CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-166

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 21-166_____ SUPPL #

Trade Name Estrogel 0.06% _____ Generic Name estradiol gel

Applicant Name Solvay Pharmaceuticals
HFD- 580
Approval Date February 9, 2004

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 questions about the submission.

   a) Is it an original NDA? YES/_X__/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X__/

      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 /_X__/ 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 /_X__/ NO /___/

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

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 /_X__/

If yes, _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 # 21-371 Estrasorb

NDA #

NDA #

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 /_X__/

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 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /_X__/ 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 9:**

(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 /_X__/

(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 /__X_/

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 /_X__/

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:

Investigation #1, Study # CV141-001

Investigation #2, Study #

Investigation #3, Study #

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 /__X_/
Investigation #2	YES /___/	NO /_ __/
Investigation #3	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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation #__, Study # CV141-001

Investigation #__, Study #

Investigation #__, Study #

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 # IND 29-020_____ YES /_X__/ 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 /_X__/ 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 /_X__/

If yes, explain: _____

_____

_____

George Lyght

Signature of Preparer Date 02/09/04

Title: Regulatory Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA 21-166
HFD-580 /Division File
HFD-580 / George Lyght,RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Daniel A. Shames
2/9/04 07:57:44 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : NDA 21-166 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: August 16, 1999 Action Date: February 9, 2004

HFD 580____ Trade and generic names/dosage form: Estrogel 0.06% (estradiol gel)

Applicant: Solvay Pharmaceuticals Therapeutic Class: Estrogen

Indication(s) previously approved: No

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Treatment of moderate to severe vasomotor symptoms associated with menopause
#2 Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause

Is there a full waiver for this indication (check one)?

x Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
X Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval

- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ection D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
George Lyght
Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication : _____

Is there a full waiver for this indication (check one)?

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
*_George Lyght*_____
Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 10-14-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

Request for 3 Year Exclusivity

In accordance with the provisions of 21 CFR 314.108(b)(4), UNIMED Pharmaceuticals, Inc. requests three years of exclusivity for the prescription marketing of ESTROGEL® (estradiol, USP) Gel for: (1) the treatment of moderate to severe vasomoter symptoms associated with menopause, (2) the treatment of vulval and vaginal atrophy, [redacted]. This application falls under 21 CFR 314.108(b)(5) which states that three years of exclusivity will be granted for applications of a drug product which contain an active moeity that has been previously approved in another application and which contain reports of new clinical investigations conducted or sponsored by the applicant which were essential to the approval of the application.

To assist the Agency in determining which applications meet the three criteria for three years of exclusivity, we are providing the following information in this request as required by 21 CFR 314.50(j).

1. **For purposes of exclusivity determinations, the Agency interprets the phrase "new clinical investigations" to mean investigations conducted on humans that have not been used by the Agency as part of the basis for a finding of substantial evidence of effectiveness for any previously approved new drug application or supplement.**

The application contains the following new clinical investigations for ESTROGEL® — (refer to section 8 of this application for more information regarding these supportive studies):

- Two pivotal, controlled clinical studies (CV141-001 and CV141-002) to support the treatment of moderate-to -severe vasomoter symptoms associated with menopause.

- Four human pharmacokinetics and bioavailability studies (S1661002, S1661003, MKL 2593, AD1245H/96 OEST 01).

- Fourteen other supportive clinical trials (studies 01 through 14) which assess the effects of vasomoter symptoms, bone mineral density, endometrial morphology, and pharmacokinetics.

We certify that these studies have not been used to provide substantial evidence of effectiveness for a previously approved new drug application or supplement.

2. The Agency interprets the phrase "essential to approval" to mean that the application or supplement could not be approved without the investigation. If an abbreviated new drug application or new drug application described by section 505(b)(2) of the Act or supplement to either could have been approved for the drug product without the submitted studies, even with a delayed effective date, or if publicly available studies, other than those conducted or sponsored by the applicant, could have supported the application or supplement, then the investigation cannot be considered essential to the approval.

This application contains two pivotal controlled clinical trials, Study No. CV141-001 and Study No. CV141-002, designed to evaluate the efficacy of ESTROGEL® —, in the treatment of moderate-to-severe vasomotor symptoms associated with menopause. These trials are considered "essential to approval" for the indications proposed in this application.

3. The Agency considers an investigation to have been conducted or sponsored by the applicant if, before, or during the investigation, (1) the applicant was the sponsor named in the Form FDA 1571 (IND) for the investigation, or (2) the applicant, or another entity that the applicant purchased or merged with, provided substantial financial support for the investigation.

The efficacy of ESTROGEL® — was demonstrated in two pivotal controlled clinical trials, Study No. CV141-001 and Study No. CV141-002, conducted under IND 29,020. Solvay Pharmaceuticals, Inc. was the sponsor named in this IND and provided the financial support for the conduct of these studies. The sponsor of this new drug application, UNIMED Pharmaceuticals, Inc., is a wholly owned subsidiary of Solvay Pharmaceuticals, Inc.

