over 3-weeks.
To determine serum levels of estrone following multiple application of Esclim 50 patch.
To evaluate local skin tolerability and adhesiveness of patch.

Principal Investigator:

Study Center:

No. of Subjects: Eighteen (18) healthy post-menopausal women aged between 46 and 64 years completed the study.

Study Design: This was an open-label, single arm, 3-week continuous application study. Each women wore six Esclim 50 (22 cm², 50 µg/day) patches during the 3-week study period. Each week, two patches were applied to the outer quadrant of the buttock: one for 3 days followed by the second one for 4 days.

Sample collection: Blood samples for the determination of estradiol and estrone levels were obtained in each week at the following time points:

During the 1st application (3 days): at 0 (just before application), 2, 4, 6, 8, 12, 24, 36, 48 and 72 h after application.

During 2nd application (4 days): at 12, 24, and 96 h after application.

Two additional blood samples were collected at 108 and 120 h after the application of the last (6th) Esclim 50.

The subject's skin was assessed prior to application and a daily inspection of the transdermal system was carried out for the evaluation of adhesiveness and skin tolerability.

Assay Methodology:

Table 1: Serum estradiol quality control data:

Control	No. of determinations	Mean value pg/ml	Imprecision		Accuracy
			Standard Deviation	Coefficient of Variation (%)	Mean value as a % of spiked value
QC 1	40	28.9	2.9	10.0	N/A
QC 2	39	76.1	6.7	8.8	N/A
QC 3	36	104.4	11.2	10.7	N/A
QC 4	39	64.5	5.4	8.4	N/A
QC 5	38	153.9	25.6	16.6	N/A
Kit Control	27	88.0	6.1	6.9	N/A
Kit Control	10	92.7	10.7	11.5	N/A
Accuracy Control Spiked value 75 pg/ml	38	67.0	6.0	9.0	89.3

Table 2: Estrone quality control data:

Control	Target conc. Pg/ml	No. of determinations	Mean value pg/ml	Imprecision		Accuracy
				Standard Deviation	Coefficient of Variation (%)	Mean value as a % of Target
Low	N/A	38	31.4	5.0	15.8	N/A
Medium	N/A	38	148.1	17.5	11.8	N/A
High	N/A	37	513.9	53.1	10.3	N/A
Accuracy	72.7	38	64.2	7.6	11.8	88.3
Accuracy	193.9	38	204.8	19.7	9.6	105.6

The limits of quantitation for estradiol and estrone were 10 and 12.5 pg/ml, respectively.

Results:

