

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20-847

ADMINISTRATIVE DOCUMENTS

Group Leader Memorandum

NDA: 20-847 JUL 30 1998

Drug: Esclim®
17β-estradiol transdermal system

Indication: Treatment of Vasomotor Symptoms Associated with Menopause

Dose: 0.025, 0.0375, 0.05, 0.075, and 0.10 mg patches administered daily through a self-adhesive matrix-type transdermal delivery system

Applicant: Fournier Research, Inc.

Date Original Submission: 8/7/97
Date Review Completed: 8/3/98

Background

Fournier Research Inc. has submitted an NDA for their product, Esclim® patch for the treatment of moderate to severe vasomotor symptoms in post-menopausal women. If approved for this indication, the current guidance allows for several other indications to follow this automatically: treatment of vulvar and vaginal atrophy, and treatment of hypoestrogenism due to hyogonadism, castration, or primary ovarian failure.

Related products available for this indication include the transdermal skin patches Estraderm®, Alora®, Climera®, and Vivelle®. Of note, dosages available with each of these products are as follows:

Estraderm: 0.050 and 0.10 mg patches available
Alora: 0.050, 0.075, and 0.10 mg patches available
Climera: 0.050 and 0.10 mg patches available
Vivelle: 0.0375, 0.05, 0.075, and 0.10 mg patches available

Thus, if approved, Esclim would provide the broadest range of dosing (and the lowest dose: 0.025 mg) among the available estrogen patches to date.

Results of Studies

The sponsor submitted results from three controlled clinical trials to support the VMS indication. The pivotal trial (9301) is described in detail below. Following this, a brief review of the other two trials follow.

Study 9301

This U.S. trial was the pivotal trial to support the VMS indication. The entry criteria were in agreement with the FDA guidance document for this indication, and the patient population were ethnically diverse and representative of the U.S. population. This was a 12 week study in which 196 women with moderate to severe VMS were randomized to receive either placebo or Esclim at a variety of doses: 0.025, 0.050, and 0.10 mg daily. The results revealed that the primary efficacy endpoint as assessed at 4 weeks in the ITT population revealed a statistically significant reduction in VMS in all three Esclim arms compared to placebo. These results were sustained at weeks 8 and 12. Moreover, the reduction in VMS at week 4 (the primary endpoint) was dose proportional, with successively higher doses of Esclim resulting in greater efficacy. The dose-response noted supports the approval of the intermediate doses of Esclim of 0.0375 and 0.075 mg, even though they were not specifically studied for this indication.

Esclim was well tolerated in this trial, and over 90% of patients randomized to an Esclim arm completed the 12 week study. Discontinuations in the Esclim arms were as follows:

Esclim 0.025 mg arm	one patient had spotting one patient had an auto accident
Esclim 0.050 mg arm	two patients had vaginal bleeding (one required a hysterectomy) one patient had multiple somatic complaints
Esclim 0.010 mg arm	one patient had vaginal bleeding one patient had rash and edema one patient had a family emergency

Common adverse events during the study included endometrial hyperplasia. Of note, however, only a small subset of enrolled patients actually had a uterus (17 placebo patients, 14 patients in the Esclim 0.025 mg arm, 22 patients in the Esclim 0.050 mg arm, and 18 patients in the Esclim 0.10 mg arm). Hyperplasia was reported in no placebo patients, but was reported by one patient in the 0.025 mg arm (7%), by 12 patients in the 0.050 mg arm (44.5%), and by 9 patients in the 0.10 mg arm (50%). Clearly, although the database is limited, there appears to be a greater risk for endometrial hyperplasia at the mid- and higher doses of Esclim, while the risk at 0.025 mg doses appeared lower. Local tolerability of the Esclim patch also appeared to be dose-related. Of note, 7.4% of placebo patch applications resulted in a local site reaction compared to 4.9%, 9.9%, and 10.7% of the low, mid, and highest dose Esclim arms, respectively.

In summary, the results of this controlled study revealed efficacy of all three doses of Esclim (0.025, 0.050, and 0.10 mg) compared to placebo. This was true for both the primary endpoint analysis performed at week 4, as well as analyses performed at weeks 8 and 12. The major safety concerns were comparable to those noted with previously approved patches and include endometrial hyperplasia and local skin reactions. There was a dose-response relationship noted for both efficacy and safety results for all three doses of Esclim studied, thus supporting the approval of the intermediate doses (0.0375 and 0.075 mg), even though they were not specifically studied.

Study 9102

This study was a 12 week, double-blind, randomized, placebo controlled trial conducted in France. There were only two arms in this study: a placebo arm (n=25) versus an Esclim 0.050 mg arm (n=28). There were several concerns with the study design which led to the reviewer to consider this trial supportive, but not pivotal to the application.

These concerns included:

- all white patients were enrolled, and in fact this was an inclusion requirement. Thus, the patient population is not representative of the United States' ethnic diversity.
- There were no FSH or estradiol levels required as inclusion criteria to assure patients were truly post-menopausal, and indeed patients only had to be amenorrheal for 3 months. This may have led to the inclusion of many peri-menopausal patients.
- The inclusion criteria also required a mean of 5 hot flushes per 24 hours, which may have allowed inclusion of patients with less severe symptoms. Arguably, however, this may have simply made it more difficult for the sponsor to show a significant effect on symptoms compared to placebo.
- The primary efficacy results presented were only those for evaluable patients. Although 105 patients were screened, only 63 were enrolled in the trial. Of these 63, primary efficacy results are shown for 53 patients who remained in the study for the full 12 week duration.