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-166	Efficacy Supplement Type SE-	Supplement Number	
Drug: Estrogel 0.06%		Applicant: Solvay Pharmaceuticals	
RPM: George Lyght		HFD-580	Phone # 301-827-4260
Application Type: (x) 505(b)(1) ( ) 505(b)(2)		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(x) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	February 9, 2003
❖ Special programs (indicate all that apply)	(x) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(x) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (x) No
• This application is on the AIP	( ) Yes ( ) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(x) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(x) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified
❖ Exclusivity Summary (approvals only)	
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	(x) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(x) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(x) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X
• Documentation of discussions and/or agreements relating to post-marketing commitments	X
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	01/12/1998
• Pre-NDA meeting (indicate date)	07/11/1995
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
Clinical and Summary Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	2/09/2004
❖ Clinical review(s) *(indicate date for each review)*	02/09/2004
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	03/17/2000
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	In Clinical review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	01/30/2004
❖ Biopharmaceutical review(s) *(indicate date for each review)*	02/09/2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA

❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	See clinical review
• Bioequivalence studies	See biopharm review
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	02/09/2004
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	See CMC Review
• Review & FONSI *(indicate date of review)*	See CMC Review
• Review & Environmental Impact Statement *(indicate date of each review)*	See CMC Review
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	See CMC Review
❖ Facilities inspection (provide EER report)	Date completed: 01/28/2004 (x) Acceptable ( ) Withhold recommendation
❖ Methods validation	(x) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	06/30/2003
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-166 Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Estrogel 0.06%
Generic Name: estradiol gel
Strengths: 0.06%

Applicant: Solvay Pharmaceuticals

Date of Application: August 13, 1999. (New review clock administratively set on April 9, 2003)
Date of Receipt: August 16, 1999
Date clock started after UN:
Date of Filing Meeting: 09/22/1999 and 10/12/1999
Filing Date: October 15, 1999
Action Goal Date (optional): User Fee Goal Date: February 9, 2004

Indication(s) requested: Moderate to severe vasomotor symptoms associated with menopause
Moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause

Type of Original NDA: (b)(1) ___X_____ (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S _____X_____ P _____
Resubmission after withdrawal? _____ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) ___3_____
Other (orphan, OTC, etc.) _____

User Fee Status: Paid ___X_____ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # _3767_____
Clinical data? YES ___X_____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A YES NO
- Is it an electronic CTD? N/A YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 years NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,

"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: 29-020

- End-of-Phase 2 Meeting(s)? Date(s) 01/12/1998
  NO
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 07/11/1995
  NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  N/A YES NO

- Has DOTCDP been notified of the OTC switch application? N/A YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
  If no, did applicant submit a complete environmental assessment? YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

MEMO OF FILING MEETING

The filing meeting minutes are in the division files. Meetings were held September 22, 1999 and October 12, 1999. The filing date was October 15, 1999.

BACKGROUND:
Solvay Pharmaceuticals purchased IND 29-020 and NDA [redacted] from LaSalle Laboratories in July 1997. Both applications are for 17ß estradiol topical gel, Estrogel. Solvay Pharmaceuticals then submitted a NDA 21-166 Estrogel 0.06% (estradiol gel) on August 13, 1999 for the indications of:
Moderate to severe vasomotor symptoms associated with menopause and
Moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause.

The application was filable.
See Clinical review.

CHEMISTRY

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:
Any comments: N/A

APPEARS THIS WAY
ON ORIGINAL

George Lyght
Regulatory Project Manager, HFD-580

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-420)

DATE RECEIVED: 08/06/03 **DATE OF DOCUMENT: 08/01/03**	**DISIRED COMPLETION DATE: 10/22/03**	**ODS CONSULT #:** 03-0225

TO: Daniel Shames
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Dale Cutright
Project Manager
HFD-580

PRODUCT NAME: **Estrogel** (Estradiol Gel) 0.06% NDA 21-166	**NDA SPONSOR:** Solvay Pharmaceuticals

SAFETY EVALUATOR: Alina R. Mahmud, R.Ph.

SUMMARY:
In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support (DMETS) re-reviewed of the proposed proprietary name "Estrogel" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. As per DMETS' phone conversation with the Medical Officer in DRUDP regarding the use of the proprietary name Estrogel in Canada and Europe, DMETS has no objections to the use of the proprietary name Estrogel in the United States. However, we also note that the proprietary name Estrogel is currently utilized for an over-the-counter herbal product sold in the U.S. via the Internet. DMETS recommends that the sponsor contact the manufacturer of the herbal product to discuss the appropriateness of the proprietary name, Estrogel, for the herbal product. DMETS does not recommend that the herbal product and the prescription utilize the same proprietary name as it may cause confusion and error among patients and health practitioners.

2. Please submit container labels and carton labeling to DMETS for review when available.

3. DDMAC has no objections to the use of the proprietary name Estrogel from a promotional perspective.

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

MEMORANDUM

To:	NDA 21-166
Through:	Dan Shames, MD Director, HFD-580
From:	Brenda S. Gierhart, MD Team Leader, HFD-580
Date:	May 27, 2004
Re:	MO Review of N-000FA-Final Labeling Letter date March 5, 2004 Stamp date March 8, 2004 Estrogel® (estradiol gel) Solvay Pharmaceuticals

Background:
On February 9, 2004, a regulatory letter was sent to the Sponsor approving Estrogel 0.06%, effective on the date of the letter, for use as recommended in the agreed-upon labeling text. The letter stated that the final printed labeling (FPL) must be identical to the enclosed labeling (package insert and patient package insert) and the immediate container and carton labels submitted February 2, 2004. In the letter, the Sponsor was asked to submit an electronic version of the FPL according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format-NDA. Alternatively, the letter stated that the Sponsor could submit 20 paper copies of the FPL as soon as it is available by no more than 30 days after it is printed.

In preparing the FPL, the Sponsor noted 4 changes they wished to make to Table 1. They wished to deleted the words " [redacted] from the main title, add "(Moderate to Severe)" to the title of the middle column, add "(Mild, Moderate, Severe)" to the title on the right column, and change the p-value for the middle column for Estrogel in the Week 4 row from [redacted] to "0.019".

These four changes were agreed to by the Division during a teleconference on February 25, 2004.

Current submission:
In the current submission, the Sponsor electronically has submitted the Final Labeling in addition to submitting a paper copy of the marked and clean copies of the physician labeling incorporating these four changes.

The changes to the physician labeling were reviewed and are in agreement to the changes agreed to by the Division on February 25, 2004.