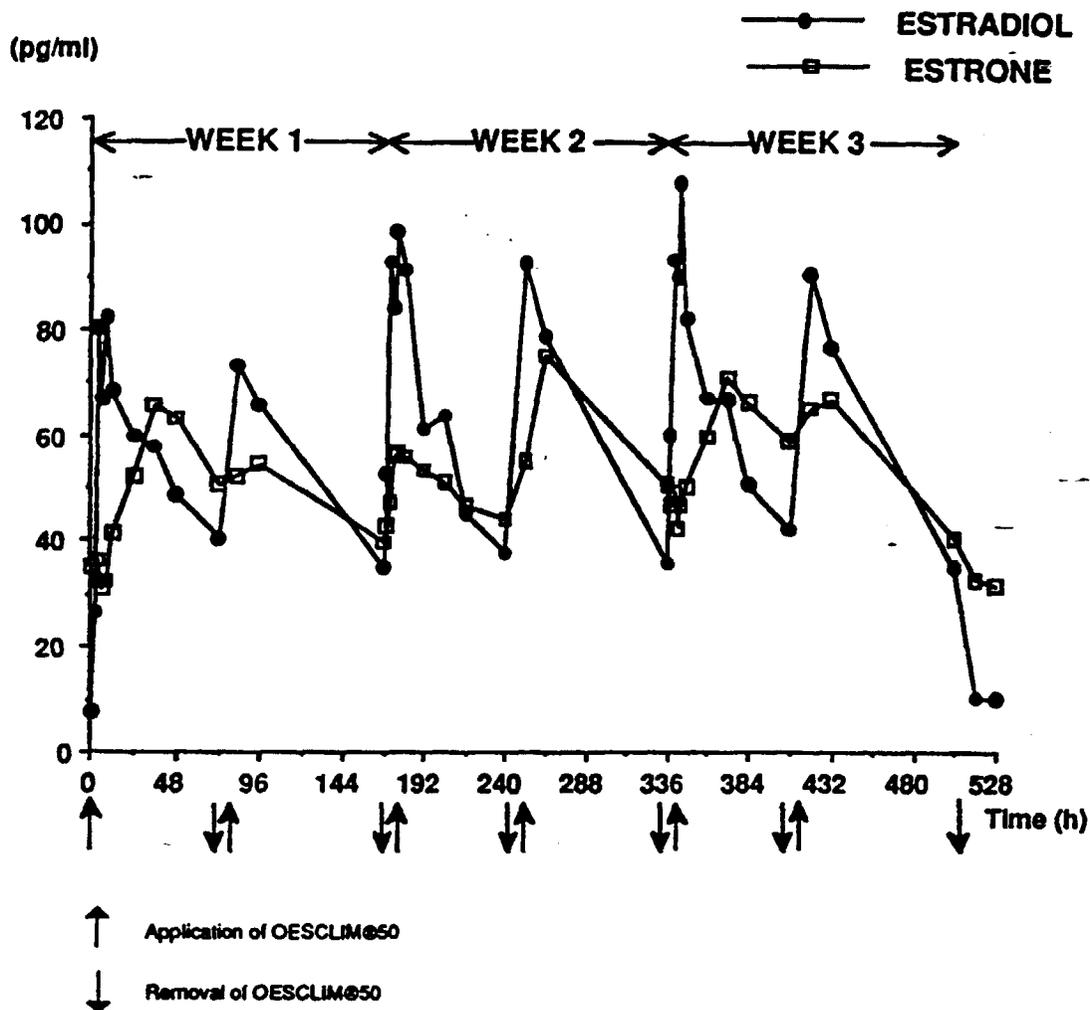


Fig 1. Mean serum levels of estradiol and estrone following multiple application of Esclim 50 for 3-weeks.

Table 3: Estradiol pharmacokinetic parameters (based on corrected serum estradiol levels) following multiple application of Esclim

Week	AUC ₍₀₋₇₂₎	AUC ₍₀₋₁₆₈₎	C _{av0-72}	C _{72h} [#]	C _{96h} [*]
Week 1	3366(1870)	7776(3804)	52(36)	33(15)	27(15)
Week 2	3749(1978)	8923(4784)	59(37)	30(16)	28(15)
Week 3	3986(1965)	9081(4444)	62(35)	35(20)	27(17)

at removal of 3-day application

* at removal of 4-day application

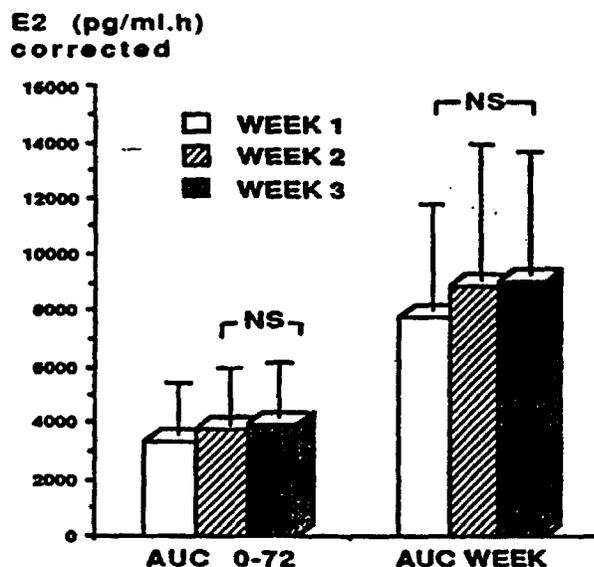


Fig 2: Comparison of mean AUC values for baseline corrected AUC values following multiple application of Esclim 50.

Estradiol steady-state:

ANOVA performed on logtransformed and corrected AUC_{0-168} failed to show any significant difference between 3 weeks. For C_{max} and AUC_{0-72} , there was no significant difference between week 2 and week 3, indicating the steady-state was reached within week 2.