The results from Study 9102 were supportive to the application in that the primary efficacy criteria of reduction in mean vasomotor symptoms/24hours was reduced from baseline to week 12 in the Esclim 0.050 arm compared to placebo. The average number of VMS was reduced 5.1 ± 6.0 in the placebo arm, compared to a reduction of 9.1 ± 4.1 in the Esclim 0.050 arm. One Esclim patient withdrew from the study due to metrorrhagia. The other study discontinuations were either due to inappropriate enrollment or occurred in the placebo arm (often due to inadequate efficacy). A total of 17 patients in the Esclim 0.050 mg arm presented with at least one adverse event during the study. The most common events were metrorrhagia (noted in 48% of Esclim patients versus 33% of placebo patients with a uterus), breast pain (noted in 22% of Esclim versus 3% of placebo patients). Three serious adverse events occurred in the Esclim arm: one patient required laparoscopy for uterine leiomyoma, one patient had menometrorrhagia, and one required phlebectomy for varicose veins. Application site reactions were noted in approximately 5% of Esclim applications, and a total of 2.8% of Esclim patches became detached.

In summary, Study 9102, while not a pivotal trial due to the deficiencies noted above, supports the approval of Esclim 0.050 mg for the indication desired.

Study 9104

This study was designed to compare the number of application site reactions between Esclim 0.050 mg patch and Estraderm 0.050 mg patches after 16 weeks of therapy in 285 Caucasian women. The results demonstrated that seven Esclim patients and 12 patients withdrew from the study due to adverse events. In the Esclim arm, 4 patients withdrew due to bleeding, one for an application site reaction, one for mastodynia, and one had suicidal ideation. In the Estraderm arm, there were 7 withdrawals due to application site

reactions, 3 for bleeding, one for eczema, and one for headaches/tiredness. The Esclim patch did appear to be better tolerated regarding significant application reactions therefore, since only one Esclim patient withdrew for this reason compared to 7 Estraderm patients. This study also demonstrated that 4.2% of 3706 Esclim applications resulted in a site reaction compared to 9.5% of 3406 Estraderm applications. This difference was statistically significant. Finally, adhesion data revealed that a total of 224 (6%) of Esclim patches and 384 (11.3%) of Estraderm patches became detached from treated patients.

These data suggest that Esclim 0.050 mg may be tolerated better regarding local skin toxicity and adhesion than Estraderm 0.050 mg patches. However, as noted in the medical officer's review, the local skin effects of Esclim may be more significant at higher doses. Also of note is that in the pivotal trial 9301, the Esclim 0.050 mg treatment arm resulted in local skin irritation in 9.9% of applications, a rate which is more comparable to the 11.3% rate noted with Estraderm. Finally, the patient population studied was 100% Caucasian, and therefore does not represent the U.S. population. An additional study which confirms these effects in a diverse patient population, and which includes multiple doses of the Esclim and Estraderm patches, is therefore required before a labeling claim of superiority can be made by the sponsor.

Conclusions

The study results support the efficacy of Esclim 0.025, 0.05, and 0.10 mg patches for the treatment of moderate to severe vasomotor symptoms associated with menopause. The intermediate doses of 0.0375 and 0.075 mg are supported by the dose-responsiveness noted in both efficacy and safety endpoints. This NDA review supports the approval, therefore, of all five doses of Esclim for this indication.

Study 9104 was designed to support a labeling claim of superiority of Esclim over Estraderm regarding local skin tolerability and adhesion. The results of this study are suggestive that Esclim is better tolerated than Estraderm regarding both of these endpoints, however a second confirmatory study involving a diverse patient population and comparing multiple doses of each patch is required to support a claim of superiority.

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Marianne Mann, M.D.
Deputy Director, HFD-580

cc:
NDA 20-847
HFD-580/Rarick/Safran/Mann

NDA 20-847

Esclim® (estradiol transdermal system)

Fournier Research Inc.

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

NDA 20-847
Esclim® (estradiol transdermal system)
Fournier Research Inc.

Safety Update Review

The safety update is included in Medical Officer review dated August 4, 1998.

NDA 20-847

Esclim® (estradiol transdermal system)

Fournier Research Inc.

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 20-847

Esclim® (estradiol transdermal system)

Fournier Research Inc.

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 20-847

Esclim® (estradiol transdermal system)

Fournier Research Inc.

Advertising Material

No advertising material has been submitted.

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 20-847 SUPPL # _____

Trade Name: Esclim® Generic Name: estradiol transdermal system

Applicant Name: Fournier Research Inc. HFD # 580

Approval Date If Known: August 1998

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES/ / NO / /

b) Is it an effectiveness supplement?

YES / / NO / /

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES / / NO / /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES / / NO / /

If yes, NDA # 19-081 . Drug Name Estraderm .

NDA # 20-323 . Drug Name Vivelle .

NDA # 20-538 . Drug Name Noven .

NDA # 20-655 . Drug Name Alora .

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-081 . Drug Name Estraderm .

NDA # 20-323 . Drug Name Vivelle .

NDA # 20-538 . Drug Name Noven .

NDA # 20-655 . Drug Name Alora .