Recommendation:
1) The Project Manager for NDA 21-166 can proceed with the Regulatory Project Manager Review of the Final Printed Labeling (FPL), which the Sponsor submitted electronically.
2) It appears to the reviewer that the Sponsor failed to provide all the final printed label electronically since only the package insert and patient package insert were submitted to the EDR to N021166 Document: 2541701 Location: \\CDSESUB1\N21166\N_000\2004-03-05. The immediate container and carton labels were not submitted.

3) Recommend that the Project Manager for NDA 21-166 clarify with the Sponsor regarding the Final Printed Labeling for the immediate container and carton labels.

cc: Original NDA 21-166
HFD-580: D. Shames, B. Gierhart, T. van der Vlugt, P. Price and G. Lyght

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/s/

Brenda Gierhart
5/28/04 12:01:14 PM
MEDICAL OFFICER

Daniel A. Shames
6/1/04 05:26:36 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 17, 2003

NDA 21-166

NAME OF DRUG: **Estrogel**
(Estradiol Gel) 0.06%

NDA HOLDER: Solvay Pharmaceuticals

I. INTRODUCTION:

This consult is written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for a re-review of the proposed proprietary name Estrogel. The package insert and patient information leaflet were provided for review and comment.

DMETS reviewed the proprietary name Estrogel on February 4, 2000, and found it acceptable. At that time, DMETS identified the names Estinyl and Estrapel as having a potential for confusion with Estrogel. After conducting a risk assessment, DMETS concluded that the potential for confusion between these names is minimal.

PRODUCT INFORMATION

Estrogel contains 0.06 % 17 β-estradiol in an absorptive hydroalcoholic gel base formulated to provide a controlled release of the active ingredient. 17 β-estradiol is a major estrogenic hormone secreted by the human ovary. Estrogel is indicated in the treatment of moderate to severe vasomotor symptoms associated with menopause, treatment of vulval and vaginal atropy The treatment is usually initiated with 1.25 gram dose applied to the skin once daily. Attempts to discontinue or taper medication should be made at 3 month to 6 month intervals. Estrogel will be available in tube Each individually packaged tube contains 80 grams of gel. A spatula, calibrated for application, is supplied with each tube for use in squeezing the correct amount of gel from the tube. Estrogel will also be available in a non-aerosol, metered-dose pump. Each individually packaged pump contains 80 grams of gel and is capable of delivering sixty-four 1.25 gram doses.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Estrogel to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[4] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Estrogel. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC did not have concerns with the name, Estrogel, in regard to promotional claims.

2. Since the completion of our initial review, the Expert Panel identified five additional proprietary names that were thought to have the potential for confusion with Estrogel. These products are listed in Table 1 (see below and page 4), along with the dosage forms available and usual dosage. In addition, the Expert Panel identified the name "Estrogel" during an Internet search.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	**Dosage form(s), Established name**	**Usual dose***	**Other****
Estrogel	Estradiol Gel	1.25 gram applied to skin once dialy.	
Erygel	Erythromycin Gel 2%	Apply to affected areas morning and evening.	SA
Androgel	Testosterone Gel 1%	Apply once daily, preferably in the morning.	SA
Ogestrel	Ethinyl Estradiol and Norgestrel Tablets 50 mcg/0.5 mg	Take 1 tablet daily.	SA
Metrogel	Metronidazole Gel 0.75%	Apply once or twice daily, morning and evening, to affected areas.	LA
Estrogel	Phytoestrogen Complex Cream	1/4 to 1/2 teaspoonful once daily	SA/LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

[1] MICROMEDEX Healthcare Intranet Series, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2003).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

[4] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

As part of the assessment, the proposed name is evaluated via a phonetic/orthographic database that is in the final states for development for DMETS. At this time of this review, the database was not available. Therefore, Estrogel was not evaluated using this tool.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. Look-alike/Sound-alike names

Since the completion of our initial review, DMETS has identified five additional proprietary names with the potential to look and sound similar to the Estrogel. The name Estrogel is currently in use for a herbal product sold over the counter. The products considered having the greatest potential for name confusion with Estrogel include Estrogel, Erygel, Ogestrel, Metrogel and Androgel.

a. A product containing 0.06 % 17 β-estradiol with the proprietary name, Estrogel, is currently available in Canada but may be purchased via the Internet. This product is identified as a Canadian product and is marketed by Schering Plough. Information on this product can be viewed at the following website: http://www.rxcanadapharmacy.com/htmFiles/Estrogel.asp. As per a phone with the Medical Officer in DRUDP, DMETS was informed that this product is also marketed in Europe with the proprietary name Estrogel. DMETS was also informed that the sponsor of this application, Solvay, and the sponsors of the Canadian and European products are all interrelated. Therefore, DMETS has no objections to use of the proprietary name Estrogel for this application. However, Estrogel is currently sold on the Internet as an herbal product for calming hot flashes and night sweats as well as restoring normal sleep pattern in most women. Information on the product may be found at the following website: http://www.wellfx.com/Shop/?ProductID=57926. Estrogel is advertised as a natural alternative to Provera and Premarin. Estrogel contains phytoestrogen and other naturally occurring ingredients such as Don Quai, Black Cohosh extract, Dermasterone, and Licorice. The over-the-counter herbal product and the proposed product share a similar dosage form, route of administration, and dosing regimen. Although the products are somewhat similar in their effects, DMETS can not assess the potential for harm if the products are inadvertently dispensed for one another, since the herbal product is not regulated by the Agency. However, DMETS has concerns that patients and health practitioners wishing to find additional information on the Internet about the prescription product, Estrogel, may encounter information regarding the herbal product which may cause confusion, error and harm. DMETS recommends that the sponsor contact the manufacturer of the herbal product to discuss the appropriateness of the proprietary name, Estrogel, for the herbal product. DMETS does not recommend that the herbal product and this product utilize the same proprietary name as it may cause confusion and error among patients and health practitioners.

