

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-847**

**CHEMISTRY REVIEW(S)**

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580  
Review of Chemistry, Manufacturing and Controls

JUL 31 1998

NDA #: 20-847

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 31-JUL-98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	07-AUG-97	07-AUG-97	14-AUG-97
Amendment	10-APR-98	17-APR-98	27-APR-98
Amendment	28-APR-98	30-APR-98	07-MAY-98
Amendment	12-MAY-98	13-MAY-98	17-MAY-98
Amendment	01-JUL-98	02-JUL-98	02-JUL-98
Amendment	15-JUL-98	16-JUL-98	20-JUL-98
Amendment	28-JUL-98	29-JUL-98	28-JUL-98
Amendment	30-JUL-98	31-JUL-98	30-JUL-98
Amendment	31-JUL-98	01-AUG-98	31-JUL-98

NAME & ADDRESS OF SPONSOR: Laboratoires Fournier S.A.  
Fournier Research, Inc.  
9 Law Drive  
Fairfield, NJ 07005

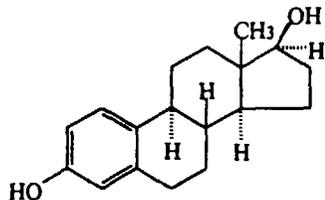
DRUG PRODUCT NAME:

Proprietary: Esclim  
Nonproprietary/Established/USAN: 17 $\beta$ -estradiol  
Code Name/#: TS-17  
Chem. Type/Ther. Class: 3S

PHARMACOLOGICAL CATEGORY/INDICATION: Estrogen/Hormone replacement therapy for menopausal women

DOSAGE FORM: Transdermal system/patch  
STRENGTHS: 0.025, 0.0375, 0.05, 0.0375, 0.1 mg/day  
ROUTE OF ADMINISTRATION: Transdermal  
DISPENSED:   x   Rx        OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



- a) Estra-1,3,5(10)-triene-3,17 $\beta$ -diol  
b) (17 $\beta$ )-Estra-1,3,5(10)-triene-3,17-diol

Molecular formula: C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>  
Molecular weight: 272.39 (281.4 for hemihydrate form)  
CAS # 50-28-2      CAS # 35 380-71-3 (hemihydrate form)

CONCLUSIONS & RECOMMENDATIONS:

The firm has adequately provided satisfactory responses to each of the issues raised in the first chemistry review. This NDA may be approved from a chemistry standpoint.

cc:

Orig. NDA #20-847  
HFD-580/Division File  
HFD-580/DMoore  
HFD-580/MRhee/DLin

/S/

7/31/98

R/D Init by:

filename: nda20847.2 (doc)

David T. Lin, Ph.D.  
Review Chemist

**SUPPORTING DOCUMENTS:**

See Chem. Rev. #1.

**RELATED DOCUMENTS:**

See Chem. Rev. #1.

**CONSULTS:**

1. The Division of Biopharmaceutics has been consulted for the dissolution specifications. DrJarugula recommended revising the specifications to:
2. The EER was sent to Compliance on October 28, 1997. It was returned as acceptable on May 26, 1998 (see appendix A).
3. The Division of Microbiology has found the NDA to be acceptable (see Micro Rev. #2: July 28, 1998).

**REMARKS/COMMENTS:**

The April 10, 1998 amendment contains the description of the manufacturing process and controls used by to produce the paper-aluminum-copolymer complex from which the sachets are made. In addition, the firm agreed to withdraw from the NDA as the alternate supplier for the polyester release liner.

The April 28, 1998 amendment contains the 9 month controlled room temperature stability data for Esclim batch 002 and the 3 month accelerated and controlled room temperature stability data for Esclim batch 003.

The May 12, 1998 amendment contains information concerning the change in name for the manufacturing site from

The July 1, 1998 amendment response contains the complete response, except for the revised Methods Validation Package, to the information request letter dated June 2, 1998.

The July 15, 1998 amendment contains the complete revised Methods Validation Package.

The July 28, 1998 amendment contains clarification of the version numbers for the test methods in the Methods Validation Package that was submitted on July 15, 1998. In addition, the firm agreed to the Division's request for tighter dissolution (drug release) specifications, and submitted revised regulatory specifications for the 5 strengths of transdermal products.

The July 30 and 31, 1998 amendments contain the revised physician package insert, and revised package labeling of the pouches and cartons.

Moore

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580  
Review of Chemistry, Manufacturing and Controls

MAY 28 1998

**NDA #:** 20-847

**CHEMISTRY REVIEW #:** 1

**DATE REVIEWED:** 11-APR-98

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Original	07-AUG-97	07-AUG-97	14-AUG-97
Amendment	05-MAR-98	06-MAR-98	14-MAR-98

**NAME & ADDRESS OF SPONSOR:** Laboratoires Fournier S.A.  
Fournier Research, Inc.  
9 Law Drive  
Fairfield, NJ 07005

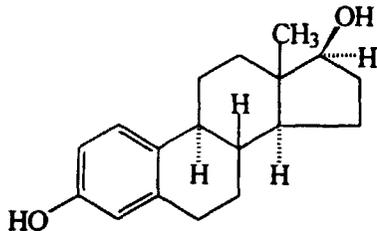
**DRUG PRODUCT NAME:**

**Proprietary:** Esclim  
**Nonproprietary/Established/USAN:** 17 $\beta$ -estradiol  
**Code Name/#:** TS-17  
**Chem. Type/Ther. Class:** 3S

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**ROUTE OF ADMINISTRATION:** Transdermal  
**DISPENSED:**    x Rx    OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**



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Molecular weight: 272.39 (281.4 for hemihydrate form)  
CAS # 50-28-2    CAS # 35 380-71-3 (hemihydrate form)

**CONCLUSIONS & RECOMMENDATIONS:**

This NDA is not approvable from the standpoint of chemistry and manufacturing controls. The application contains a number of deficiencies delineated in the draft letter, which need to be addressed by the sponsor before approval. In addition establishment evaluations must be completed, with satisfactory results for all facilities.

cc:  
Orig. NDA #20-847  
HFD-580/Division File  
HFD-580/DMoore  
HFD-580/MRhee/DLin

R/D, Init by: *MLD* 5/28/98  
filename: nda20847.1 (doc)

*IS!*  
\_\_\_\_\_  
David T. Lin, Ph.D.  
Review Chemist

5/26/98

**SUPPORTING DOCUMENTS:**

Type/Number	Subject	Holder	Status	Review Date	Letter Date
IND			Active	N/A	N/A
DMF			Acceptable	2/26/98	12/9/96
DMF			Acceptable		3/25/95
DMF			Acceptable	4/2/98	1/24/97
DMF			Acceptable		3/20/97
DMF			Acceptable		1/13/97

**RELATED DOCUMENTS:****Patent Information**

U.S. Patent No. 4,842,864

Expiration Date- March 25, 2008

Type of Patent- Drug product (formulation of 17 beta-estradiol)

Patent Owner of Record: Laboratoires d'Hygiene et de Dietetique

**CONSULTS:**

1. The Division of Biopharmaceutics has been consulted for the dissolution specifications.
2. The EER was sent to Compliance on October 28, 1997. The results of the inspections are not back from Compliance.
3. The proposed tradename, Esclim, was sent to the Nomenclature and Labeling Committee on September 26, 1997. The Committee determined the tradename to be acceptable (Feb. 18, 1998; see appendix A).

**REMARKS/COMMENTS:**

This NDA is for an estradiol transdermal system being proposed as a hormone replacement therapy for menopausal women. The proposed clinical uses are: 1) treatment of moderate to severe vasomotor symptoms associated with menopause; 2) treatment of vulval and vaginal atrophy; and 3) treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure. This product will be manufactured in five dosage strengths, corresponding to the amount of estradiol delivered per day through the skin (25, 37.5, 50, 75, and 100 µg/day).

The Nov. 26, 1997 and Dec. 1, 1997 amendments are for a claim of categorical exclusion from Environmental Assessment.

The Mar. 5, 1998 amendment contains 6 month stability data for Esclim batch 002, and 1 month stability data for Esclim batch 003.