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / / NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO / /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO / /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

-
- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / / NO / /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / / NO / /

If yes, explain:

- (2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES / / NO / /

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

TS 17 9301

TS 17 9102

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES / / NO / /

Investigation #2 YES / / NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

___ TS 17 9301 _____

___ TS 17 9102 _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES / / NO / / Explain: _____

Investigation #2

IND # _____ YES / / NO / / Explain: _____

- b) **For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?**

Investigation #1

YES / / Explain _____ NO / / Explain _____

Investigation #2

YES / / Explain _____ NO / / Explain _____

- (c) **Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)**

YES / / NO / /

If yes, explain: _____

Signature:

IS/

Date:

7/15/98

Title:

Project Manager

Signature of Office/Division Director

Signature:

IS/

Date:

7/17/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

A/BLA # NDA 20-847 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE6

HFD-580 Trade and generic names/dosage form: Esclim® (estradiol transdermal system) Action: AE NA

Applicant Fournier Research Inc. Therapeutic Class 3S

1. Indication(s) previously approved 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.

Pediatric information in labeling of approved indication(s) is adequate inadequate

Proposed indication in this application none

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? Yes (Continue with questions) No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

Neonates (Birth-1 month) Infants (1month-2yrs) Children (2-12yrs) Adolescents (12-16 yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.

(1) Studies are ongoing.

(2) Protocols were submitted and approved.

(3) Protocols were submitted and are under review.

(4) If no protocol has been submitted, attach memo describing status of discussions.

d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? Yes No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical review (e.g., medical review, medical officer, team leader)

Signature Of Preparer And Title

Project Manager

Date

7/13/98

CC: ORIG NDA/BLA # NDA 20-847
HFD-580 /DIV FILE
NDA/BLA ACTION PACKAGE
HFD-006/ KROBERTS

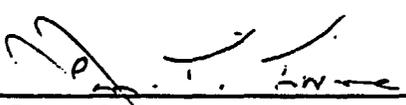
(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

DEBARMENT CERTIFICATION

Laboratoires Fournier, SA certifies that no person, or affiliated person, responsible for the development or submission of records or data for this New Drug Application for Esclim® (estradiol transdermal system) has been convicted of any crime described in Section 306(a) and (b) of the Generic Drug Enforcement Act of 1992 ("Act"). This certification covers the period within five years before the date of this application.

Laboratoires Fournier, SA certifies that it did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) of the Act in connection with this or any other application.



Alan Irvine, MD
Director, Development & Regulatory Affairs
Laboratoires Fournier, SA

22 July 1997
Date

SUBMISSION OF PATENT INFORMATION
IN ACCORDANCE WITH 21 C.F.R. § 314.53

In accordance with the requirements of 21 C.F.R. § 314.53(c)(1), applicant Laboratoires Fournier S.A. submits the following patent information:

- (i) Patent Number and the Date on which the patent will expire:
 - (a) Patent Number: 4,842,864
 - (b)(1) Expiration Date under the provisions of the Uruguay Round of the General Agreement on Tariffs and Trade ("GATT"):
March 25, 2008.
- (ii) Type of Patent:
Drug product (formulation of 17 beta-estradiol)
- (iii) Name of Patent Owner:
Laboratoires d'Hygiene et de Dietetique
- (iv) U.S. Agent
R. Lance Boyett, Fournier Research, Inc., 9 Law Drive, Fairfield, NJ 07004

In accordance with the requirements of 21 C.F.R. § 314.53(c)(2), the following original declaration is submitted; in accordance with 21 C.F.R. § 314.53(c)(4), the original declaration has been signed by the patent owner's attorney.

"The undersigned declares that Patent Number 4,842,864 covers the formulation, composition, and/or method of use of Esclim[®] (TS-17). This product is the subject of the application for which approval is being sought."



Henri Normand
Assistant Director, Industrial Property



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-847

Food and Drug Administration
Rockville MD 20857

JUL 21 1998

Fournier Research Inc.
Attention: Mr. R. Lance Boyett
Director, Clinical Development
9 Law Drive
Fairfield, NJ 077004

Dear Mr. Boyett:

Please refer to your pending August 7, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Esclim® (17β-estradiol transdermal system) 0.025, 0.375, 0.05, 0.075 and 0.10 mg/24hr.

We also refer to your submission dated November 14, 1997.

We have completed our review of the physician and patient package inserts and cartons for your submission and have several comments. Revisions have been incorporated directly into the enclosed labeling. Additions have been noted with **highlighting**, deletions have been noted as **strikeouts**. Additional comments requiring response are in **14 pt bold face type**.

Please submit your revised physician and patient package inserts as soon as available so that we can continue the evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified.

If you have any questions, contact Diane Moore, Project Manager at (301) 827-4260.

Sincerely,

/S/

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-847

JUL 6 1998

Fournier Research Inc.
Attention: Mr. R. Lance Boyett
Director, Clinical Development
9 Law Drive
Fairfield, NJ 07004

Dear Mr. Boyett:

Please refer to your pending August 12, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Esclim (17 β -estradiol transdermal system) 0.025, 0.375, 0.05, 0.075 and 0.10 mg/24 hr.

We have completed our review of the Microbiology section of your submission and have the following comments and information requests:

1. The units of measurement for the microbial limits tests should be clarified. The limit does not explain whether the units of measure (grams) include the adhesive and the foam backing, or just the adhesive, or if it is based on the mass of the active ingredient.
2. Details of product sample preparation and microbial cultivation for the microbial limits tests should be provided. Quantitative measurement of the microbial content may require dissolving the sample, and these methods should be explained since they are not detailed in USP. It would be helpful to describe how many patches are used to prepare the tested sample. If the methods for dissolving the product use solvents or procedures which are not described in compendia, a demonstration of their appropriateness should be provided. Please refer to the sections "Preparatory Testing" and "Procedures" in USP chapter <61>.
3. The frequency of the proposed stability test is high, however, because IND batches were not tested microbiologically, these tests should remain at this frequency for at least the first 2 years of production.