b. Erygel was thought to have a sound-alike potential with Estrogel. Erygel is the proprietary name for the erythromycin and is indicated for the topical treatment of acne vulgaris. Erygel is available as a 2% gel. Erygel and Estrogel are somewhat similar in sound in that they share the first letter "E" and the ending "gel." However, the names are distinguishable due a difference in the first and second syllable (er- vs. es- and -ee- vs. -tro-). Although the products share and overlapping dosage form and route of administration, differences in dosing regimen (twice daily vs. once daily) and minimal sound-alike potential minimize the potential for error.

c. Androgel and Estrogel were found to have sound-alike potential. Androgel contains testosterone and is available as a 1% gel. Androgel is indicated for replacement therapy in primary hypogonadism and hypoganodotropic hypogonadism. The names Androgel and Estrogel are comprised of three syllables. The second syllable (-dro- vs. -tro-) and third syllable (-gel) are identical in sound. However, the first syllable "Es" in Estrogel versus "An" in Androgel is distinguishable. The products share an overlapping dosage form, route of administration, and dosing schedule. Each product is available in one strength, thus it is possible for the strength to be omitted on a prescription. Although these products share many characteristics, DMETS believes that the likelihood for confusion is minimal given the differences in the sound-alike potential.

d. Metrogel and Estrogel have the potential to look similar. Metrogel contains metronidiazole and is indicated for use in the topical treatment of inflammatory papules and pustules of rosacea. The names Metrogel and Estrogel share the letters "trogel". The names are somewhat distinguishable due to first letter of each name (M vs E). Metrogel and Estrogel contain an overlapping dosage form and route of administration. Both products will be available in one strength, therefore a prescription for either can be scripted without a strength. Although the products do not share a similar dosing regimen post-marketing experience has shown errors occurring between products that look and/or sound similar and share some but not all product characteristics (not sure, wait to see what happens with estrogel issue).

Estrogel Metrogel

e. Ogestrel and Estrogel were thought to have sound-alike potential. Ogestrel contains 50 mcg of ethinyl estradiol and 0.5 mg of norgestrel. Ogestrel is indicated for use as an oral contraceptive. Ogestrel and Estrogel contain three syllables each, share the "estr" sound and end with "el". However, the "estr" sound appears in a different position within each name which helps to distinguish one name from the other. Additionally, the first letter "O" in Ogestrel has a long vowel sound whereas the first letter "E" in Estrogel has a short vowel sound. The products differ in dosage form, route of administration, and packaging. Although a prescription for either drug product can be written without a strength and a once daily dosing regimen, a difference in dosage form, route of administration and lack of convincing sound-alike potential, minimize the potential for confusion.

2. Established name

The expression of the established name as 17-ß Estradiol, USP is not in accordance to the United States Pharmacopeia nomenclature. Please revise the established to read "Estradiol Gel".

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES:

DMETS has reviewed the proposed package insert patient information labeling for Estrogel in an attempt to focus on safety issues to prevent possible medication errors. We have identified the following areas of improvement, in the interest of minimizing potential user error and patient safety.

A. General Comments

The expression of the established name as 17-ß Estradiol, USP is not in accordance to the United States Pharmacopeia nomenclature. Please revise the established to read "Estradiol Gel" on all labels and labeling.

B. Package Insert Labeling (DOSAGE AND ADMINISTRATION Section)

1. Instructions with regard to the use of the pump are provided yet instructions with regard to the use of the tube and spatula are omitted. Please include instructions for both delivery mechanisms.

2. Include a statement indicating the amount of drug delivered with each pump. For example, each pump delivers or is calibrated to deliver XX mg of Estrogel.

3. The Patient Package insert states that the gel is applied to the arms yet the package insert states that the gel must be applied to the skin. Please revise the package insert to include specific instructions on where the gel should be applied as done in the patient package insert.

IV. RECOMMENDATIONS:

A. As per DMETS' phone conversation with the Medical Officer in DRUDP regarding the use of the proprietary name Estrogel in Canada and Europe, DMETS has no objections to the use of the proprietary name Estrogel in the United States. However, we also note that the proprietary name Estrogel is currently utilized for an over-the-counter herbal product sold in the U.S. via the Internet. DMETS recommends that the sponsor contact the manufacturer of the herbal product to discuss the appropriateness of the proprietary name, Estrogel, for the herbal product. DMETS does not recommend that the herbal product and this product utilize the same proprietary name as it may cause confusion and error among patients and health practitioners.

B. Please submit container labels and carton labeling to DMETS for review when available.

C. DDMAC has no objections to the use of the proprietary name Estrogel.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Alina R. Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Alina Mahmud
10/21/03 11:54:39 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/21/03 04:56:13 PM
DRUG SAFETY OFFICE REVIEWER

Office of Drug Safety

MEMO

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

From: Alina R. Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

Jerry Phillips, R.Ph.
Associate Director, Office of Drug Safety
HFD-400

CC: George Lyght
Project Manager
HFD-580

Date: December 22, 2003

Re: ODS Consult 03-0225-1; Estrogel (Estradiol Gel); NDA 21-166.

This memorandum is in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for the Division of Medication Errors and Technical Support (DMETS) review the container labels and carton labeling for Estrogel. The package insert and patient package insert were reviewed in a previous consult (see ODS consult 03-0225). Estrogel will be available in tubes and metered dose pumps containing 80 grams each.

DMETS has reviewed the proposed container labels and carton labeling for Estrogel in an attempt to focus on safety issues to prevent possible medication errors. We have identified the following areas of improvement, in the interest of minimizing potential user error and patient safety.