Accumulation at steady-state :

As mentioned above, there was no significant difference in AUC_{0-168} , C_{72h} (at the end of 1st patch application) and C_{96h} (at the end of 2nd patch application) between week 1 and week 3. Therefore, it can be concluded that the accumulation of serum estradiol is minimal with multiple application of Esclim 50.

Estradiol/Estrone Ratio:

Corrected Data	Mean	SD	CV%	Min	Max
E2/E1 Ratio					
(during 1 week wearing)					
Week 1	1.05	0.25	23.4		
Week 2	1.05	0.29	28.0		
Week 3	1.05	0.29	28.1		

Comment: No individual ratio data available in the submission to support the results listed in the above table. However these values are close to the ratios of estradiol to estrone mean AUC values.

Sponsor's Conclusions:

- Steady-state of serum estradiol was attained during week 2 application Esclim 50 patch.
- Continuous application of Esclim 50 for a period of 3 weeks did not lead to any estradiol accumulation.
- The mean estradiol/estrone ratio of serum levels was equal to 1 and remain unchanged for the 3 weeks.

Reviewer Comment:

The sponsor's conclusion are appropriate and acceptable based on the results reported in Study K TS 17 93 02.

**APPEARS THIS WAY
ON ORIGINAL**

Double-blind, multicenter, Placebo-controlled clinical trial in parallel groups to evaluate the efficacy and safety of 12 weeks treatment with TS 17 on vasomotor symptoms in menopausal patients

C TS 17 93 01

Objective:	To compare the efficacy of 12 weeks of treatment with the three dosages of TS 17 (25, 50, and 100 µg /24hours) with that of Placebo on moderate to severe vasomotor symptoms (MSVMS) in women presenting with menopause-related estrogen deficiency.
Study design:	Prospective, randomized, Placebo-controlled, double-blind, multicenter study conducted in the United States
Number of patients (total):	199 allocated, 196 treated.
Number/treatment:	TS 17 25: 50 allocated, 48 treated; TS 17 50: 48 allocated, 47 treated; TS 17 100: 47 allocated and treated; Placebo: 54 allocated and treated.
Diagnosis and criteria for inclusion:	Menopausal women having an average of 56 MSVMS/per week over a 2-week baseline self-evaluation period.
Test product, dosage regimen, route of administration, batch no.:	TS 17 25 (11 cm ²), TS 17 50 (22 cm ²), and TS 17 100 (44 cm ²), which deliver (respectively) 25, 50, and 100 µg/24 hr. Each week two transdermal systems were applied (one for 3 days and one for 4 days). The batch numbers were C TS 17 93 01/1 and C TS 17 93 01/2.
Duration of treatment:	12 to 13 continuous weeks without treatment-free intervals. Each patient was to have used 24 to 26 transdermal systems during the study. Study visits occurred at baseline and weeks 5, 9, and 13 of treatment.
Reference therapy, dosage regimen, route of administration, batch no.:	Placebo transdermal systems were strictly identical to each of the three TS 17 systems, i.e., 11 cm ² , 22 cm ² , and 44 cm ² except that the matrix did not contain 17β-estradiol. Each week two transdermal systems were applied (one for 3 days and one for 4 days). The batch number for the Placebo systems was identified on the clinical trial supply label as C TS 17 9301/n.
Criteria for evaluation:	Efficacy on vasomotor symptoms, assessment of nine additional symptoms of menopause, vaginal smears, hormone levels, local skin tolerability, specific estrogen replacement therapy tolerability (including hyperestrogenism and bleeding), adverse events, safety monitoring measurements (blood pressure and pulse, weight, breast examination), biological assessments, transdermal system adhesion, and overall evaluation of efficacy and tolerability of the study treatment by the investigator and by the patient.
Statistical methods:	Both descriptive and inferential methods were used. Two-sided

Double-blind, multicenter, Placebo-controlled clinical trial in parallel groups to evaluate the efficacy and safety of 12 weeks treatment with TS 17 on vasomotor symptoms in menopausal patients

C TS 17 93 01

statistical tests were used at the 5% significance level, except for biological assessments where the 10% significance level was used. A test of difference was performed on the primary efficacy criterion, which was the mean reduction in MSVMS per day.