The frequency of microbiological testing for stability batches may be reduced after 2 years, if tested batches reveal no evidence of microbiological problems, particularly growth. A supplement to the NDA should be filed to notify the Agency of your intentions before this change is made.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. In addition, we may identify other information that must be provided prior to approval of this application. If you respond in the current review cycle we may or may not consider your response prior to taking an action on your application. In the meantime, we are continuing our review of your application.

NDA 20-847

Page 2

If you have any questions, contact Diane Moore, Project Manager, at (301) 827-4260.

Sincerely,

JSI 7/6/98

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for
Division of Reproductive and Urologic Drug
Products (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:

Archival NDA 20-847

HFD-580/Div. Files

HFD-580/D.Moore

HFD-580/LRarick/MMann/JSafran/MRhee/DLin/Jordan

HFD-580/KRaheja/ADorantes/VJarugula/KMeaker

HFD-805/PCooney/DHussong

HFD-820/DNDC Division Director (only for CMC related issues)

DISTRICT OFFICE

7/6/98

Drafted by: dm/June 24, 1998

filename: N20847IR.DOC

Concurrence:

LPauls 06.24.98/DHussong, DLin, MRhee, 06.25.98/MMann 06.26.98/LRarick 07.02.98

INFORMATION REQUEST (IR)



Moore

Food and Drug Administration
Rockville MD 20857

NDA 20-847

JUN 02 1998

Laboratories Fournier S.A.
Fournier Research
Attention: Mr. R. Lance Boyett
Director, Clinical Development
9 Law Drive
Fairfield, N.J. 07005

Dear Mr. Boyett:

Please refer to your pending August 7, 1997, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Esclim® (estradiol) transdermal system 0.025, 0.0375, 0.05, 0.05, 0.0375, 0.1 mg/day.

We have completed our review of the chemistry section of your submission and have identified the following comments and information requests:

Drug Substance:

1. Specifications for related substances should be included in the estradiol drug substance specifications on page 3-33 (vol. 1.3). Following ICH guidelines, any related substances greater than 0.1% need to be reported and limits set.

Drug Product:

1. Please specify the cross-linking agent that is used to lower the melt index of the low viscosity EVA copolymer. The information on page 3-196 (vol. 1.3) is not legible.
2. You indicate that the printing system is currently under investigation and not yet implemented in the production area. Information is needed on the type of printing system that was used for the batches currently on stability testing.
3. Please provide the sampling plans used during the drug product manufacturing process and the release testing of the product.
4. Please provide specifications for the control tests in the coating and drying step, and the final cutting and packaging step.
5. In the method of manufacturing section, you indicate that the foam film is white on the side contacting the adhesive mass and beige on the other side. However, in this appearance test on page 3-1322 (vol. 1.7), the transdermal system is described as also having two beige colored surfaces. Please explain this discrepancy.
6. The statement, "Legible print on the beige face of the foam film", should be included in the appearance specifications of the transdermal system.

7. Please comment on why the result of the mean coated mass is reported to 1 decimal place, but the specification is set at 2 decimal places.
8. In the "Detection and Quantitation Limits" section of the ethanol quantitation method validation report, there are errors in the calculations for quantitation limit for each size of transdermal system. Based on the information provided, the limit should be as follows: mg for 11 cm² systems; mg for 22 cm² systems; mg for 44 cm² systems. The same errors are noted with the calculations for detection limit. Please comment.
9. For the degradation products method, a system suitability parameter should be performed and set for capacity factor, k', and tailing factor, T. This is in addition to the other two parameters reported, precision/injection repeatability, RSD, and resolution, R_S.
10. For the method used in the dissolution method, a system suitability parameter should be performed and set for capacity factor, k', and tailing factor, T. This is in addition to the other parameter reported, precision/injection repeatability, RSD.
11. In the composition table on page 3-52 (vol. 1.3), dipropylene glycol is listed as a solvent, and octyldodecanol as a plasticizer. However, if they function as enhancers in the transdermal system, a specification for their content needs to be added to the product regulatory specifications.
12. Specifications for the peel test should be added once enough data is obtained.
13. In the technical data sheet for the heat-sealing paper-aluminum-copolymer complex (sachet) on page 3-1218 (vol. 1.7), the compositional information indicates that one of the components is bleached kraft paper coated on one side. Please provide information on the composition of this coating.
14. Please clarify as to whether the number of crystals observed under freeze/thaw conditions were more than the number observed at 25 °C and 37 °C.
15. On page 3-1600 (vol. 1.8) in the appearance section, the term "slight creep" needs to be defined. Please also comment on whether the number and size of crystals formed were quantitated.
16. Please provide an explanation as to why the ethanol content test was not included in the stability protocol for Esclim batches 002 and 003 on page 3-1611 (vol. 1.8).
17. Please clarify if the same stability program will be used with Esclim 004 as Esclim 002 and 003.
18. In the stability results of Esclim 002 in the March 5, 1998 amendment, please clarify whether the degradation product with RRT 0.83 is the same as degradation product unknown 4, reported for batches 651VP, 652VP, 620VP and 659VP.
19. Based on the available stability data from the commercial Esclim batches 002 and 003, and other clinical batches as well as the European batches, the proposed 30 month expiration date should be changed to 24 months. It can be extended when data from the 25 °C/60 % RH stability studies of Esclim batches 002, 003, and 004 become available to support such an extension.
20. Please provide an explanation as to why the ethanol content, dipropylene glycol content, and

octyldodecanol content tests are no longer in the protocol on page 3-1644 (vol. 1.8).