- had undergone laboratory tests obtained after the selection visit after an overnight fast, as follows;
- hormone assays demonstrating a low plasma concentration of estradiol and a high concentration of Follicle Stimulating Hormone, compatible with a diagnosis of menopause according to the normal values of the laboratory facility;
- liver function tests that did not demonstrate any severe hepatic disorder
- assay of lipid concentration not showing severe hyperlipidemia
- biological, hematological, and biochemical tests which had not shown severe anemia or diabetes;
- coagulation tests showing normal results:
- 2 tumor markers: CA 125 and SccTA4 < upper limits normal range [This criteria was amended to permit patients with a CA 125 two times normal range to participate;

**Reviewers comments: The inclusion and exclusion criteria of this study present problems similar to those noted in study TS 17 91 02. The patient population is not representative of the US population. There are no defined levels of FSH and estradiol as entry criteria, which possibly results in the inclusion of perimenopausal patients. This study permits inclusion of patients who have had only one vasomotor symptom, which limits our ability to use this study in evaluating efficacy related to treatment of vasomotor symptoms. However, since the primary objective of this study was safety (and not efficacy), results regarding tolerability and adhesion of the patches should still be interpretable.**

#### 6.5 Screening period:

During screening period informed consent was obtained from the patient. A physical examination was performed, this exam included measurement of height, weight, blood pressure, pulse, gynecological exam including vaginal smears and breast exams were performed to assess the patients eligibility. Laboratory tests and mammography were requested. Patients previously treated for menopause were required to undergo a washout period of at least one month from last dose of hormonal treatment. The number and severity of vasomotor symptoms, which occurred daily for the seven days that preceded the baseline visit, were recorded.

#### 6.6 Treatment period:

##### Inclusion visit:

At inclusion visit diary, laboratory parameters, vaginal smear and mammography results were checked. A clinical exam identical to that performed during the screening visit was performed and the buttock skin was examined. Patients were randomized to treatment groups.

The treatment period was 96 days divided into four 28 day cycles. Patient used the estrogen patches twice a week for the first 24 days of each treatment cycle; therefore patients would use 7 patches each cycle. All non-hysterectomized patients were given a

progesterin to take for the last 12 days of the 24 day estrogen cycle. Patients were medication free for the last four days of each treatment cycle.

#### Visit 1 (week 5) and visit 2 (week 9)

At these visits, interim physical examinations were performed, and diary data were reviewed,

The patient was asked about any change in symptoms, and the patch sites were examined. Data was extracted from the diary and case report forms were completed. An assessment of safety and adverse events was obtained.

#### Visit 3 (week 13)

All the evaluation of visit 1 were performed, in addition a vaginal smear and laboratory tests were performed. An overall evaluation of efficacy, acceptability, general safety and local skin tolerability were performed.

#### Final visit (week 17)

During the final visit adverse events were recorded. A physical exam was performed. Laboratory tests obtained at visit 3 including vaginal cytology were checked.

#### 6.7 Evaluation criteria:

The primary criteria for evaluation in this study was the assessment of the total number of application site reactions. Secondary criteria for evaluation was the assessment of the number (%) of patients with at least one site reaction.

#### 6.8 Withdrawal and compliance

Seven patients in the TS 17 50 group and twelve patients in the Estraderm TTS®50 group withdrew prematurely for adverse events. In the TS 17 50 group four patients withdrew because of bleeding, one for an application site reaction, one for mastodynia and one for suicidal ideation. In the Estraderm group seven patients withdrew for application site reactions, three for bleeding, one for eczema, and one for headaches and a sensation of being tired.

#### Reviewer's comment:

**The difference in the percent of patients (0.7% of Esclim® and 5.1% of Estraderm®) who withdrew prematurely due to application site reactions was significant, supporting the sponsors conclusion that the local skin tolerability of Esclim® is better than EstradermTTS®.**

#### 6.9 Efficacy analysis

The primary criteria for evaluation was comparing the number of application site reactions relative to the total number of applications between the TS 17 50 patients and those treated with Estraderm TTS®. The definition of a site reaction included patients having either redness, spots, swelling, itching or burning sensation. In the TS 17 50

patients, 157 (4.2%) site reactions occurred in 3706 applications. In the Estraderm TTS@50 patients 323 (9.5%) site reactions occurred in 3406 applications. Statistical analysis revealed a statistically significant difference in the number of site reactions relative to the total number of applications between TS 17 50 and Estraderm TTS @.

**Reviewer's comments:**

**This study demonstrated a significant difference in skin reactions between Esclim® (4.2%) and Estraderm TTS® (9.5%). However, in study 9301 the rate of skin reactions with Esclim® 50 was 9.9%. In study 9301 it appeared that the incidence of skin reactions was dose dependent. Since different studies demonstrate different rates of skin reactions, and since this may be dose dependent it is difficult to make a claim comparing skin reaction between Esclim® and Estraderm TTS® from study 9104 alone. These data are supportive, however, and an additional well-designed trial comparing Esclim® to Estraderm TTS® (at multiple comparable doses) and in a racially diverse population may support a claim of superiority.**

**Secondary criteria**

There was a statistically significant difference ( $p=0.013$ ) in the number (%) of patients having an application site reaction. In the TS 17 50 group, only 37 patients (25.9%) experienced an application site reaction, versus 55 patients (39.9%) in the Estraderm TTS@ 50 group. Evaluation of each type of reaction (itching, redness, spots, burning sensation, swelling) revealed a statistically significant difference when comparing the TS 17 50 patients to the Estraderm @TTS 50 patients. The patterns of each type of reaction were similar in the Estraderm@TTS 50 and the TS 17 50 patients.

Table 14  
Types of application site reactions as a percentage of all reactions

Type of application site reaction	Number(%) of each type of reaction	
	TS 17 50 (reactions =157)	Estraderm (reactions=323)
itching	100(63.7)	200(61.9)
redness	105(66.9)	250(77.4)
spots	29(18.5)	50(15.5)
burning sensation	7(4.5)	22(6.8)
swelling	9(5.7)	46(14.2)

Modified from table 37 page 20729

There was no statistically significant difference between the time in days to onset of the first application site reaction between the two treatment groups. The mean duration of application site reaction was 24 hours in both treatment groups. None of the reactions in the TS 17 50 group lead to premature removal, compared with 11 (3.4% of total reactions) in the Estraderm@TTS 50 group.

Vasomotor symptoms were analyzed as a secondary aim of this study. Since no minimum number of vasomotor symptoms was required for inclusion in this study, the

analysis was performed on a highly symptomatic (i.e., 5 or more symptoms per day at baseline) subgroup patients.

There was a statistically significant decrease in the number of vasomotor symptoms in each highly symptomatic subgroup from baseline to each treatment visit.

The analyses of efficacy were noted to show comparable results between Esclim® and Estraderm TTS®

#### Hormone levels

There was a significant difference ( $p < 0.001$ ) between estradiol and FSH between baseline and endpoint in both treatment groups. Results are given in table below.

Table 15

Estradiol and FSH levels at baseline and endpoint in all included patients

Hormone levels	TS 17 50 (n=143)	EstradermTTS®50 (n=140)
Estradiol (pmol/l)		
Baseline		
N	141	138
Mean (SD)	74.3(83.5)	68.3(73.4)
Median (Range)	50.0(5.1, 697.5)	42.2(2.2, 594.7)
Endpoint		
N	131	125
Mean (SD)	317.5(264.4)	197.7(223.7)
Median (Range)	250.0(18.3, 1387.6)	132.2(18.3, 1306.9)
FSH (mIU/ml)		
Baseline		
N	142	137
Mean (SD)	88.4(165.0)	75.0(38.6)
Median (Range)	71.7(2.4, 2000.0)	72.7(0.5, 318.5)
Endpoint		
N	131	120
Mean (SD)	34.4(28.3)	43.7 (23.2)
Median (Range)	26.9(0.8, 150.0)	43.3(2.0, 161.4))

Modified from table 70

**Reviewer's comments:** The mean serum estradiol levels at endpoint for TS 17 50 patients is 1.6 times greater than the level achieved in the EstradermTTS® 50 patients. No central laboratory was used, and there were no consistent normal values used by the different labs. Therefore, this data is difficult to interpret meaningfully.

**Adhesion of the transdermal systems:**

Detachment of the transdermal system was analysed both globally and by circumstance. A total of 224 (6.0%) and 384 (11.3%) applications became detached from patients being treated with TS 17 50 and Estraderm TTS® 50 respectively. The proportion of TS 17 50 systems which became detached during bathing, showering and dressing was less than that for Estraderm TTS® 50, this difference was statistically significant.

**Reviewer's comments:**

**This study demonstrated a significant difference in detachments between Esclim® and Estraderm TTS®. To obtain a labeling superiority claim the sponsor would need to compare the products in a racially diverse population that is representative of the United States. The study should include the various dosages of each product to confirm the detachment rates for each dose. The study should be designed and powered to demonstrate a clinically significant difference in detachment rates as a primary endpoint.**

**Global assessment:**

The global success rate as evaluated by the investigator was higher for the TS 17 50 group than for the Estraderm TTS® 50. This difference, however, was not statistically significant ( $p=0.051$ ), and this was not a blinded study.