A. GENERAL COMMENT

1. The expression of the established name as 17-ß Estradiol, USP is not in accordance to the United States Pharmacopeia nomenclature. Please revise the established to read "Estradiol Gel" on all labels and labeling.

2. The proprietary name is presented such that the "Gel" part of "Estrogel" is bolded. This presentation interferes with the readability of the name as the proprietary name may be inadvertently read as "Estro" and the bolded part of the name "Gel" may be thought of as the dosage form. This misunderstanding may cause confusion as the full proprietary name is Estrogel rather than Estro. We recommend utilizing the same font size for the whole name.

B. CARTON LABELING (tube)

The package insert states that a [ ] spatula, calibrated for application, is supplied with each tube for use in squeezing the correct amount of gel from the tube. If supplied in the carton with the tube, we recommend including a statement to this effect on the carton.

If you have any questions or need clarification with the recommendations, please contact the project manager, Sammie Beam at 301-827-3242.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Alina Mahmud
12/24/03 12:26:20 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/24/03 02:04:26 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: September 12, 2003

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Drug Products
HFD-580

VIA: George Lyght, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products
HFD-580

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Toni Piazza-Hepp, Pharm. D., Acting Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Estrogel (17ß-estradiol, USP Gel), NDA 21-166

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Estrogel (17ß-estradiol, USP Gel), NDA 21-166. We have made them consistent with the January 3, 2003, suggested labeling changes for estrogen and progestin containing products, based on the WHI study. The detailed instructions for use of the product (pump and tube) were moved to the end of the respective leaflets to allow for easier readability of important information. These revisions are based on draft labeling submitted by the sponsor on August 1, 2003.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised document in Word if requested by the review division.

13 page(s) of draft labeling has been removed from this portion of the review.

DIV

SEP 27 1999

MEMORANDUM

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

DATE:	September 23, 1999
FROM:	Venkateswar R. Jarugula, Ph.D. (HFD-870) VR Jarugula 9/27/99
THROUGH:	Ameeta Parekh, Ph.D., Team Leader (HFD-870) Ameeta Parekh 9/27/99
TO:	HFD-580
RE:	Filing Meeting for NDA 21-166, Estrogel®

SYNOPSIS

Unimed Pharmaceuticals, Inc. submitted NDA 21-166 for Estrogel® on August 13, 1999. Estrogel® is a topically applied hydroalcoholic gel containing 0.06% estradiol and the proposed indications for this product are: 1) the treatment of moderate to severe vasomotor symptoms associated with menopause, 2) treatment of vulval and vaginal atrophy, and [redacted]

[redacted] Estrogel® is supplied in a non-aerosol, metered pump containing 80 g of gel and capable of delivering sixty-four 1.25 g doses. The gel is to be applied on hands from wrist to shoulder. Treatment is usually initiated with Estrogel 1.25 g dose applied to the skin once daily [redacted]

Laboratoires Besins Iscovesco, France submitted [redacted] Estrogel in late 1980s and it was found to be non-approvable by FDA in August 1990. Subsequently, this drug product license has been transferred to and has been investigated by many sponsors over the years including Shering-Plough Corporation, Bristol Myers Squibb, and Solvay Pharmaceuticals, Inc. Presently, Unimed owns the license and is using the studies conducted by Bristol Myers as the basis for the approval of the NDA. The clinical program for Estrogel was comprised of two pivotal controlled clinical trials conducted in the United States for the treatment of moderate to severe vasomotor symptoms associated with menopause in 582 menopausal women.

The Human Pharmacokinetics and Bioavailability section of the NDA consists of four pharmacokinetic studies conducted in healthy postmenopausal women: single dose proportionality study, multiple dose bioequivalence study, multiple dose comparative bioavailability study between Estrogel and Estraderm patch, and another multiple dose comparative bioavailability study between Oestrodose gel and Estreva gel (these two are approved in Europe). Sparse blood samples were collected in two phase III clinical trials in postmenopausal patients. The reports of these two studies were included in clinical section. Serum concentration data is included in PK section. It should be noted that no population pharmacokinetic analysis of this data was carried out. Sponsor claimed that there were some unexpectedly high serum estradiol (>500 pg/ml) concentrations observed in these studies, that do not permit further analysis using NONMEM.

According to the sponsor, *in vitro* release study report is included only in Chemistry section of the NDA.

In addition, Fourteen other pharmacokinetic studies were conducted by other companies or sponsors that previously investigated this drug product. Two of these studies involved application of estradiol gel preparations similar or identical to Estrogel. A description of each study was provided in Section 6 of the NDA. However, full study reports are not submitted. These studies evaluated skin absorption, skin surface area effects, the influence of wiping after Estrogel application and potential for transfer upon skin contact. Depending on the study objectives and its relevance to the approvability or labeling of the NDA, full report for some of these studies may be necessary during the review process.

The assay method validation reports for estradiol, estrone and total estrone are included in the application. The bioanalytical study reports for the individual studies are attached with each study report. However bioanalytical reports for the phase III studies (with sparse blood sampling) are not available, but the serum estradiol and estrone levels in these studies are included. According to the sponsor, assay validation for these studies does not meet FDA and industry guidelines for validation of bioanalytical methods for human studies. Lack of this information will be a review issue depending on the importance of blood level data obtained in the phase III studies.

Estrogel used in clinical trials is packaged in glaminate tube (80 g) and supplied with marked spatulas to dispense 1.25 g or 2.5 g doses. The formulation contains ethyl alcohol, carbomer 934P, trolamine and purified water as inactive components. Two estrogel formulations, made by Bristol Mayer Squibb (BMS, Buffalo, NY) and BI (Paris, France) were used in the clinical development program and contain slightly different amounts of ethanol. The BMS formulation contains approximately — weight/weight ethanol and was used in pivotal clinical trials. The BI formulation contains about — weight/weight ethanol and is the proposed to be marketed formulation. Comparative *in vitro* drug release studies were conducted to support this change in the formulation and only confidence interval results were included in Section 6.8 of the NDA. Individual data regarding the release rates of the two formulations were not submitted. Sponsor did not submit the quantitative composition of the formulations and the differences in manufacturing process between the BMS and BI formulations in Section 6. It was noticed in the previous Biopharm reviews that the alcohol contents reported for these formulations were different (— for BMS vs —, for BI).