Results:

Efficacy:

This study demonstrated that each of the TS 17 doses (25, 50, and 100 µg/24 hr) were clinically and statistically superior ($p < 0.05$) to Placebo in reducing the frequency of MSVMS. Statistical significance vs Placebo in reduction of MSVMS from baseline was obtained within the first 2 weeks of treatment for the two higher doses, and within 3 weeks for the lowest dose (Dunnett's test). Complete relief of MSVMS was obtained in a dose-related fashion, with statistical significance vs Placebo demonstrated within the first 2 weeks for TS 17 50, within 3 weeks for TS 17 100, and within 8 weeks for TS 17 25. Estradiol, estrone, and estrone sulfate levels were increased in a dose-related fashion, and FSH was concurrently reduced. Trophicity of vaginal smears was improved in all patients treated with TS 17 who had atrophic or subatrophic smears at entry.

Patients eligible for efficacy				
	Placebo (N = 45)	TS 17 25 (N = 42)	TS 17 50 (N = 39)	TS 17 100 (N = 40)
Frequency of MSVMS per day (Means ± SD)				
Baseline	11.6 ± 3.9	12.0 ± 5.4	11.1 ± 4.5	11.2 ± 2.9
Week 4	5.8 ± 5.5	2.8 ± 3.3	1.5 ± 2.7	1.0 ± 1.9
Patients with complete relief of MSVMS n (%)				
Week 4				
Week 8	1 (2.1)	7 (16.7)	16 (41.0)	21 (55.3)
Week 12	5 (10.9)	14 (35.0)	25 (64.1)	27 (71.1)
	6 (13.0)	23 (57.5)	24 (64.9)	29 (80.6)
Estradiol levels (Means ± SD)				
Baseline (pg/mL)	17.6 ± 11.7 19.6 ± 14.0	18.0 ± 7.7 48.2 ± 27.4	18.1 ± 8.2 102.8 ± 63.6	16.9 ± 9.1 165.3 ± 116.1

Week 12				
FSH levels (Means ± SD)				
Baseline (mIU/mL)				
Week 12	112.6 ± 38.9	130.4 ± 50.6	130.6 ± 50.8	112.4 ± 37.9
	113.6 ± 39.6	75.6 ± 28.8	34.4 ± 19.8	19.2 ± 15.0
Vaginal Smears (n, %)				
Non-trophic at Baseline				
Non-trophic at Week 12	10 (27.7)	7 (19.5)	13 (37.1)	9 (29.1)
	10 (33.3)	0	0	0

Safety:

From the perspective of local tolerability, the TS 17 estradiol transdermal system was well tolerated. Excluding isolated erythema of short duration, only 4.5% of TS 17 25 applications caused any type of application site reaction, vs 9.7% and 9.4% of the TS 17 50 and 100 applications, respectively. These application site reactions caused discomfort or only slight discomfort in less than 10% of the TS 17 25 and 100 applications, and in 35.3% of the TS 17 50 applications. Premature removal due to inadequate tolerability was required for only six transdermal systems. A trend toward an increase in application site reactions with increase in the size of the TS 17 system was suggested.

Systemic tolerability of the TS 17 system was consistent with reported experience with estrogen replacement therapy (ERT). The most commonly reported adverse effects (AEs) were related to the genito-urinary system, and included breast pain (3.7%, 22.9%, 44.7%, and 40.4% in the Placebo, and TS 17 25, 50, and 100 groups, respectively), metrorrhagia (9.5%, 31.6%, 56.0%, and 57.1% of non-hysterectomized patients, respectively) and endometrial hyperplasia (0%, 8%, 50% and 50% of biopsied patients, respectively). The last two AEs are expected with unopposed estrogen therapy and support the use of concomitant progestogen therapy. There was a statistically significant increase in AEs attributed to the study medication with increased dose.

Adhesivity:

The percentage of systems that became spontaneously detached was very low across all groups, ranging from 4.3% of the applications in the Placebo group to 5.5% of the applications in the TS 17 25 group.

Acceptability:

Patient satisfaction with the active study treatment was good in most cases, with only 2.2-8.7% of the patients on active treatment expressing lack of satisfaction, compared to 51.8% of the Placebo-treated patients, probably due to lack of efficacy in that group. Similarly, 82.6-87.0% of patients treated with the active treatment would have been willing to continue the study treatment, compared to only 48.2% of Placebo-treated patients.