**6.10 Safety analyses:**

Fifty two (36.4%) of patients in the TS 17 50 group and 45 (32.1%) in the Estraderm TTS®50 group experienced at least one adverse event attributed to hormone replacement therapy. Metrorrhagia were experienced by 26 (18.2%) patients in the TS 17 50 group and 21 (15.0%) patients in the Estraderm®TTS 50 group. This difference was not statistically significant. Other than altered hormonal levels no category of adverse events attributed to hormone replacement therapy had more than one patient. Of all included patients 93 (90.3%) in the TS 17 50 group and 88(93.6%) of patients in the Estraderm®TTS 50 group had at least one withdrawal or non-menstrual bleed. The difference between the two groups for one episode of withdrawal bleeding was not statistically significant. There was no statistical difference between treatment groups in the duration or quantity of withdrawal bleeding.

There were no deaths in either treatment group. Four serious adverse events were reported in patients treated with medication. Three patients were in the TS 17 50 group: one had hyperthyroidism, one was hospitalized with hypoesthesia (which spontaneously improved), and one patient had a nephrectomy for a kidney tumor. The one serious adverse reaction in the Estraderm®TTS 50 group was a patient hospitalized for hemorrhoids.

In the TS 17 50 group there was a statistically significant decrease between baseline and endpoint in total cholesterol, LDL-cholesterol, and triglycerides.

### 6.11 Reviewers assessment of safety and efficacy:

This study supports the conclusion that TS 17 50 was better than Estraderm TTS® when evaluated for local skin tolerability and adhesion. To obtain a labeling superiority claim for skin tolerability and adhesion, however, the sponsor would need to compare the products in a racially diverse population that is representative of the United States. In addition, the study should include the various dosages of each product to confirm the skin irritation and detachment rates for each dose. The study should be designed and powered to demonstrate a clinically significant difference in these desired endpoints.

This study demonstrated TS 17 50 to be equivalent to Estraderm TTS® 50 when evaluated for relief of vasomotor symptoms. There are many issues with the study design which make it difficult to evaluate and compare the results to other trials therefore this trial will not be weighted heavily when considering efficacy related to vasomotor symptoms. There were no unexpected adverse events.

### 7.0 Overview of Efficacy

The clinical development program presented includes three trials to support effectiveness of this product. A total of 540 patients were enrolled in the three trials. Study 9301 compared three Esclim® patches (TS 17 25, TS 17 50 and TS 17 100) to placebo and was the pivotal trial. Study 9102 compare the Esclim® TS 17 50 patch to placebo. The third study 9104 was primarily a safety study and compared the Esclim® patch to Estraderm TTS®50. Table summarizes the efficacy results regarding vasomotor symptoms for each of these three trials.

Table 16  
Summary of controlled clinical trials

Protocol Number Study Design	Duration of treatment (weeks)	Treatment and Doses	Number of patients entered per regimen	Mean Change from baseline Weekly Hot Flush Rate to final visit $\pm$ SD	Symptom Criteria	Application Site	Race Caucasian/ Other
9301 Double blind Randomized, 4-parallel groups vs placebo,	12 to 13 weeks	TS 17 25	48	10.3 $\pm$ 4.4	$\geq$ 56 moderate to severe hot flushes per week during the 14 day self assessment	buttock	92.1% Caucasian
		TS 17 50	47	10.8 $\pm$ 4.4			6.1% African American
		TS 17 100	47	10.5 $\pm$ 2.7			1.0% Other
		Placebo	54	5.4 $\pm$ 5.2			
9102 Double blind Randomized, parallel vs. placebo,	12 to 13 weeks	TS 17 50 Placebo	32 29	9.1 $\pm$ 4.1 5.1 $\pm$ 6.0	$\geq$ 5 hot flushes per day and $\geq$ 1 night sweat both on 4 days during the 7 day assessment	buttock	100% Caucasian
9104 Open label randomized Parallel vs. Estraderm®TTS	16 weeks	TS 17 50 Estraderm® TTS 50	143 140	9.4 $\pm$ 6.7 10.0 $\pm$ 5.8	$\geq$ 1 hot flushes per day and $\geq$ 1 night sweat during the 7 day assessment	buttock	100% Caucasian

Study 9301 (the pivotal U.S. study) demonstrated a statistically significant difference between all active treatment groups from the placebo control in mean reduction of moderate to severe vasomotor symptoms at week 4. There was a dose response noted in

the active treatment groups in the first three weeks of therapy. By the end of the study all active treatment groups demonstrated at least an 80% reduction in vasomotor symptoms in the majority of women treated with Esclim®. There was a dose response noted in the three active treatments regarding the percentage of patients who had complete relief of symptoms as well as the change from baseline in the severity of symptoms. Study-9102 demonstrated a statistically significant difference between TS 17 50 and placebo in the mean reduction of moderate to severe vasomotor symptoms at week 4. Study 9104 demonstrated TS 17 50 to be equivalent to Estraderm TTS® 50 when evaluated for relief of vasomotor symptoms. These three studies showed consistent effects of Esclim® on moderate to severe vasomotor symptoms, and support the approval of this application.

### 8.0 Overview of Safety Phase II/III trials

The adverse events seen in patients treated with Esclim patches were consistent with the events described in general class labeling for estrogen preparations.

#### Application site reactions:

In the Phase 2/3 trials, the most frequently reported adverse events were application site reactions. The local safety and tolerability of TS 17 was assessed in a total of 80,586 TS 17 systems, 2,014 for the placebo control and 3,406 for the Estraderm TTS®50 in the clinical program. Some degree of irritation was seen in 38.0% of patients who used TS 17 in the Phase 2/3 studies. Application site reactions as a percentage of total applications were 3.6% of TS 17 systems applied in all Phase 2/3 studies. This compares favorably to the incidence of site reactions noted using other estrogen skin patches.

Long term use of Esclim® did not result in an increased incidence of skin reactions. The application site reactions as a percentage of total applications were 3.3% in patients who used TS 17 system in the long-term adjustable dose study.

#### Menorrhagia

Menorrhagia was the most common estrogen related adverse event. It occurred at an incidence of 38.1% in patients in the active treatment arms of the controlled trials and compared to an incidence of 21.7% in the placebo group. Premature discontinuations from menorrhagia occurred in 2.6% of actively treated patients in the controlled trials.

#### Breast Pain

Breast pain occurred in 23.7% of actively treated patients in the controlled trials. In the placebo group only 3.6% of the patients had breast pain.

### Endometrial Hyperplasia

Trial 9301 (the pivotal U.S. study) was the only trial which included evaluation of the endometrium by biopsy or sonography as part of the protocol. Endometrial hyperplasia occurred in 41.5% (22 of 53) of Esclim® patients with a uterus, and was noted primarily in the 0.05mg and 0.10mg dose groups. No placebo group patients had endometrial hyperplasia.

### Deaths

There were 3 deaths in patients who applied the Esclim® patch. Two of the deaths (0.30% of the 665 patients) occurred in the Phase 2/3 trials. Both deaths occurred during the long-term extension study 9201. One patient died in Syria of severe dehydration related to gastroenteritis. The second patient had a long-term history of depression and committed suicide. One patient in a Phase 4 study who died had a long term history of chronic respiratory insufficiency. She had an episode of acute respiratory distress and a subsequent cardiac arrest. None of these deaths appeared related to study drug.

### 9.0 Conclusions

The three well controlled trials demonstrate strong clinical evidence that Esclim transdermal systems (0.025 mg/day, 0.050 mg/day, and 0.100 mg/day) are effective and safe as estrogen replacement therapy for the treatment of moderate to severe vasomotor symptoms associated with menopause.

### 10.0 Labeling:

Labeling negotiation with the sponsor is complete. The patient package insert submitted July 30, 1998 is acceptable. The immediate container and carton submitted July 31 is acceptable, as is the physician package insert submitted August 3, 1998.

/S/

Julian Safran  
Medical Officer HFD-580

J concu

/S/

cc: NDA 20-847/ NDA Archive/DMoore/MMann/JSafran

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-847**

**PHARMACOLOGY REVIEW(S)**

110000

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9-9-1997

NDA 20-847

SEP - 9 1997

Laboratoires Fournier S.A.  
50 Rue de Dijon  
21121 Daix, France

Submission dated: 8-7-1997

Received at CDER: 8-7-1997

Pharmacology Review of Original NDA

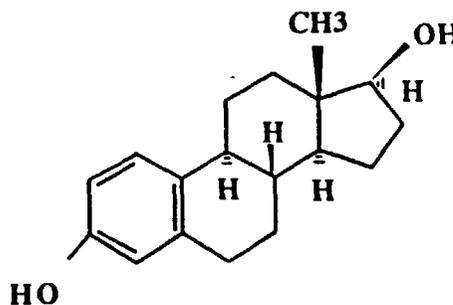
Drug product:

Established name: 17 Beta-estradiol

Proprietary name: Esclim

Pharmacologic class: steroid hormone

Structural formula for estradiol:



Chemical formula: estra-1,3,5 (10)-triene-3, 17B-diol.