Two strengths of Estrogel, 0.03% and 0.06% were used in the pivotal clinical trial, CV141-002. Sponsor conducted a multiple dose bioequivalence study to support the use of two strengths in the clinical trial. Bioequivalence was concluded by the sponsor at steady state for unadjusted estradiol and estrone levels. Single dose bioequivalence was not reported. Division actually recommended single dose bioequivalence in a meeting with sponsor on January 12, 1998 and lack of single dose bioequivalence may be a review issue.

Comments:

1. Complete information regarding the differences in qualitative and quantitative composition, manufacturing process, and batch sizes between clinical trials formulation and to be marketed formulation; and the lot numbers and batch sizes used in pivotal clinical trials should be submitted to Section 6 of the NDA.

2. Sponsor should explain the discrepancy in alcohol amounts reported for the formulations in the NDA and in the previous submission, IND 29,020, S.No. 040 dated 10/10/97.

3. In the multiple dose bioequivalence study, it appears that blood samples were collected until 48 hours after Day 1 administration. As previously recommended by the FDA, sponsor should submit the single dose bioequivalence analysis (on baseline adjusted and unadjusted parameters) between 0.03% and 0.06% strengths of Estrogel to the bioequivalence study (Report S1661003).

4. Complete data regarding the development and validation of *in vitro* release test method and specifications; and data regarding the *in vitro* release comparison for clinical and to be marketed formulations should be submitted to Section 6 of NDA.

5. In order to facilitate the review process, sponsor is requested to provide the summary of pharmacokinetic section, synopses of individual PK studies, and the raw data (plasma concentration vs time data) in electronic format.

6. The previous pharmacokinetic studies conducted with Estrogel and similar formulations of gel, reported that estradiol in alcoholic gel formulation can transfer to other individuals upon skin contact. The draft physicians labeling of Estrogel does not seem to address this issue. Therefore, this will be a review/labeling issue.

7. If the only differences between the clinical and to be marketed formulations are amount of alcohol (—— vs ——) and the manufacturing cite change, *in vitro* release comparison data can be used to support these changes.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the NDA 21-166 for its fileability and is of the opinion that the NDA is fileable. Sponsor should be requested to address the Comments 1 through 5 appropriately.

cc: NDA 21-166, HFD-580 (Price, Spell-Lasane), HFD-870 (M.Chen, Parekh, Lau), CDR (B.Murphy for Drug).

9 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Teleconference Minutes

Date: April 24, 2000 **Time:** 2:30-3:30 p.m. **Location:** Parklawn, 17B-43

NDA 21-166

Sponsor: Unimed

Drug: Estrogel

Indication: Treatment of moderate to severe vasomotor symptoms

Type of Meeting: Chemistry Guidance

Meeting Chair: Rajiv Agarwal

External Lead: Kirk Rosemark

Meeting Recorder: Dornette Spell-LeSane

FDA Attendees

Rajiv Agarwal, Ph.D. Chemistry Reviewer, Division of New Drug Chemistry (DNDCII) @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D., Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Dornette Spell-LeSane, NP-C, Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:

Kirk Rosemark, Director, Regulatory Affairs, Unimed Pharmaceuticals, Inc.
Jean Kirkeleit Davis Manager, Regulatrory Affairs

Meeting Objectives:

To convey chemistry review issues and respond to April 20, 2000 facsimile.

Background:

The division received a facsimile from the sponsor dated April 20, 2000, requesting a consideration from chemistry team to review a proposal [redacted] This request raised further concerns regarding discrepancies in data and a teleconference was scheduled to discuss these issues and convey initial request for information items. In addition, the reviewing statistician requested an opportunity to convey information request items during the teleconference.

Discussion:

The following chemistry issues were conveyed to sponsor as initial concerns with the understanding that additional chemistry issues would be forthcoming via an IR letter within the next week.

Chemistry:

1. Please verify the pump canister used to store the to be marketed product and primary stability batches.
2. Please confirm the pump size used in combination with the pump canister to store the to-be-marketed product and primary stability batches.
3. Please provide the specifications of the type of pump canister/components used to store the to-be-marketed product and primary stability batches.
4. The dimensions of the pump canister and its components defined in the FAX dated April 20, 2000, do not match the specifications of the pump described on page 100 of the NDA (Vol. 1.5); please clarify.
5. Please confirm that the dimensions of the pouch for the pump dispenser used to store the to-be-marketed product and primary stability batches are identical.
6. According to the drawing in the FAX dated April 20, 2000, the upper and lower clack are in contact with the drug product, but are defined as a "non drug contact" components. Please explain the discrepancy.
7. Please list all of the "drug contact components" of the pump and tube and please provide what USP tests were performed on these components.
8. Please follow USP 24, <661> entitled "Physicochemical tests-Plastics" and please provide specifications and results of water and alcohol extractable on the relevant "drug contact" components.
9. Please provide the compatibility study between the gel and the tube.
10. Please provide the rationale of [redacted] if the orifice of the tube is open.

Statistics:

April 21, 2000, sponsor submitted documents missing from a January 21, 2000 submission. After review of the latest submitted document, the statistician had the following request.