21. Please clarify as to why there are two methods, 02 DAP 120-02/01 on page 3-1651 (vol. 1.8) and 02 DAP 120-02/03 on page 3-1346 (vol. 1.7) for assaying residual ethanol, and 02 DAP 120-03/01 on page 3-1704 (vol. 1.8) and 02 DAP 120-02/02 on page 3-1736 (vol. 1.8) for the identification and assay of dipropylene glycol, and 02 DAP 120-04/01 on pages 3-1716 (vol. 1.8) and 02 DAP 120-02/02 on page 3-1753 (vol. 1.8) for the identification and assay of octyldodecanol.
22. Please explain why there are two methods for quantitating estradiol related products. In addition please indicate which one is the regulatory method.
23. The peel test in the stability protocol on page 3-1612 (vol. 1.8) refers to a ASTM D3330-96 (90° angle) procedure. However, the method described in the NDA on page 3-1647 (vol. 1.8) is for a test at an 180° angle. Please clarify whether the method in the NDA is the one being used or whether there a modified method. In addition, there are three test methods described. Please specify the exact method used.
24. Please provide three copies of the revised methods validation package. For validation of the Method, you will need to provide a sample of estrone and estrone reference standard. In addition, a Material Safety Data Sheet for estradiol and estrone needs to be provided.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. These comments are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to taking an action on your application.

If you have any questions, contact Diane Moore, Project Manager, at (301) 827-4260.

Sincerely yours,

/S/

6/2/98

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
Division of New Drug Chemistry II (DNDC)
@ DRUDP (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-847
Fournier Research
Esclim®

Page 4

Original NDA 20-847
HFD-580/Div. Files
HFD-820/ONDC Division Director
DISTRICT OFFICE
HFD-92/DDM-DIAB
HFD-580/D Moore/JMarkow/MRhee/LPauls/LRarick/Mmann

Drafted by: jm/June 1, 1998/wordfiles/nda/letters/20847def.doc
Concurrences: DLin 6.1.98/MRhee 6.2.98/LPauls 6.2.98/LRarick 6.2.98

6/2/98

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

APR 02 1998

DATE: April 2, 1998
FROM: Diane Moore
Division of Reproductive and Urologic Drug Products (HFD-580)
FAX; (301) 827-4267
SUBJECT: Chemistry discussion items for Esclim (estradiol transdermal system) NDA 20-847
TO: R. Lance Boyette
Director, Clinical Development
Fournier Research Inc.

Agenda items for TELECON discussion:

1. The DMF that was referenced to in the NDA refers to the polymer used in the manufacture of the product sachet. The DMF that is required for the NDA is the DMF that refers to the entire sachet product owned by Fournier must provide either complete manufacturing information for the sachet product or a letter from that gives permission for Fournier to cross-reference their DMF for the sachet product.
2. The protective polyester film on the matrix coating is made by two suppliers. In order to use both suppliers, a commercial batch scale from each manufacturer must be placed on stability. The first commercial scale batch for Esclim (batch 02) was submitted to the NDA. Which manufacturer supplied the polyester film used in this batch?

Please call me at (301) 827-4260 to discuss a mutually convenient date and time for the teleconference.

Sincerely,

/s/

Diane Moore
Project Manager
Division of Reproductive and Urologic Drug
Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-847
Page 2

Concurrence:
LPauls 04.02.98

cc:
HFD-580
HFD-580/LRarick/MMann/MRhee/DLin



110020

NDA 20-847

SEP 25 1997

Fournier Research Inc.
Attention: Mr. R. Lance Boyett
Director, Clinical Development
9 Law Drive, Fairfield, NJ 07004

Dear Mr. Boyett:

Please refer to your pending August 7, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Esclim® (Estradiol Transdermal System).

In order to optimize the review of the Biopharmaceutics section of your submission, we request the following:

1. The human pharmacokinetics and bioavailability summary section of the NDA (in Vol. 1.13) should be rewritten according to the "Division Internal Guidelines for the Preparation of the Pharmacokinetic Section of an NDA for Transdermal Systems"
2. In the 'Drug Formulation Information' sub-section, the formulation and manufacturing changes between the clinical trials formulation and the to-be-marketed formulation should be described.
3. *In vitro* dissolution method development and validation data, and the *in vitro* release comparison data between the batches from clinical trial formulations and the to-be marketed formulation including the graphs of release profiles and individual data should be included in the '*In-vitro* testing methodology and Data' sub-section.
4. The pharmacokinetics section of the labeling should be rewritten according to the Division Internal Guidelines for the Preparation of the Pharmacokinetic Section of the Labeling for Transdermal Products"
5. Please submit the summary of human pharmacokinetics and bioavailability section, all individual study report summaries including the raw data of individual studies and the draft of the physician's package insert should be submitted in electronic format.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.



If you have any questions, please contact Diane Moore, Consumer Safety Officer, at (301)-827-4260.