Molecular formula: C18 H24 O2      Molecular weight: 272.39

Dosage form: Transdermal

Patch dose strengths: Five systems are proposed with nominal in-vivo delivery of 0.025, 0.0375, 0.05, 0.075, 0.10 mg of estradiol per day via skin of average permeability. Each corresponding system having an active surface area of 11, 16.5, 22, 33 or 44 cm<sup>2</sup> and contains 5, 7.5, 10, 15 or 20 mg of estradiol USP, respectively.

Patch description: The system is composed of a soft, flexible, rectangular foam backing material with rounded corners, covered on one side with a self-adhesive polymer matrix which contains estradiol and pharmacologically inactive components and lined by peelable protective film. The system is designed to release 17 $\beta$ -estradiol continuously upon application to intact skin.

Related IND: IND

Patch composition:

Esclim 25 Transdermal system

component	function	% w/w	mg/cm <sup>2</sup>	mg/system
✓Estradiol	active ingredient			
✓EVA	Adhesive Polymer			
EVA				
✓Ethylcellulose, NF (Ethocel)	Binder			
✓Octyldodecanol, NF (Eutanol G)	Plasticizer			
✓Dipropylene glycol	Solvent			

Total

Beige foam film (polyolefin foam Alveolit 0500) which acts as backing for the adhesive matrix is 11 cm<sup>2</sup> and the siliconized polyester film which acts as adhesive protective film is 17 cm<sup>2</sup>.

It was stated that inactive ingredients, i.e. ethylcellulose 20 cP, octyldodecanol, comply with USP/NF monographs. Other inactive ingredients i.e. dipropylene glycol, beige foam film, siliconized polyester and brown printing ink comply with in-house monographs.

Route of administration: Topical (buttocks, thigh, upper arm or abdomen)

Frequency of application: twice weekly

Proposed indications: 1) Treatment of moderate to severe vasomotor symptoms associated with the menopause, 2) treatment of vulval and vaginal atrophy and 3) treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

Rationale for the development of TS 17 system: The sponsor has stated that the first generation self-adhesive transdermal system containing estradiol i.e. Estraderm TTS has estradiol in the form of an alcohol gel in a central reservoir. It is pointed out that although Estraderm system provides satisfactory efficacy in the control of menopausal-related symptoms, its local tolerability is relatively poor and its cosmetic aspect, in terms of thickness and discreteness as well as its adhesion properties are also suboptimal.

The present patch is a second generation estrogen replacement therapy transdermal system based on matrix approach rather than reservoir for storage and delivery of the active drug. The present matrix system being available in 5 concentrations will allow tighter and more flexible titration of 17B-estradiol in patients. Following potential clinical benefits are reported:

1. A dosing regimen using the lowest dose of TS 17 (TS 17 25), which delivers 25 ug of 17B-estradiol can provide complete relief of vasomotor symptoms within 3 weeks,
2. Plasma levels remain stable and continue to provide effectiveness throughout the dosing period, and
3. TS 17 has local skin tolerability and adhesive properties that are superior to those of Estraderm TTS and a comparable general safety profile.

Nonclinical pharmacology and toxicology:

Toxicity studies were conducted 1) to evaluate the potential of the individual components to induce systemic or local toxic reactions, 2) to evaluate the potential of the intact system to induce local reactions and 3) to assess the potential of the intact system to induce sensitization.

Primary cutaneous irritation studies after one estradiol transdermal system for 4 days (studies Nos. T TS17 92 01 J and T TS17 92 02 J) and after repeated application for 4 weeks (studies Nos. T TS17 92 03 J and T TS17 92 04 J) as well as studies Nos. T TS17 92 05 J and T TS17 92 06 J to evaluate the sensitization potential by topical application in the guinea pig were reviewed under Sponsor's IND

Attached sponsor's table 2-20 provides an overview of the toxicity studies conducted. All these studies were conducted in accordance with GLP Regulations. All studies were sponsored by Fournier except studies of \_\_\_\_\_ which were sponsored by the supplier of that product.

Systemic toxicity was evaluated by intravenous and intraperitoneal injections of extracts from the polymers while local assessment included intradermal injections of extracts as well as direct application of the copolymers. Pre-mass Osclim (mixture of \_\_\_\_\_ ethylene cellulose and octyldodecanol) and individual components of the system (ethylcellulose, octyldodecanol, dipropylene glycol and \_\_\_\_\_) were evaluated for local toxicity by topical application. Intact transdermal systems and the \_\_\_\_\_ were also tested for the potential to induce sensitization. The \_\_\_\_\_ was also tested in an in vitro cytotoxicity assay.

For the cutaneous primary irritation (P.C.I.) in rabbits for ELVAX 46 of batch 1318 AR and 46L batch 1319 AR (studies Nos. 950538 ST and 950539 ST), and that of Pre-mass Osclim batch 130 (study No. 950543 ST), one patch of 10 cm was applied to scarified right flank and non-scarified left flank and dressing was held in place for 24 hours. Application site was examined and evaluated according to Draize criteria one hour after removal and then 48 hours later. Mostly 3 rabbits per treatment were used.

For P.C.I. of Eutanol G (study No. 950540 ST) and Dipropylene glycol batch 33249 (study No. 950542 ST), 0.5 ml and for Ethocel 20, batch No. 35535 (study No. 950541 ST) 0.5g of the compound were used.

In evaluation of the primary irritation index determination following intradermal injection of extracts in the rabbit and evaluation of systemic toxicity following intravenous injection of extract in mouse, compound ELVAX 46 (study No. 950544 ST) and ELVAX 46L (study No. 950545 ST) were added to extraction solvent at a dose of 4 g per 20 ml of solvent

Five i.d. injection of 0.2 ml of saline extract or saline solution into left flank and 5 injection in or into right flank were administered. Site were examined 24, 48 and 72 hour after injections. --

For assessing systemic toxicity in mice, test material ELVAX 46L (Fournier Lab study No. TELV 46L 96 01 A 97 02) and ELVAX 46, lot B008 (study No. TELV 46 96 01 R 97 02) were prepared as extracts in saline (iv), (ip), % at a dose volume of 50 ml/kg.

extracts (5 injection sites/extract of 0.2 ml of 0.2 g of test material/ml of extraction media) were used for intracutaneous reactivity test of ELVAX 46L lot 29491 (study No. TELV 46L 96 02 R 97 02) in rabbits. Sites observed for hemorrhage, erythema and edema at 24, 48 and 72 hours after injection and scored according to Draize technique.

Acute dermal irritation test for was conducted in rabbits by direct topical administration to both intact and abraded test sites

Delayed contact sensitization for this product was determined using both in guinea pig (HLS report nO. 95/av1006/1012).

During first induction 50% v/v extracts as collected in FCA were administered by intradermal injection. Second induction consisted of occluded topical application of control or test extracts as collected. Challenge was with 30% v/v extract in saline as collected for the saline group and with 50% or 10% v/v extract in

In-vitro cytotoxicity assay for was evaluated using mouse cell line L929 (XTT-test) using extracts of the test material (CCR ROJECT 573100). The extracts were tested after 24,

48 and 72 h to reach a better course of the release of toxic substances. With this test cell proliferation and viability as well as the mitochondrial metabolic competence of the cells after treatment with test material is determined colorimetrically using yellow tetrazolium salt XTT.

Summary of preclinical studies: Results of the studies reviewed using complete transdermal system or its individual components showed no significant systemic or local adverse effects. Also all components are listed in the FDA Inactive ingredient guide. Dipropylene glycol as a component of Vivelle (estradiol transdermal system) has been approved under Novartis Pharmaceuticals Corporation's NDA 20-323.

All studies reviewed are summarized in appended Sponsor's table 20-2.

Human experience with TS 17: The following 17 completed studies with TS 17 comprise the clinical trial basis of this submission:

3 controlled clinical studies, 2 vs placebo and one vs Estraderm TTS 50;

2 uncontrolled clinical studies

1 clinical pharmacology study evaluating the sensitization potential of the formulation;

8 clinical pharmacokinetics studies;

3 other studies which were pharmacokinetics in nature.

Also preliminary safety data clinical trials are included in this submission.

Oesclim is approved in France, China and Denmark.

As given in Labeling Safety and efficacy comparison of Esclim 50 vs Estraderm TTS 50 resulted in following significant findings:

Esclim system resulted in fewer than half as many application site reaction per patch application than Estraderm TTS system (4.4% vs 9.5%). This in turn led to fewer treatment discontinuations (0.7% for Esclim vs 5.1% for Estraderm TTS 50).

Compared to oral estrogens administration which increase renin substrate, transdermally administered estradiol Esclim like Estraderm did not affect renin substrate.