> For the endpoint "change from baseline in frequency of moderate-to-severe hot flushes", please fit ANCOVA models with the following terms and please provide estimates of the coefficients for each term in the ANCOVA models. A submission containing copies of the SAS output of these analyses will be sufficient for the purpose of our review.
>
> a. center
> b. treatment
> c. center by treatment
> d. baseline
> e. baseline by treatment

Decisions Reached:

Sponsor should submit facsimiles as official documents referencing the NDA 21-166

Documents received May 11, 2000

Action Items:

1. A formal information request letter will be sent to the sponsor within one week outlining chemistry concerns discussed at this meeting as well as relevant statistical and clinical pharmacology biopharmaceutical questions.

   IR letter to sponsor May 1, 2000

2. Meeting minutes to be conveyed to sponsor within 30 days.

Post teleconference note:

Sponsor submitted a fax April 25, 2000, requesting further clarification on the USP <661> testing of the resins in the pump. Dr Agarwal explained that the same procedures described in USP should be used for testing with the exception that alcohol be substituted.

Minutes Preparer

Meeting Chair

Note to Sponsor:
These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original NDA 21-166
HFD-580/Div. Files
HFD-580/Mann/Slaughter/Price/Kammerman/Lau/Parekh/Rhee/Agarwal
HFD-580/Spell-LeSane

Drafted by: Spell-LeSane, 5.15.00
Concurrence: Rumble, 5.15.00/Agarwal, 5.15.00

Teleconference

D/F

Meeting Minutes

Date: September 22, 1999 **Time:** 3:30- 4:15 p.m. **Location:** Parklawn, 17B43

NDA 21-166

Sponsor: Unimed **Drug**: Estrogel

Indication: Treatment of moderate to severe vasomotor symptoms

Type of Meeting: Filing Meeting

Meeting Chair: Marianne Mann

Meeting Recorder: Dornette Spell-LeSane

FDA Attendees

Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products, (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D., Team Leader, DRUDP (HFD-580)
Lisa Kammerman, Ph. D., Team Leader, Division of Biometrics @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sue Tran, Ph.D., Chemistry Reviewer, DNDC II @ DRUDP (HFD-80)
Johnny Lau, R.Ph., Ph.D., Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DPE II; (HFD-870) @ DRUDP (HFD-580)
Dornette Spell-LeSane, NP-C, Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objectives:

To discuss filing status of NDA 21-166 for Estrogel

Background:

The previous NDA for this drug, Estrogel, [ ] was issued a non-approval action by DRUDP in August 1990; Solvay Pharmaceuticals purchased the application July 1997, and initiated resolution of some of the non-approvable issues; Solvay purchased Unimed in July 1999, and Unimed submitted this NDA on August 13, 1999, with a filing date of October 15, 1999; Solvay is currently on AIP, therefore, General Council was consulted; and informed the Division that the application was not reviewable if Solvay Inc. participated in the clinical development of this NDA; Unimed issued a statement August 23, 1999, indicating that no data in the NDA 21-166 was generated within Solvay Pharmaceuticals, Inc.

Discussion:

Clinical:
- fileable
- adverse event profiles require further review
- similar review issues may exist for this NDA as did for the previous NDA [ ] for Estrogel; Sponsor should address those Pre-NDA issues for this review

Chemistry:
- fileable

Pharmacology
- fileable

Clinical Pharmacology and Biopharmaceutics:
- fileable
- filing review comments may be conveyed to Sponsor via information request letter

Statistical:
- filability is pending
- the statistical plan has not been submitted as part of the NDA for review

Decisions Reached:

- filability status is pending review of statistical data

Action Items:

1. Sponsor should submit the full statistical analysis plan for the pivotal studies.
2. Sponsor should submit a revised master index.
3. Sponsor should submit a summary volume.
4. Sponsor should confirm submission of all data requested during the Pre-NDA process.
5. Schedule meeting with statistician and clinical reviewers to finalize NDA filing status prior to October 15, 1999. **(Meeting held October 12, 1999)**

Minutes Preparer:

Meeting Chair
12/13/99

cc:
Original NDA 21-166
HFD-580/Div. Files
HFD-580/Mann/Slaughter/Price/Kammerman/Lau/Parekh/Rhee/Agarwal/Rumble/
HFD-580/Spell-LeSane
Drafted by: Spell-LeSane December 1, 1999
Concurrence: Rumble, 12.6.99, Tran, 12.7.99, Price, 12.8.99,Mann, 12.9.99
Final: Spell-LeSane, 12.13.99

MEETING MINUTES

MEETING MINUTES

Date: January 12, 1998 **Time:** 10:45 p.m.- 12:15 p.m. **Location:** Potomac

IND: IND 29,020 **Drug Name:** Estrogel®

Type of Meeting: Industry End of Phase 2

Meeting Chair: Dr. Lisa Rarick

Meeting Recorders: Mr. John C. Markow

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP;HFD-580)
Heidi Jolson, M.D., M.P.H. - Deputy Director, DRUDP (HFD-580)
Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Amit Mitra, Ph.D.- Chemist, DNDCII @ DRUDP (HFD-580)
Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Division of Pharmaceutical Evaluation II
(DPE II) @ DRUDP (HFD-580)
Sam H. Haidar, R.Ph., Ph.D. - Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)
Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)
John C. Markow, R.Ph., J.D. - Consumer Safety Officer, DRUDP (HFD-580)

External Attendees:

Dr. Greg Perkins - Senior Vice President, Regulatory and Quality Systems
Dr. Roland Gerritsen van der Hoop - Vice President Clinical Research and Development
Dr. John Brennan - Director of Clinical Pharmacology
Dr. Jennifer Phillips - Director, Regulatory Affairs
Dr. James Ward - Director of Biometrics
Ms. Barbara Block - Manager, Clinical Operations
Mr. Joey Pollack - Associate Director, Regulatory Affairs

Meeting Objectives:

This is an industry meeting with Solvay Pharmaceuticals to discuss a proposed submission of an NDA for Estrogel®. During this meeting the questions outlined in the background package submitted December 18, 1997, will be discussed.