Conclusion:

The TS 17 estradiol transdermal system is a safe, effective, and well-accepted treatment for symptoms associated with estrogen deficiency due to natural or surgical menopause. A trend toward a dose response was demonstrated between the lowest and highest doses, but all three dosages were significantly more effective than Placebo ($p < 0.05$). The onset of activity was demonstrated to be within 2 weeks in the two highest dose groups, and within 3 weeks in the lowest dose group. Adverse events were typical of those reported during ERT with other products.

Reviewer Comment:

The sponsor's conclusions are acceptable from pharmacokinetic perspective. However, it should be noted that the sponsor did not attempt to find a PK/PD relationship between steady state serum estradiol levels and the relief of hot flushes.

APPEARS THIS WAY
ON ORIGINAL

**Comparative bioavailability study of estradiol from two different aged TS 17 transdermal systems
(recent versus 24-month old)
KH TS 17 92 02**

Investigator (s) :	
Study center.(s) :	
Publication (reference) :	
Study period (years) :	1993
Clinical phase :	I
Objective :	To compare estradiol serum levels after application of two different LF transdermal systems: one from a recent batch (TS 17 0.05), the other from a 24-month old batch (TS-17 20 cm ²).
Methodology :	Open, balanced, randomized, two-part crossover.
Number of subjects :	Six.
Diagnosis and criteria for inclusion :	Healthy post-menopausal women, with estradiol serum levels < 25 pg/mL, LH serum levels > 16 IU/L, FSH serum levels > 18 IU/L and no vaginal bleeding for at least 12 months.
Test product, dosage regimen, route of administration, batch no.:	24-month old TS 17 20 cm ² (batch 484 VP), 4-day application on the buttock, percutaneous route.
Duration of treatment :	2 x 4 days with a 3-day washout period.
Reference therapy, dosage regimen, route of administration, batch no.:	Recent TS 17 0.05 22 cm ² 4-day application on the buttock, percutaneous route. Batch 700 VP
Criteria for evaluation :	Estradiol serum levels, pharmacokinetic parameters.
Statistical methods :	ANOVA.

Summary:

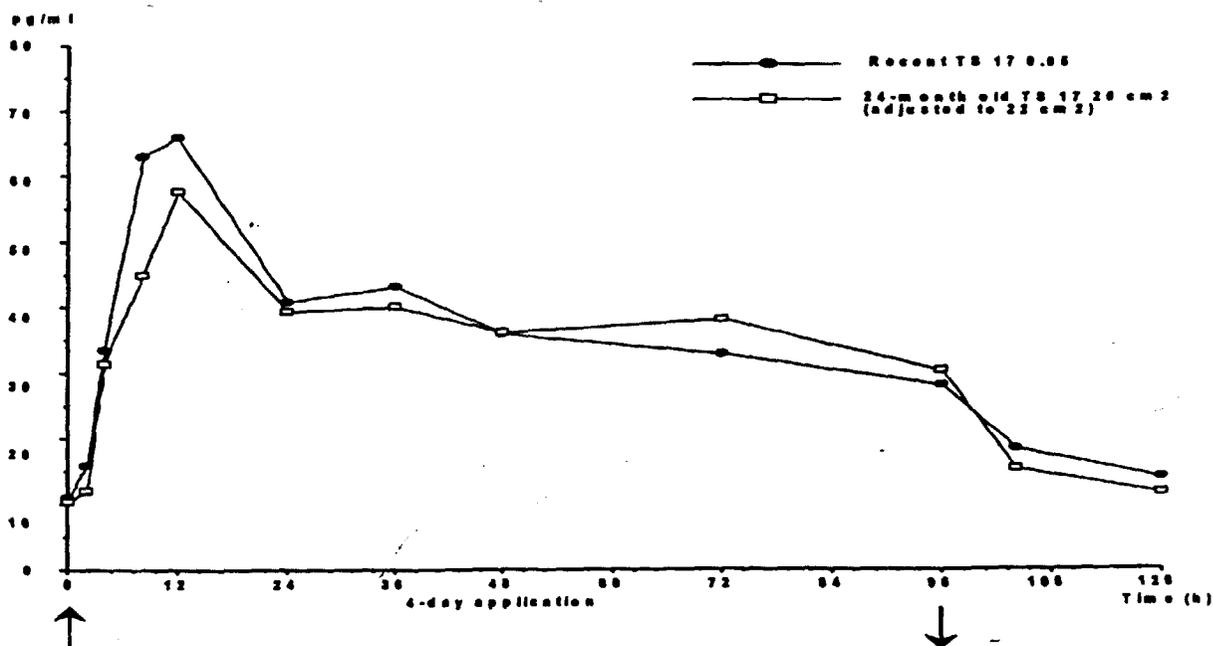
Six healthy post-menopausal women (aged 56-67 years) who complied with the entry criteria and restrictions, attended the clinical pharmacology unit on the morning prior to each transdermal system application. Blood samples were taken before the transdermal system application and then 2, 4, 8, 12, 24, 36, 48, 72, 96, 104, and 120 hr following application of the two transdermal systems. Immediately following the 96 hr blood collection, the transdermal system was removed. Estradiol serum levels were determined by