N20847.ori

Proposed Labeling: Labeling information is stated to be in accord with Physician Labeling Guidance for Estrogen Drug Products, Revised Edition, August 1992.

Recommendations: Based on the results of the preclinical data submitted and extensive human experience with the proposed product, Pharmacology recommends approval of NDA 20-847 for Esclim for the proposed indications.

ISI

9/9/97

Krishan L. Raheja, DVM, PhD

Original NDA 20-847  
HFD-345  
HFD-580  
HFD-580/A.Jordan  
HFD-580/K.Raheja, 9-9-1997, N20847.ori

A. Jordan  
9/9

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:NDA 20-847**

**STATISTICAL REVIEW(S)**

**Statistical Review and Evaluation**  
**Clinical Studies**

Date: **AUG 05 1998**

NDA #: 20-847

Applicant: Fournier Research Inc.

Name of Drug: Esclim<sup>®</sup> (estradiol transdermal system)

Indication: Treatment of moderate to severe vasomotor symptoms associated with menopause

Documents Reviewed: Vol. 1.1, 1.2, 1.140-1.249; 3.1; 6.1

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Julian Safran, M.D. (HFD-580)

Summary of Studies

The applicant submitted the results of 3 clinical trials to establish the efficacy of Esclim for the treatment of vasomotor symptoms associated with menopause. These trials are summarized in Table 1 below.

Table 1: Summary of Randomized, Controlled Studies

Study Number (Dates Conducted)	# of Centers (Locations)	Treatment Arms (# Randomized) Total Sample Size	Type of Control	Study Design	Duration of Treatment
C TS 17 9301 (12/94 - 6/96)	25 (U.S)	Esclim 25 (n=50) Esclim 50 (n=48) Esclim 100 (n=47) Placebo (n=54)  199 total subjects	placebo- control	randomized, double-blind, multicenter, parallel arms	12 to 13 weeks
C TS 17 9102 (9/92 - 7/94)	13 (France)	Esclim 50 (n=32) Placebo (n=29)  61 total subjects	placebo- control	randomized, double-blind, multicenter, parallel arms	12 to 13 weeks
C TS 17 9104 (4/92 - 11/93)	48 (Europe)	Esclim 50 (n=143) Estraderm 50 (n=140)  283 total subjects	active- control	randomized, open-label, multicenter, parallel arms	16 weeks

Studies (9102 and 9104) were conducted in Europe and excluded non-Caucasian subjects. Esclim is a transdermal patch, and skin type may impact the safety and/or efficacy results. Therefore the Medical Officer decided that the 2 European studies were not pivotal studies, but would be considered as supportive evidence. Study 9301 is considered the pivotal study for approval and is the focus of this review.

Study 9301 was a randomized, double-blind, placebo-controlled, multicenter study conducted at 25 centers in the U.S. There were 4 treatment arms: Esclim 25, Esclim 50, Esclim 100, and placebo. Subjects were postmenopausal women who had at least 56 moderate to severe vasomotor symptoms (VMS) per week during the baseline screening period. Randomization of subjects to the treatment arms was done using a minimization algorithm. The goal of this procedure was to balance the treatment groups on origin of menopause, patient's age group, and number of VMS at baseline. Patients received treatment for 12 to 13 weeks, during which vasomotor symptoms were recorded in daily diaries.

Study 9102 was a randomized, double-blind, placebo-controlled, multicenter study conducted at 13 centers in France. There were 2 treatment arms: Esclim 50 and placebo. Subjects were Caucasian women, age 48 or above, who had had natural menopause. The entry criteria specified that subjects must have at least 5 hot flushes per day and be woken by at least 1 nocturnal sweating episode more than once a week (protocol section 7.1). These are not the standard criteria suggested by the FDA for a vasomotor symptom study, which are a total of at least 56 moderate to severe vasomotor symptoms (VMS) per week. Nocturnal sweating episodes are included in the total VMS. Subjects were randomly assigned to one of the treatment arms, and received treatment for 12 to 13 weeks. During treatment, vasomotor symptoms (hot flushes and nocturnal sweating) were recorded in daily diaries.

Study 9104 was a randomized, open-label, active-controlled, multicenter study conducted at 48 centers in 6 countries in Europe. There were 2 treatment arms: Esclim 50 and Estraderm TTS 50. Subjects were postmenopausal, Caucasian women who had at least 1 hot flush and at least 1 nocturnal sweating episode during the baseline screening week (protocol section 7.3). Subjects were randomly assigned to one of the treatment arms, and received treatment for 16 weeks. During treatment, vasomotor symptoms (hot flushes and nocturnal sweating) were recorded in daily diaries. The inclusion criteria for vasomotor symptoms are less conservative than the standard criteria suggested by the FDA for a vasomotor symptom study. However, the main goal of this study was to assess skin reactions, and vasomotor symptom data was collected as a secondary variable.

## STUDY #9301

### Background

Study 9301, the primary focus for this review, was a randomized, double-blind, placebo-controlled, multicenter study conducted at 25 centers in the U.S. There were 4 treatment arms: Esclim 25, Esclim 50, Esclim 100, and placebo. Subjects were postmenopausal women who had at least 56 moderate to severe vasomotor symptoms (VMS) per week during the baseline screening period. Patients received treatment for 12 to 13 weeks, during which vasomotor symptoms were recorded in daily diaries.

The primary variable of interest specified in the protocol is the mean change in number of vasomotor symptoms (VMS) from baseline to week 4. The mean change from baseline to each of the separate weeks (week 1 through week 12) during treatment are listed as secondary variables in the protocol. The Medical Officer agrees with week 4 as the primary time point, but wants to limit the secondary analyses to only the week 8 and week 12 time points.

The three Esclim doses (25, 50, and 100) required different size transdermal patches (11, 22, and 44 cm<sup>2</sup>, respectively). In order to design a double-blinded study, the placebo group was divided into 3 subgroups, each of which got a placebo patch of the same size as one of the Esclim treatment patches. Eligible subjects were assigned to one of the 6 possible treatment groups (3 Esclim doses, 3 placebo sizes). The number of subjects to be assigned to each of the placebo subgroups was 1/3 of the number assigned to each of the Esclim groups. Thus, the total number who received placebo would be the same as the number in each of the Esclim groups. The 3 placebo subgroups were then combined for the efficacy analyses, after testing that there were no significant difference between the subgroups on baseline VMS (Vol. 3.1, Appendix A, pg. 33-42).

Randomization of subjects to the treatment arms was done using a minimization algorithm. The goal of this procedure was to balance the treatment groups on 4 factors: center, origin of menopause, patient's age group, and number of VMS at baseline. When a subject was determined to be eligible for entry into the study, that subject's characteristics were entered into a program which simulated the resulting balance across treatment groups which would occur if the subject was assigned to each of the groups, given the previous subjects already assigned. If assigning the patient to 1 specific treatment group provided better balance than any other, then the subject was assigned to that group (non-randomly). If 2 or more of the possible group assignments provided equally desirable balance, then the subject was randomly assigned (with equal probability depending on the number of tied groups) to one of those groups. This method was developed by Pocock and Simon (Vol. 3.1, Section 2).

As shown in Table 2 on the following page, the groups were fairly well balanced on age and number of VMS at baseline, but not on the type of menopause. The applicant discussed this in the study report (Section 4.1.4), and pointed out that this may be due to

the fact that too many stratification factors were used considering the number of study arms and centers.” This reviewer agrees that the number of factors is most likely the source of this imbalance.

Table 2: Results for Minimization Criteria (Study #9301)

	Esclim 25 (n = 48)		Esclim 50 (n = 47)		Esclim 100 (n = 47)		Placebo (n = 54)	
	n	%	n	%	n	%	n	%
Type of Menopause								
Natural	27	56%	38	81%	35	74%	34	63%
Surgical	21	44%	9	19%	12	26%	20	37%
Age Group								
< 45	8	17%	8	17%	7	15%	10	19%
45 - 49	12	25%	14	30%	12	26%	15	28%
50 - 54	18	38%	15	32%	18	38%	17	31%
55 +	10	21%	10	21%	10	21%	12	22%
Number of VMS (in 14-day baseline period)								
Under 112	1	2%	1	2%	0	0%	1	2%
112 - 153	27	56%	32	68%	26	55%	30	56%
154 - 195	11	23%	8	17%	13	28%	15	28%
196 +	9	19%	6	13%	8	17%	8	15%

Source: Vol. 1.164, Tables 14 and 22, and Section 9.1

A total of 196 patients were included in the intent-to-treat group (all treated). The 4 treatment groups were similar with regard to most of the demographic characteristics at baseline, as shown in Table 3. The exception is the lack of balance on type of menopause, which is discussed in the Background section for study 9301.