Sincerely,

LSI 9/25/97

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ATTACHMENTS

1. Division Internal Guidelines for the Preparation of the Pharmacokinetic Section of an NDA for Transdermal Systems.
2. Division Internal Guidelines for the Pharmacokinetic Section of the Labeling for Transdermal Products.

cc:

Original NDA 20-847
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/HJolson/VJarugula/ADorantes
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: dm/September 19, 1997/n20847ad.918

LPauls 09.24.97/VJarugula, GBarnette, HJolson 09.23.97/LRarick 09.24.97

INFORMATION REQUEST (IR)

D Moore 9/25/97

ATTACHMENT 1

DIVISION INTERNAL GUIDELINE FOR THE PREPARATION OF THE PHARMACOKINETIC SECTION OF AN NDA FOR TRANSDERMAL SYSTEMS

1. Overall Summary Information (including summary of studies, summary tables and overall conclusions)
2. Background Information
3. Protein Binding and Metabolic Information (including drug metabolism, mass balance, metabolic pathway, and active metabolites)
4. Drug Formulation Information (including investigational and to-be-marketed formulations)
5. *In Vitro* Testing Methodology and Data (including *in vitro* release rate and *in vitro* skin permeation information)
6. *In Vivo* Adhesion Data (lifting and detachment)
7. Residual drug remaining in the patch after removal of the transdermal system
8. Analytical Methodology (including assay validation data for parent drug, major active metabolites and analytical kits used to determine PD parameters such as LH, FSH, etc.)
9. Bioavailability/Bioequivalence Information
 - Bioavailability (absolute and/or relative)
 - Bioequivalence (clinical formulation vs. To-be-marketed formulation and/or possible dosage strength bioequivalence)
 - Site of application
10. Pharmacokinetic Information
 - Healthy subjects (single and multiple dose)
 - Target population (single and multiple dose)
11. Dose Proportionality (covering the dosage range recommended in the labeling)
12. Special Populations
 - Elderly
 - Obese
 - Disease States
 - specific diseases(s)
 - renal impairment
 - liver insufficiency
13. Drug-drug Interactions
14. Pharmacokinetic/Pharmacodynamic Relationships
15. Population Pharmacokinetics and Population Pharmacodynamic Analysis (as a function of different covariates such as age, race, body-weight, height, smoking habits, concomitant medications, disease states, etc.,

related to pharmacokinetic parameters such as clearance volume of distribution, C_{max} , etc., and/or to pharmacodynamic safety and efficacy endpoints or surrogate endpoints, as appropriate)

15. Labeling

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 2

DIVISION INTERNAL GUIDELINE FOR THE PREPARATION OF THE PHARMACOKINETIC SECTION OF THE LABELING FOR TRANSDERMAL PRODUCTS

Currently, the FDA is attempting to standardize the content and presentation of the information that is to be given in the *Pharmacokinetics* portion of the *Clinical Pharmacology* section of the package insert of transdermal products. The *Pharmacokinetics* portion should present information as appropriate under the subheadings of *Absorption, Distribution, Metabolism, Excretion, Special Populations (i.e., Geriatric, Pediatric, Race, Renal Insufficiency, Hepatic Insufficiency, and Drug-Drug Interactions, etc.), and Adhesion*. The subsection *Adhesion* should indicate that adhesion is a critical factor related to efficacy and the pharmacokinetic & therapeutic implications of patch lifting and detachment, and include information on the percentage of systems that lifted and were replaced during the clinical and pharmacokinetic studies. The package insert additional information may be obtained from both sponsor's biostudies or published references. Where relevant information is lacking it should be so stated.

Also, a table(s) with mean (\pm SD) pharmacokinetic parameters determined under single and steady state conditions should be prepared. This table(s) should include bioavailability, maximum peak concentration (C_{max}), minimum peak concentration (C_{min}), average peak concentration (C_{avg}), clearance, and half-life for the studied drug and its active metabolites for each studied population including the drug's intended target population. Also, if appropriate a plot(s) that illustrates drug and metabolite(s) plasma/serum concentration vs. Time (i.e., different dosage strengths, different sites of application, comparison to a reference product, etc.) may be included.

In addition, the **DOSAGE AND ADMINISTRATION** section of the labeling should include instructions regarding "what the patient should do" in the event that the system lifts or falls off.

APPEARS THIS WAY
ON ORIGINAL

n/2012c

AUG 14 1997

NDA 20-847

Fournier Research Inc.
Attention: Mr. R. Lance Boyett
Director, Clinical Development
9 Law Drive, Fairfield, NJ 07004

Dear Mr. Boyett:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Esclim® (17 Beta-estradiol), 0.025, 0.0375, 0.05, 0.075 and 0.10 mg/24 hr
Therapeutic Classification:	Standard
Date of Application:	August 7, 1997
Date of Receipt:	August 12, 1997
Our Reference Number:	20-847

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 11, 1997, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Diane Moore, Consumer Safety Officer, at (301) 827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

ISI

8/13/97

Lana L. Pauls, M.P.H.
Chief Project Manager
Division of Reproductive and Urologic Drug
Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-847

Page 2

cc:

Original NDA 20-847

HFD-580/Div. Files

HFD-580/CSO/D.Moore

HFD-580/LRarick/HJolson/MRhee/AJordan/ADorantes/LKammerman

DISTRICT OFFICE

Drafted by: dm/August 13, 1997/n20847ac.812

ACKNOWLEDGEMENT (AC)

8/12/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-847

CORRESPONDENCE

FOURNIER

RESEARCH INC.

ORIGINAL

July 31, 1998

VIA TELEFAX

Dr. Lisa Rarick,
Director, Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration,
Room 17 B 45
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP



Re : NDA # 20,847
Esclim® (estradiol transdermal system)
Revised Package Labeling: Physician Package Insert

We refer to the telephone conversations of today between the undersigned and Ms. Diane Moore of the Division regarding the Draft Labeling (Physician Package Insert) submitted on July 30, 1998.

As agreed, the requested revision to the Pharmacokinetics Section, pages 5 and 6 has been incorporated into the Insert. A clean copy of the Insert is submitted herewith.

Hard copies of these items are being forwarded in triplicate under separate cover.

Thank you for your continued review of the NDA.

Please feel free to telephone the undersigned at 973-575-1010 (ext. 12) if you have any further questions or requests.