Background:

Solvay Pharmaceuticals purchased IND 29,020 and NDA —— from LaSalle Laboratories in July of 1997. Both of these applications are for a 17-β-estradiol topical gel, Estrogel®. The indications for Estrogel® are ———————————— the treatment of postmenopausal vasomotor symptoms.

On September 24, 1997, Dr. Woodcock invoked the Application Integrity Policy (AIP) for Solvay Pharmaceuticals. Under this policy, review of New Drug Applications is prohibited. In December of 1997, Solvay submitted a meeting request and background package to discuss registration strategies for Estrogel®. The package included a list of 18 questions to be addressed.

Discussion Points:

Questions:

1. [redacted]

2. Are there any concerns from the Agency which have not been expressed in the official correspondence between FDA and Schering?

   Ans:

   Additional concerns have been raised in letters to prior sponsors. These letters are the official correspondence from the Agency.

3. Based on the novelty of dosage form, does the Agency consider the ESTROGEL® NDA a candidate for priority review?

   Ans:

   This could be considered a priority review only if it has a modest but real advantage (i.e. improved safety profile) over available marketed drugs. However, data must be provided to support that advantage. Currently, without additional data this application would be a standard review because other formulations of estrogen are available in topical and oral regimens.

CMC:

4. Will clinical data derived from studies using tubes be directly applicable to pump dispensers?

   Ans.

   A dosing accuracy method measuring comparability and consistency will show that there is no clinically significant difference between the dose administered from the tube and the dose administered from the pump dispenser.

5. If a comparison study between tube and the pump is advisable, what level of validation would be necessary?

   Ans.

   The level of validation is comparability of delivery on release and on stability using appropriate statistical analysis.

6. Will the pump dispenser be considered a device? If so, what is the process for registration? (Note: This question is being considered under a separate request, but Agency input at this time would be welcomed.)

   Ans.

   The dispenser will not be considered a device because Estrogel's primary purpose is achieved through chemical action. The dispenser will be consulted to devices when the NDA is submitted.

7. Will literature data be sufficient to substantiate that there is no impact due to the small difference in alcohol between the Bristol Meyers Squibb formulation (used in the pivotal studies) and the Bevins Iscovesco product for commercial distribution?

   Ans.

   To support the proposed change between the clinical (Bristol Myers Squibb: ——— alcohol, W/W) and the to-be marketed (Besins Iscovesco, France: — , alcohol W/W) formulations, appropriate comparative *in vitro* release data according to the SUPAC for semisolids, should be provided.

8. Is there a need to address child -resistance in the packaging of the product?

   Ans.

   A child safety closure system is recommended.

NON-CLINICAL PHARMACOLOGY and TOXICOLOGY:

9. Is the proposed presentation of data (as described under ATTACHMENT III) acceptable? Are other non-clinical data required?

   Ans.

   This is acceptable.

HUMAN PHARMACOKINETICS:

10. Does the appended dose proportionality study protocol and proposed population pharmacokinetic investigation satisfy FDA's request for proposed multi-dose exposure data over the ESTROGEL® dose range?

    Ans.

    Single, multiple and dose proportionality data for all the to-be-marketed formulations should be provided.

11. Does the planned comparison of patient concentrations following CLIMARA® and ESTROGEL® treatments satisfy FDA's request for systemic drug exposure comparisons in the active control study?

    Ans.

    Yes.

12. Are there any additional issues regarding the human Pharmacokinetics of ESTROGEL® which should be addressed prior to NDA submission?

    Ans.

    Yes, the formulation used in the clinical studies was manufactured in the United States. The to-be-marketed formulation will to be manufactured in France. This is a level 3 change under SUPAC guidelines. Therefore, *in vitro* release testing data should be provided.

CLINICAL/SAFETY:

13. Are the two ongoing Phase III clinical studies (CV141-001 and -002) acceptable for establishing efficacy and safety of ESTROGEL®?

    Ans:

14. As described in the protocol amendment included in this submission, is the comparison of the 1.25 g and 2.5 g groups with the 0.625 g group sufficient to establish the lowest effective dose for ESTROGEL® in study CV141-002? Are there any additional comments or questions about the revised statistical analysis described in the protocol amendments for CV-141-001 and -002?

Ans:

A full statistical plan should be provided. The primary analysis of the change in frequency of hot flushes should include only moderate to severe hot flushes. The percent change from baseline in the number of moderate to severe hot flushes and the number of moderate to severe hot flushes for weeks 4, 8 and 12 should be provided. The number of dropouts over time should be fully explained and analyzed.

15. The inclusion criteria for protocols CV141-001 and CV141-002 require serum FSH levels of ≥ 40mIU/ml for enrollment in the study. At present, approximately 4% of the patients enrolled in the studies have FSH values of less than 50mIU/ml (i.e., between 40 and 50). Is it acceptable to include the data from patients with FSH values < 50mIU/ml in the intent to treat analysis group?

Ans:

Yes, it is acceptable to include patients with an FSH >40 in the intent to treat group.

16. Which covariates other than body weight, menopausal type and age should be included in the statistical analysis of the efficacy results for NDA submission?

Ans:

It would be valuable to include interval of time from onset of menopause as a covariate.

17. In the "Description of Clinical Data Sources" in Section V, we present a plan to integrate foreign safety data into the ISS. Is this plan acceptable for NDA submission?

Ans:

Yes, this is acceptable to the Agency.

18. In the same part of Section V, we propose a plan to summarize the foreign efficacy results for ESTROGEL®. Is this plan acceptable for NDA submission?

Ans:

Yes, this is acceptable to the Agency.

Decisions reached:

- See answers to the above questions.

1/22/98
Signature, minutes preparer

1/22/98
Concurrence, Chair