**Table 3: Demographic characteristics (Study #9301)**

	Treatment Group			
	Esclim 25	Esclim 50	Esclim 100	Placebo
	n = 48	n = 47	n = 47	n = 54
	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range	Mean (SD) Range
Age (years)	50.7 (6.3)	50.1 (6.8)	49.9 (7.1)	49.8 (6.6)
BMI (kg/m <sup>2</sup> )	28.5 (7.3)	26.8 (5.6)	28.0 (4.4)	28.5 (5.4)
Age at onset of menopause (years)	43.8 (7.6)	42.8 (8.7)	43.1 (7.5)	45.7 (7.2)
Duration of menopause (years)	7.0 (6.8)	4.3 (5.2)	5.1 (6.3)	6.0 (5.5)
	n (%)	n (%)	n (%)	n (%)
Type of Menopause:				
Natural	27 (56%)	38 (81%)	35 (74%)	34 (63%)
Surgical	21 (44%)	9 (19%)	12 (26%)	20 (37%)
Race:				
Caucasian	42 (88%)	43 (91%)	45 (96%)	52 (96%)
Black	4 (8%)	4 (9%)	2 (4%)	2 (4%)
Other	2 (4%)	0 (0%)	0 (0%)	0 (0%)

Source: Vol. 1.164, Tables 21, 22, 25, 26 and 27; Vol. 1.172, Appendix V.2

The disposition of the subjects in the 4 treatment groups is shown in Table 4. The placebo group and the Esclim 25 group had slightly higher drop-outs towards the end of the study. The protocol planned for a 15% drop-out rate, and the actual rate for all the treatment groups was less than that.

Table 4: Disposition of Subjects by Treatment Group (Study #9301)

	Treatment Group			
	Esclim 25 n = 48	Esclim 50 n = 47	Esclim 100 n = 47	Placebo n = 54
	n (%)	n (%)	n (%)	n (%)
Baseline	48 (100%)	47 (100%)	47 (100%)	54 (100%)
Week 4	48 (100%)	47 (100%)	47 (100%)	54 (100%)
Week 8	46 (96%)	46 (98%)	46 (98%)	49 (91%)
Week 12	44 (92%)	45 (96%)	46 (98%)	49 (91%)

Source: Vol. 1.164, Table 16.

As shown in Table 5, the 3 Esclim treatment groups were similar with regard to the reasons for discontinuing treatment. The placebo group had a higher rate of drop-outs due to lack of efficacy, which would be expected. However, the numbers were not high enough to be of concern.

Table 5: Reasons for Discontinuation by Treatment Group (Study #9301)

	Treatment Group			
	Esclim 25 n = 48	Esclim 50 n = 47	Esclim 100 n = 47	Placebo n = 54
	n (%)	n (%)	n (%)	n (%)
Adverse Event	2 (4%)	3 (6%)	2 (4%)	0 (0%)
Lack Of Efficacy	0 (0%)	1 (2%)	0 (0%)	5 (9%)
Consent Withdrawn	1 (2%)	0 (0%)	0 (0%)	2 (4%)
Other/ Lost-to Follow-up	1 (2%)	0 (0%)	2 (4%)	1 (2%)

Source: Vol. 1.164 Table 17

Applicant's Analysis - Study #9301

The analysis discussed in the protocol was a 1-way ANOVA model with treatment as the only factor, followed by multiple comparisons using Dunnett's method to compare each Esclim dose to placebo. A separate analysis was done at each weekly time point, rather than a repeated measures analysis. The applicant considered week 4 as the primary time point of interest, and reported the results of all 12 weeks individually as secondary analyses. The intent-to-treat patient population (all treated), with last observation carried forward (LOCF), was used for these analyses. Table 6a and 6b summarize the applicant's results for weeks 4, 8, and 12. The applicant concluded that there was a significant difference between each of the Esclim doses and placebo in the mean change in number of VMS from baseline for all 3 time points.

Table 6a: Applicant's Results (ITT subjects): (Study #9301)

	Esclim 25 (n=48)		Esclim 50 (n=47)		Esclim 100 (n=47)		Placebo (n=54)	
	Actual Mean VMS per Day	Mean Change from Baseline *	Actual Mean VMS per Day	Mean Change from Baseline *	Actual Mean VMS per Day	Mean Change from Baseline *	Actual Mean VMS per Day	Mean Change from Baseline *
Baseline Mean (SD) Range	11.6 (5.4)		10.9 (4.2)		11.2 (2.8)		11.4 (3.7)	
Week 4 Mean (SD) Range	3.0 (3.5)	8.6 (5.7)	1.7 (2.7)	9.2 (4.5)	1.0 (2.0)	(10.2)2.9	6.1 (5.3)	5.3 (4.1)
Week 8 Mean (SD) Range	2.1 (3.1)	9.4 (5.7)	0.6 (1.3)	10.3 (4.3)	0.6 (1.6)	10.6 (2.8)	5.9 (6.0)	5.5 (4.7)
Week 12 Mean (SD) Range	1.7 (3.1)	9.9 (5.8)	0.5 (1.2)	10.4 (4.2)	0.6 (1.6)	10.7 (2.8)	6.2 (6.8)	5.2 (5.1)

\* Negative numbers indicate an increase from baseline in the number of VMS.

Source: Vol. 1.178, Appendices V.8.15.1 and V.8.17.1

**Table 6b: Applicant's Results: Multiple Comparisons of Esclim vs. Placebo  
(ITT subjects): (Study #9301)**

<b>Difference in Mean Change From Baseline vs. Placebo</b>	<b>Esclim 25 (n=48)</b>	<b>Esclim 50 (n=47)</b>	<b>Esclim 100 (n=47)</b>
<b>Week 4</b>			
Mean (SD)	3.3	3.9	4.9
Adjusted 95% CI *	(1.2, 5.4)	(1.8, 6.0)	(2.9, 7.0)
<b>Week 8</b>			
Mean (SD)	4.0	4.8	5.2
Adjusted 95% CI *	(1.9, 6.1)	(2.7, 7.0)	(3.1, 7.3)
<b>Week 12</b>			
Mean (SD)	4.7	5.2	5.5
Adjusted 95% CI *	(2.5, 6.9)	(3.0, 7.4)	(3.3, 7.7)

\* Confidence Intervals are adjusted for 3 pairwise comparisons within each time point using Dunnett's method. A confidence interval which excludes the value zero indicates the Esclim dose is significantly different from placebo at the .05  $\alpha$ -level.

Source: Vol. 1.179, Appendix V.8.19.1

**APPEARS THIS WAY  
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### Reviewer's Analysis- Study #9301

The applicant's analyses were appropriate and used the correct intent-to-treat subject data set. However, this reviewer had a few additional concerns about the study results. The first concern was the possible impact of using the minimization algorithm for treatment assignment instead of complete randomization. I consulted with Paul Flyer, Ph.D. (HFD-725), who has a strong background in assessing the results from studies using minimization algorithms. After much discussion, we concluded that since the results in this study are highly significant (3 ANOVA F-tests, all p-values were 0.0001), any potential effect of the algorithm would not have changed the conclusions.

A second issue, mentioned in the background section for study 9301, was that the treatment assignments from the minimization algorithm resulted in an imbalance on one of the 4 balancing criteria: type of menopause. The applicant noted in the study report that this may be due to using too many criteria for the number of subjects per treatment group. In order to rule out a possible systematic cause for the imbalance, this reviewer reviewed materials submitted by the applicant tracking the results of the algorithm as each subject was randomized (Vol. 3.1 and 6.1). No systematic explanation was evident, so this reviewer agrees with the applicant that the imbalance on the type of menopause variable was probably due to including too many balancing criteria.

The last concern about the data for this reviewer was the appropriateness of combining the 3 placebo sub-groups as 1 treatment group for the analyses. The applicant provided analyses testing for between-group differences among the placebo sub-groups on number of VMS at baseline and found no differences. This reviewer also considered the baseline characteristics and balancing criteria, and found the 3 sub-groups to be similar. Therefore, this reviewer feels it is appropriate to combine the 3 placebo sub-groups for the efficacy analyses.

### Conclusions - Study #9301

This reviewer found the applicant's analyses to be appropriate. The results show that there is a significant difference in the mean change in number of VMS from baseline to Week 4, Week 8, and Week 12 between each of the 3 Esclim dose groups and the placebo group. A greater reduction in mean change in number of VMS was shown by all 3 Esclim groups than the placebo group.

## STUDY #9102

### Background

Study 9102 was a randomized, double-blind, placebo-controlled, multicenter study conducted at 13 centers in France. The study included Caucasian women, age 48 or above, who had natural menopause. Subjects were randomly assigned at a 1:1 ratio to receive either Esclim 50 or placebo treatment for 12 to 13 weeks. During treatment, vasomotor symptoms (hot flushes and nocturnal sweating) were recorded in daily diaries.