Sincerely,

A handwritten signature in black ink, appearing to read "R. Lance Boyett".

R. Lance Boyett
Director, Clinical Development
Fournier Research, Inc.

Enclosures (in triplicate): Physicians Package Insert, Edition date July 31, 1998

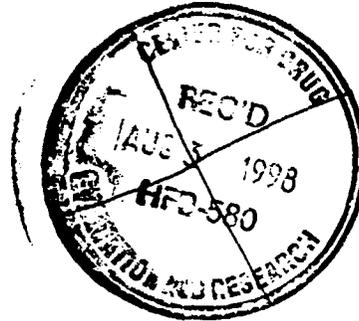
FOURNIER

RESEARCH INC.

July 30, 1998

VIA TELEFAX

Dr. Lisa Rarick,
Director, Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration,
Room 17 B 45
5600 Fishers Lane
Rockville, MD 20857



Re : NDA # 20,847
Esclim® (estradiol transdermal system)
Response to FDA Labeling Comments of July 21, 1998: Patient Package Insert

We refer to your correspondence of July 21, 1998, and the Revised Patient Package Insert received therewith. We also refer to our teleconference of July 29, 1998, and subsequent telephone conversations today between the undersigned and Ms. Diane Moore of the Division.

We have reviewed the proposed revisions to the Patient Package Insert and have incorporated all of the suggestions into the current version (July 30, 1998). A copy of this Patient Package Insert is enclosed herewith.

As requested by telephone, we are forwarding an electronic version of the revised Physician Package Insert submitted earlier today, and the Patient Package Insert submitted herewith, to Ms. Diane Moore.

Thank you for your continued review of the NDA.

Please feel free to telephone the undersigned at 973-575-1010 (ext. 12) if you have any further questions or requests.

Sincerely,

R. Lance Boyett
Director, Clinical Development
Fournier Research, Inc.

ORIGINAL

FOURNIER

RESEARCH INC.

July 28, 1998

VIA TELEFAX

Dr. Lisa Rarick,
 Director, Division of Reproductive and Urologic Drug-Products (HFD-580) **NEW CORRESP**
 Food and Drug Administration,
 Room 17 B 45
 5600 Fishers Lane
 Rockville, MD 20857

Re : NDA # 20,847
 Esclim® (estradiol transdermal system)
 Response to CMC Comments

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS _____ DATE _____

We refer to the telephone calls of July 15, and July 21, 1998 from Ms. Diane Moore of the Division to Ms. Jessica Steinert and Mr. Lance Boyett (respectively) of Fournier Research, Inc., regarding Chemistry, Manufacturing, and Controls requests and questions. We also refer to the teleconference of July 23, 1998 between Laboratoires Fournier and the Division regarding these same issues.

As agreed at the July 23, 1998 teleconference, Laboratoires Fournier has revised the regulatory specifications for the product as requested by the Division on July 15, 1998. The revised specifications for each of the dosage forms (0.025, 0.0375, 0.050, 0.075 and 0.10 mg/24 hours) may be found on pages 1 through 5 of the current submission.

During the teleconference, Dr. Lin pointed out that there were differences between several of the SOP version numbers described in the final regulatory specifications, when compared to the Validation Reports for the methods. As indicated during the teleconference, the changes in the version numbers reflect the fact that there were minor modifications to the methods. However, the Validation Reports for each of these methods are applicable to the subsequent version numbers. The differences in methods, and confirmation that the Validation Reports are applicable are given on pages 6 and 7 of the current submission.

Please feel free to telephone the undersigned at 973-575-1010 (ext. 12) if you have any further questions or requests.

Sincerely,



R. Lance Boyett
 Director, Clinical Development
 Fournier Research, Inc.

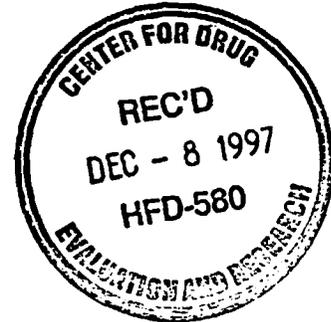


FOURNIER

RESEARCH INC.

December 5, 1997

Lisa Rarick, M.D.
Director, Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration,
Room 14 B 04
5600 Fishers Lane
Rockville, MD 20857



Re : NDA # 20-847 (Esclim[®] estradiol transdermal system)
4-Month Safety Update Report

Dear Dr. Rarick:

We reference our proposal for the above referenced report dated November 10, 1997, and the Division's agreement with this proposal conveyed by telephone to the undersigned on November 21, 1997.

Enclosed herewith is the 4-Month Safety Update Report for the above referenced NDA, required under 21 CFR §314.50. As agreed, the principal data in this report is limited to listings of Adverse Effects received by the Pharmacovigilance Department of Laboratoires Fournier, and a brief summary of these data.

In addition, the report provides an update on the Foreign Marketing Status of Esclim. Finally, a copy of the original and translated Summary of Product Characteristics as approved in Denmark is included as an appendix to this report. This final item is being submitted as indicated in the original NDA submission on August 7, 1997.

We thank you for your continued review of the NDA. Please contact the undersigned, Laboratoires Fournier's authorized agent (973-575-1010), if there are any questions regarding this submission.