Both TS 17 transdermal systems were well tolerated with only eight adverse events reported, which were distributed evenly between the two transdermal systems. (The most common events were loose bowels, headache, and sore throat.) The drug relationship and the severity of these adverse events are summarized below.

SEVERITY	Mild	Moderate	Severe
DRUG RELATIONSHIP			
Definite			
Probable			
Possible	1		
Unlikely	1	1	
Unrelated	5		

Mean estradiol serum concentrations versus time profiles obtained following 4-day application of the two different aged TS 17 transdermal systems, with normalization to 22 cm² for the old transdermal system (TS 17 20 cm²) are illustrated in the following figure.

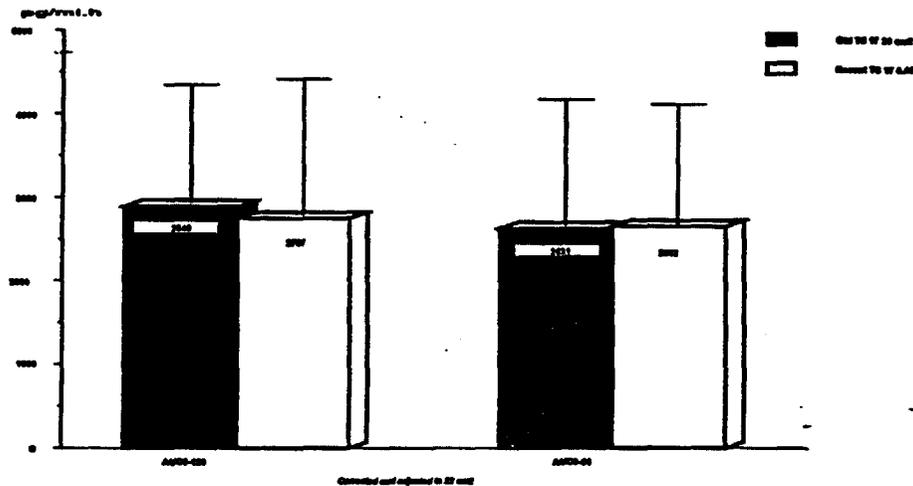
Mean estradiol serum levels following a 4-day application of two different aged TS 17 Transdermal Systems (N = 6)



Comparison of mean corrected and adjusted to 22 cm² pharmacokinetic parameters

(AUC_{0-120} and AUC_{0-96}) is illustrated in the following figure.

Comparison of mean \pm SD corrected and adjusted to 22 cm² pharmacokinetic parameters (AUC_{0-120} and AUC_{0-96}) obtained following a 4-day application of two different aged TS 17



(Analysis of log transformed, basal corrected and adjusted to 22 cm² data (AUC_{0-120} , AUC_{0-96} , C_{max} , $C_{av,0-96}$, and C_{min}), showed no significant difference between the two TS 17 transdermal systems.

(These results suggest that the rate and extent of estradiol absorption from the 24-month old TS 17 20 cm², normalized to 22 cm², are statistically similar to the recent TS 17 0.05. The estradiol serum levels determined at the removal of the two different aged TS 17 Transdermal Systems (4 days after the application) are very close.

Reviewer Comment:

(Although the number of subjects used in this study was only six, the results of the study could be supportive of stability data in determining the shelf-life of Esclim.