The entry criteria specified that subjects must have at least 5 hot flushes per day and be woken by at least 1 nocturnal sweating episode more than once a week (protocol section 7.1). The standard criteria suggested by the FDA for a vasomotor symptom study are a total of at least 56 moderate to severe vasomotor symptoms (VMS) per week. Nocturnal sweating episodes are included in the total VMS. Of the 61 subjects enrolled and treated in this study (32 in Esclim group; 29 in placebo group), only 26 had at least 56 total VMS per week (14 in Esclim group; 12 in placebo group).

Study 9102 is considered as a supportive study for this review, mainly because it included only Caucasian women. This reviewer has found other concerns with the conduct of the study as well. The protocol originally planned for a total of 72 subjects (36 per treatment group), but enrollment was stopped after 63 subjects because of difficulty in recruiting subjects (Section 4.1.3.2.4). Also, the inclusion criteria for the efficacy analyses were expanded after the study was conducted. There were 10 subjects (4 in Esclim group; 6 in placebo group) who did not meet the study inclusion criteria, but had been enrolled and treated. From these wrongly included subjects, 3 in the Esclim group were found to have met the efficacy-related criteria for menopausal symptoms and were then put back into the "evaluable for efficacy" patient group for the applicant's analyses (Section 4.1.4).

Applicant's Analysis - Study #9102

The protocol specified that the primary efficacy variable would be mean change in number of vasomotor symptoms (VMS) from baseline to Week 12, with the mean change to Week 4 and Week 8 as secondary endpoints. The applicant's analyses used only the "evaluable for efficacy" patient population, defined as patients meeting the efficacy-related inclusion criteria and treatment compliance criteria. Four subjects from each treatment group were excluded from the efficacy analyses.

The applicant applied the last observation carried forward (LOCF) approach for the "evaluable" patient group. These results are shown in Table 7. Between group comparisons for the mean change in number of VMS from baseline were done at each of the 3 time points of interest using the Wilcoxon Rank-Sum test. The applicant concluded that there was a significant difference between Esclim 50 and placebo in the mean change in number of VMS from baseline for all 3 time points.

Table 7: Applicant's Analysis - Evaluable Patients (Study 9102)

	Esclim 50 (n=28)		Placebo (n=25)		Wilcoxon Rank-Sum Test p-value:
	Actual Mean VMS per Day	Mean Change from Baseline	Actual Mean VMS per Day	Mean Change from Baseline *	Esclim vs. Placebo on Mean Change from Baseline
Baseline Mean (SD) Range	9.3 (4.2)		8.3 (3.4)		
Week 4 Mean (SD) Range	1.2 (2.1)	8.2 (3.8)	4.0 (3.9)	4.3 (3.2)	0.0002
Week 8 Mean (SD) Range	0.3 (1.1)	9.0 (4.0)	3.2 (4.8)	5.1 (5.3)	0.0024
Week 12 Mean (SD) Range	0.3 (0.8)	9.1 (4.1)	3.2 (5.0)	5.1 (6.0)	0.0057

\* Negative numbers indicate an increase from baseline in the number of VMS.

Source: Vol. 1.191, Table 33 and Vol. 1.197, Appendix V-2-17-5

### Reviewer's Analysis - Study #9102

The distribution of the data was right-skewed, which is not unusual for this type of variable. The Wilcoxon Rank-Sum analysis method used by the applicant is appropriate for this data. However, the applicant did not use the Intent-to-Treat patient population. In this study, the ITT population is all randomized subjects who received treatment. This reviewer repeated the applicant's analysis, using the ITT patient set, as shown in Table 8. The results indicate that there is a significant difference in the mean change in number of VMS from baseline for all 3 time points. These results agree with the conclusion reached by the applicant.

Table 8: Reviewer's Analysis - ITT Patients (Study 9102)

	Esclim 50 (n=32)		Placebo (n=29)		Wilcoxon Rank-Sum Test p-value:
	Actual Mean VMS per Day	Mean Change from Baseline	Actual Mean VMS per Day	Mean Change from Baseline *	Esclim vs. Placebo on Mean Change from Baseline
Baseline Mean (SD) Range	8.8 (4.3)		8.1 (3.3)		
Week 4 Mean (SD) Range	1.0 (2.0)	7.8 (3.9)	4.1 (3.8)	4.0 (3.6)	0.0005
Week 8 Mean (SD) Range	0.3 (1.0)	9.5 (4.1)	3.7 (4.7)	4.4 (5.3)	0.0014
Week 12 Mean (SD) Range	0.2 (0.7)	8.6 (4.2)	3.2 (4.6)	4.9 (5.7)	0.0046

\* Negative numbers indicate an increase from baseline in the number of VMS.

### Conclusions - Study #9102

Between group comparisons on the mean change in number of VMS from baseline to Week 4, Week 8, and Week 12 indicate there is a significant difference between Esclim 50 to placebo at all time points. A greater reduction in mean number of VMS was shown by the Esclim 50 treatment group than in the placebo treatment group.

## STUDY #9104

### Background

Study 9104 was a randomized, open-label, active-controlled, multicenter study conducted at 48 centers in 6 countries in Europe, with 2 treatment arms: Esclim 50 and Estraderm TTS 50. Subjects were postmenopausal, Caucasian women who had at least 1 hot flush and at least 1 nocturnal sweating episode during the baseline screening week (protocol section 7.3). Subjects were randomly assigned at a 1:1 ratio to one of the treatment arms, and received treatment for 16 weeks. During treatment, vasomotor symptoms (hot flushes and nocturnal sweating) were recorded in daily diaries.

The Medical Officer feels this should only be considered as a supportive study because only Caucasian women were included. Also, the primary objective of this study was the assessment of skin reactions. The efficacy analysis for vasomotor symptoms was planned as a secondary goal, but the study was not powered for equivalence comparisons of Esclim to the active-control. Lastly, the inclusion criteria for vasomotor symptoms were much less stringent than those suggested by the FDA (at least 56 moderate to severe vasomotor symptoms per week) so the study patient population is not the desired patient population for this indication.

As in study 9102, the inclusion criteria for the efficacy analyses were altered after the study was conducted due to some subjects being wrongly included in the study. In the Esclim treatment group, 143 subjects were assigned, of whom 22 were wrongly included based on the protocol inclusion criteria. Of these 22, 6 were later reclassified as evaluable for efficacy based on only the menopausal status criteria. In the Estraderm group, 140 were assigned, of whom 27 were wrongly included. Of these 27, 13 were later determined to be evaluable for efficacy.

### Applicant's Analysis - Study #9104

The protocol specifies the efficacy analyses for vasomotor symptoms would use the mean percent change from baseline to Week 4, 8, 12, and 16. Within group analysis with Wilcoxon Paired Signed Rank tests, and between group comparisons with Wilcoxon Rank Sum tests were planned. The patient population for these analyses was defined as "evaluable for efficacy", based on menopausal status criteria at baseline along with compliance criteria for the treatment period. There was no mention of subgroup analyses based on the number of vasomotor symptoms at baseline.

The results presented in the clinical study report used the mean change from baseline to Week 4, 8, 12, and 16 as the primary focus (along with the mean percent change). The within group and between group analyses were done using the proposed non-parametric tests, but these are not of interest for this review. In addition, a subgroup analysis was done for "highly symptomatic" subjects, defined as those with 5 or more vasomotor

symptoms per day at baseline. The definition of this subgroup is still less conservative than the FDA suggested criteria of a mean of 8 vasomotor symptoms per day at baseline.

For the purposes of this review, only the Esclim 50 treatment group results are of interest. The study was not designed for comparisons to the Estraderm treatment group on vasomotor symptoms. The results reported by the applicant include only the “evaluable for efficacy” subjects (Table 9). The applicant concluded that there was a significant reduction in the mean number of vasomotor symptoms from baseline to each of the 4 time points in both the Evaluable patient subset, and in the Highly Symptomatic patient subset.

Table 9: Applicant’s Analysis - Evaluable Patients (Study 9104)

	Esclim 50 All Evaluable for Efficacy Subjects (n=110)		Esclim 50 Highly Symptomatic Evaluable for Efficacy Subjects (n=50)	
	Actual Mean VMS per Day	Mean Change from Baseline *	Actual Mean VMS per Day	Mean Change from Baseline *
Baseline Mean (SD) Range	5.8 (5.8)		10.0 (6.3)	
Week 4 Mean (SD) Range 95% CI on Change	1.4 (2.3)	4.5 (5.0) (3.6, 5.4)	2.5 (2.9)	7.4 (6.0) (5.7, 9.1)
Week 8 Mean (SD) Range 95% CI on Change	0.5 (1.5)	5.3 (5.8) (4.2, 6.4)	1.0 (2.0)	9.0 (6.9) (7.0, 11.0)
Week 12 Mean (SD) Range 95% CI on Change	0.5 (2.2)	5.3 (5.9) (4.2, 6.4)	1.1 (3.2)	8.8 (7.2) (6.8, 10.8)
Week 16 Mean (SD) Range 95% CI on Change	0.3 (1.1)	5.6 (5.8) (4.5, 6.7)	0.6 (1.6)	9.4 (6.7) (7.5, 11.3)

\* Negative numbers indicate an increase from baseline in the number of VMS.

Source: Vol. 1.199, Table 63; Vol. 3.1, Appendix D; Vol. 1.213, Appendix V-2-17-1-2

Reviewer's Analysis - Study #9104

This study was not powered to make between group comparisons on the mean change in number of VMS from baseline to any of the time points. Therefore this reviewer will only focus on the results of the Esclim 50 treatment group, using the ITT patients and also looking at the Highly Symptomatic patient subgroup as defined by the applicant. Descriptive statistics for the mean change in number of vasomotor symptoms from baseline to each of the 4 time points are presented in Table 10. These results are very similar to the applicant's. No statistical tests were done by this reviewer, but all the 95% confidence intervals on the change from baseline exclude the value zero, supporting the sponsor's conclusions.

Table 10: Reviewer's Analysis - ITT Patients (Study 9104)

	Esclim 50 All Included Subjects (n=143)		Esclim 50 Highly Symptomatic Included Subjects (n=65)	
	Actual Mean VMS per Day	Mean Change from Baseline *	Actual Mean VMS per Day	Mean Change from Baseline *
Baseline Mean (SD) Range	5.6 (5.3)		9.5 (5.6)	
Week 4 Mean (SD) Range 95% CI on Change	1.3 (2.2)	4.2 (4.7) (3.5, 5.0)	2.3 (2.8)	7.2 (5.4) (5.8, 8.5)
Week 8 Mean (SD) Range 95% CI on Change	0.6 (1.4)	5.0 (5.4) (4.1, 5.9)	0.9 (1.9)	8.6 (6.2) (7.0, 10.1)
Week 12 Mean (SD) Range 95% CI on Change	0.5 (2.0)	5.0 (5.5) (4.1, 5.9)	1.0 (2.9)	8.5 (6.4) (6.9, 10.0)
Week 16 Mean (SD) Range 95% CI on Change	0.3 (1.1)	5.2 (5.4) (4.3, 6.1)	0.6 (1.5)	8.9 (6.0) (7.4, 10.4)

\* Negative numbers indicate an increase from baseline in the number of VMS.

Conclusions - Study #9104

The descriptive statistics and confidence intervals indicate that there is a reduction in mean number of vasomotor symptoms from baseline to Week 4, 8, 12, and 16. This was shown in the "all subjects" group and in the subgroup of highly symptomatic patients.

Summary

The results in study 9301 indicate that there is a significant difference in the mean change in number of VMS from baseline to Week 4, Week 8, and Week 12 between each of the 3 Esclim dose groups (25, 50, and 100) and the placebo group. A greater reduction in mean change in number of VMS was shown by all 3 Esclim groups than the placebo group. Study 9102 included only the Esclim 50 dose group and placebo, and confirms the greater reduction in VMS for the Esclim 50 group than the placebo group at Weeks 4, 8, and 12. Study 9104 provided further support of the efficacy for the Esclim 50 dose group; descriptive statistics for the change in VMS from baseline showed similar results as studies 9301 and 9102 for the Esclim 50 group.

The applicant has requested approval for 5 dose levels: 0.025 mg/day, 0.0375 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day. These correspond to patch sizes of 11, 16.5, 22, 33, and 44 cm<sup>2</sup>. Study 9301 included the 11 cm<sup>2</sup> (Esclim 25), 22 cm<sup>2</sup> (Esclim 50), and 44 cm<sup>2</sup> (Esclim 100) size patches. Studies 9102 and 9104 included only the 22 cm<sup>2</sup> (Esclim 50) size patch. No clinical data was presented in these studies for the 16.5 or 33 cm<sup>2</sup> patches.

The proposed label included only the results from study 9301 in the clinical studies section, and reported the mean percent reduction in VMS from baseline. The primary efficacy variable is the mean reduction in number of VMS from baseline. The Medical Officer agrees with this reviewer that the results should be reported as mean reduction, not mean percent reduction. The proposed label also reports results and hypothesis tests for weeks 2, 3, 4, and 12. The week 2 and 3 time points were not previously mentioned as efficacy time points, and are not included in other labels for this indication. The Medical Officer selected weeks 4 and 12 as being important to present, and possibly week 8 to be consistent with other labels. This reviewer suggests that only those 2, or possibly 3, time points appear in the label.

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Katherine B Meaker, M.S.  
Mathematical Statistician

Concur: Dr. Nevius *Jan 8-3 98*

Ms. Mele *J. Mele 7/31/98*

cc:

Archival NDA 20-847

HFD-580

HFD-580/JSafran, MMann, LRarick

HFD-580/DMoore

HFD-715/ENevius, JMele, KMeaker, Division File, Chron

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APPEARS THIS WAY  
ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-847**

**MICROBIOLOGY REVIEW(S)**

JUL 28 1998

REVIEW FOR HFD-580  
OFFICE OF NEW DRUG CHEMISTRY  
MICROBIOLOGY STAFF  
MICROBIOLOGISTS REVIEW #2 OF NDA 20-847  
28 July 1998

A. 1. Application Numbers: NDA 20-847 BC

APPLICANT: Fournier Research, Inc.  
9 Law Drive  
Fairfield, NJ 07004

2. PRODUCT NAMES: Esclim® (estradiol transdermal system)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:

The product is a transdermal patch.

4. METHODS OF STERILIZATION:

The product is not a sterile dosage form but, is subject to microbial limits specifications..

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:

The product is used in the treatment of moderate to severe vasomotor symptoms associated with menopause, vulval and vaginal atrophy, hypoestrogenism due to hypogonadism, and abnormal uterine bleeding due to hormonal imbalance.

B. 1. DATE OF INITIAL SUBMISSION: 7 August 1997

2. DATE OF AMENDMENT: 15 July 1998

3. RELATED DOCUMENTS: (none)

4. ASSIGNED FOR REVIEW: 28 July 1998

C. REMARKS: The amendment was submitted in response to deficiencies cited in Microbiologist's Review #1 completed by Dr. David Hussong.

Fournier Research, Inc., NDA 20-847, Esclim®; Microbiologist's Review #2

D. CONCLUSIONS: The application is recommended for approval on the basis of microbial quality of the drug product.

*/S/*

Paul Stinavage, Ph.D.

28 July 1998

*PK 7/28/98*

cc: Original Application: NDA 20-847  
HFD-805/Stinavage/Consult File  
HFD-550/Div. Files/D. Moore/L. Pauls

Drafted by: P. Stinavage, 28 July 1998  
R/D initialed by P. Cooney

Moore

JUN 12 1998

REVIEW FOR HFD-580  
OFFICE OF NEW DRUG CHEMISTRY  
MICROBIOLOGY STAFF  
MICROBIOLOGIST'S REVIEW #1 OF NDA

10 June 1998

A. 1. NDA 20-847

SPONSOR Fournier Research Corporation  
9 Law Drive  
Fairfield, NJ 07004

2. PRODUCT NAMES: ESCLIM® 17β-Estradiol Transdermal System

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Transdermal adhesive foam patches of 5 sizes (surface area) containing estradiol in a polymeric adhesive. The patch is applied to the buttocks or abdomen as a method of hormone replacement. The patch is replaced twice weekly.

4. METHOD(S) OF STERILIZATION: The product is not sterile, but is manufactured under conditions providing control of microorganisms.

5. PHARMACOLOGICAL CATEGORY: Estrogen replacement

6. DRUG PRIORITY CLASSIFICATION: 3S

B. 1. DATE OF INITIAL SUBMISSION: August 7, 1997

2. DATE OF AMENDMENT: none

3. RELATED DOCUMENTS: none

4. ASSIGNED FOR REVIEW: September 16, 1997

C. REMARKS: The application is for a synthetic estrogen used as a hormone supplement, and administered by a transdermal drug delivery system (TDS). Microbiological requirements for TDS products have been under development within the Center and the USP, but current limits are based on those for topical products.

D. CONCLUSIONS: The application is approvable pending resolution of deficiencies.

ISI

David Hussong, Ph.D.

PHZ 6/12/98

cc:

HFD 160/Consult File  
HFD 580/CSO/D. Moore  
HFD 580/Review Chemist/D. Lin  
HFD 805/D. Hussong

Drafted by: D. Hussong, 06/01/98  
R/D initialed by: P. Cooney

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