Sincerely,


R. Lance Boyett
Director of Clinical Development
Fournier Research, Inc.

Encl.: Section 9, Volume 5.1 (In triplicate)



ORIGINAL

NEW CORRESP

December 1, 1997

Lisa Rarick, M.D.
Director, Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration,
Room 14 B 04
5600 Fishers Lane
Rockville, MD 20857



Re : NDA # 20-847 (Esclim[®] estradiol transdermal system)
Waiver Request for Environmental Assessment

Dear Dr. Rarick,

We reference a telephone conversation held between the Applicant's authorized US agent (Mr. Lance Boyett) and Diane Moore on September 24, 1997 concerning the Applicant's intentions to request a waiver of the Environmental Assessment submitted in the above-cited application.

In this regard, enclosed you will find in duplicate, a letter claiming categorical exclusion from an Environmental Assessment and Environmental Impact Statement.

Please contact the Applicant's authorized US agent at (973) 575-1010 if you have any questions or comments regarding this waiver or if additional information is required.

We thank you for your continued review of the above-referenced NDA.

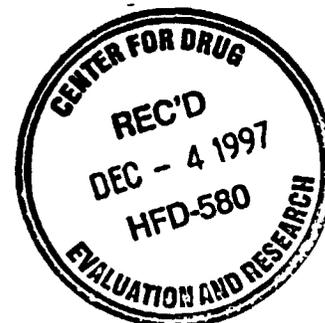
Sincerely,

L. Ospital
Regulatory Affairs
Project Manager

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

November 26, 1997

Lisa Rarick, M.D.
Director, Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration,
Room 14 B 04
5600 Fishers Lane
Rockville, MD 20857



Subject: **NDA 20-847 (Esclim[®] estradiol transdermal system)**
**Claim of categorical exclusion from Environmental Assessment and
Environmental Impact Statement**

Dear Dr Rarick,

Reference is made to the above pending NDA and to the FDA Final Rule for Policies and Procedures for Compliance with the National Environmental Policy Act. The new rules were published in the Federal Register on July 29, 1997 at 62 FR 40570 and made effective on August 28, 1997.

In accordance with the general procedural rules at Sec. 25.15(d) of the above Final Rule we hereby amend the pending application to claim categorical exclusions under the new rule.

The Sponsor claims categorical exclusion under Sec. 25.31, paragraphs (a) and (c). The Sponsor is in compliance with the criteria of the following two categorical exclusions:

- (a) *Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, if the action does not increase the use of the active moiety.*

.../...

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

(c) Action on an NDA, abbreviated application, application for marketing approval of a biologic product, or a supplement to such applications, or action on an OTC monograph, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

To the best of the applicant's knowledge no extraordinary circumstances exist.

In the event that a FONSI may have already been signed for the above NDA, the Sponsor waives the claim for categorical exclusions.

Sincerely yours,



Claude MIKLER
Director Tilderm Systems

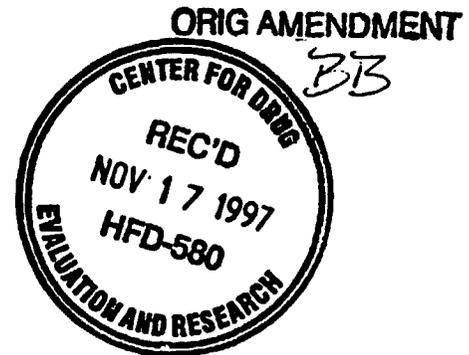
FOURNIER

RESEARCH INC.

ORIGINAL

November 14, 1997

Lisa Rarick, M.D.
Director, Division of Reproductive and
Urologic Drug Products (HFD-580)
Food and Drug Administration,
Room 14 B 04
5600 Fishers Lane
Rockville, MD 20857



Re : NDA # 20-847 (Esclim® estradiol transdermal system)
Response to Biopharmaceutics Request: Rewrite of Section 6

Dear Dr. Rarick:

We reference your letter of September 25, 1997 and our letter of commitment dated October 6, 1997, our partial response of October 23, 1997 and our submission of electronic data on October 24, 1997.

Enclosed is the remainder information we agreed to provide with respect to the biopharmaceutics section of the NDA.

- Section 6, Human Pharmacokinetics & Bioavailability, has been rewritten according to the Division Internal Guidelines provided to us with your letter.
- The "Pharmacokinetics" section of the labeling has been rewritten according to the Division Internal Guidelines for labeling, also provided with your letter. The revised draft labeling incorporating the rewritten section is provided in Section 6.16 of the current submission.
- The electronic versions of these documents are provided on the diskette forwarded herewith.

It should be noted that the subheadings of "Renal Insufficiency, Hepatic Insufficiency, and Drug-Drug Interactions" described under the "Special Populations" section in the guideline are not included in the proposed labeling because there are no pharmacokinetic data with Esclim appropriate to these sections. However, it is important to note that the relevant safety information for these subsections is already described in the "Precautions" section of the labeling according the Labeling Guidelines for Estrogen Drug Products.

In Appendix 6.5 of the current submission, we are also providing a revised Annotation of the Proposed Labeling, previously provided in Section 2.1 (Volume 1.2) of the original NDA submission (August 7, 1997). This revised version differs from the previously submitted version only with respect to the "Pharmacokinetics" section of the proposed labeling, which was revised

Dr. Lisa Rarick
November 14, 1997

Page 2 of 2

according to the Division Internal Guidelines as requested. Appropriate referencing is included for the information that has been added pursuant to the requested revision.

We believe that this submission resolves all outstanding requests received to date from the Division.

We thank you for your continued review of the NDA. Please contact the undersigned, Laboratoires Fournier's authorized agent (973-575-1010), if there are any questions regarding this correspondence, or if you require further clarification.

Sincerely,



R. Lance Boyett
Director of Clinical Development
Fournier Research, Inc.

Encl.: Section 6, Volume 4.1, in triplicate
One diskette

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE