CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-166

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

2/10/04

Cicely Vaughn
Manager, Regulatory Affairs
Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, GA 30062

RE: **NDA#** 21-166
EstroGel (estradiol gel)
MACMIS# 12244

Dear Ms. Vaughn:

This letter concerns your February 9, 2004, request to the Division of Drug Marketing, Advertising, and Communications (DDMAC) for comments on a proposed press release for EstroGel (estradiol gel).

In consultation with the Division of Reproductive and Urologic Drug Products, DDMAC has reviewed your proposed press release and has the following comment. The product name in the press release should be consistent with the spelling of the product name in the approved product labeling.

If you have any questions or comments, please contact Dr. Lisa Stockbridge by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, rm. 8B-45, 5600 Fishers Lane, Rockville, MD 20857.

DDMAC reminds you that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS #12244 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

APPEARS THIS WAY
ON ORIGINAL

Lisa L. Stockbridge, Ph.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Lisa Stockbridge
2/10/04 09:50:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-166

INFORMATION REQUEST LETTER

2/9/04

Solvay Pharmaceuticals
Attention: Cicely N. Vaughn, MPH
Manager, Regulatory Affairs
901 Sawyer Road
Marietta, GA 30062

Dear Ms. Vaughn:

Please refer to your new drug application (NDA) under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estrogel Gel (Estradiol 0.06% Topical gel).

The Division of Reproductive and Urologic Drug Products (DRUDP) is requesting a Phase IV Clinical Trial Commitment for the NDA. We request a prompt written response in order to continue our evaluation of your NDA.

Solvay Pharmaceuticals must design a Phase IV clinical trial study to find the lowest effective dose of Estrogel gel for the indications of:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.

The following is the timeline for this commitment:

1. Protocol Submission: Within 6 months of the date of the receipt of the action letter.
2. Study Start: Within 6 months of the protocol agreement with DRUDP
3. Final Report Submission: Within 6 months of the study completion

If you have any questions, please call George Lyght, R.Ph., Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.,
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Margaret Kober
2/9/04 01:45:02 PM
Chief, Project Management Staff

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DEPARTI

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S. BASS
J. BEDARD
J. BUSH
T. CITRON*
R. CRANE
A. ERBSKORN
T. FOLGIA*
D. FRY**
K. GIVEN
D. GOLDSTEIN*
G. HECKMAN
R. KEANE
J. KENNEY
H. KESSLER
S. LENART
L. LEVINSKY
M. LIPSTEIN
C. LONSTEIN
C. MASKIN
J. MC CARTHY
G. MILLER
M. O'BRIEN
G. PICOT
M. PILLO
R. PLAKYDA
M. PROPSNER
W. RANDOLPH
W. REGAN**
M. RITZERT**
R. ROGAN
A. SANTOPOLO
R. SIMON
J. SONK
D. UPMALIS
C. WOLLEBEN
T. WOODWARD***
RIC (L. DEAN)

Public Health Service

Food and Drug Administration
Rockville MD 20857

AUG 16 1995

Bristol-Myers Squibb Company
Attention: Janice K. Bush
P.O. Box 4000
PRINCETON NJ 08543-4000

Dear Dr. Bush:

Please refer to your new drug application submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estrogel (estradiol gel).

We also refer to the meeting between representatives of your firm and FDA on June 6, 1995. During that meeting several questions which you raised were deferred pending an internal meeting. The following represents a summary of the subsequent internal meeting.

1. [redacted]

2. Two well-controlled safety and efficacy trials will be required. The first should be a placebo-controlled, double-blind study (as proposed above). The second is recommended to be an active control study against one of the currently marketed patches. It was suggested that you use the newly approved Climara patch.

3. Your proposed application procedure was discussed and found acceptable. However, it will be necessary for you to specify the site of application as the inner aspect of the upper arm (either arm will be acceptable).

4. A numerical scale for both frequency and severity of vasomotor symptoms will be required for the patient diaries. Further, the diaries must be kept weekly such that each week can be evaluated separately for symptoms and severity in your NDA submission.

5. Your proposed statistical plan appears acceptable. Please send a desk copy of the final protocol for statistical review when it becomes available.

6. Your proposal to give [redacted] to all women with an intact uterus at the end of the study is acceptable provided that an endometrial biopsy be performed at the end of the trial but prior to the [redacted] treatment. It was noted that the use of [redacted] in the pivotal trials will necessitate the inclusion of a [redacted] course every three weeks for women with an intact uterus in the labeling of the product.

7. Regarding your proposed serum studies, you should note that systemic drug exposure data for the doses to be marketed will be required for the pharmacokinetic section of the package insert. Such information can be obtain from cohorts within the to-be-conducted clinical studies, and/or from separate biopharmaceutic studies. Multiple-dose exposure data to help evaluate intra- as well as inter-subject variability for the product will also be needed. You are requested to assess different covarieates as related to systemic drug exposure (e.g., effects of age, weight, etc.) in these studies. In the active control study systemic drug exposure comparisons should be assessed. The Division of Biopharmaceutics also requested copies of your proposed protocols for review prior to your initiation of the studies.

8. Fasting insulin levels will not be necessary.

9. Finally, it was suggested that the reason for some of the high variability you seem to be getting between subjects may be due to variability of drug application by the study subjects.

If you have any questions, please contact Ms. Christina Kish, CSO at (301) 443-3510.

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Center of Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ATTACHMENT 2

RESPONSES TO FDA REQUESTS

1. [redacted]

2. **Two well-controlled safety and efficacy trials will be required. The first should be a placebo-controlled, double-blind study (as proposed above). The second is recommended to be an active control study against one of the currently marketed patches. It was suggested that you use the newly approved Climara patch.**

Our second pivotal trial will include the Climara® patch system and the lower (0.625 g) dose of Estrogel®. The sample size will be 340 patients, 85 patients in each of the following arms:

0.625 g Estrogel®
1.25 g Estrogel®
2.5 g Estrogel®
12.5 sq cm Climara® patch system.

The second study will be designed similarly to the first, e.g., 3 months duration, naturally or surgically post-menopausal women experiencing ≥60 hot flushes per week for 2 weeks prior to randomization. In order to assess systemic drug exposure comparisons, blood samples will be collected from all subjects monthly for analysis of serum estradiol, estrone and estrone sulfate levels. A protocol summary is provided in Attachment 4. The summary is entitled, "Efficacy and Safety Comparison of Estrogel® (17β-estradiol in a topical gel) and the Climara® Patch in the Treatment of Menopausal Women with Vasomotor Symptoms."

3. **Your proposed application procedure was discussed and found acceptable. However, it will be necessary for you to specify the site of the application as the inner aspect of the upper arm (either arm will be acceptable).**

The Clinical Expert Report prepared by Besins-Iscovesco (available upon request), France states, in topical steroid absorption, skin surface becomes a significant and limiting factor only when the surface area is limited and the skin becomes saturated. With a larger surface area, absorption is only dependent on the dose administered. Therefore, since we are splitting the application to 1.25 g of either Estrogel® or placebo, we have indicated in the protocol that one applicator of gel be applied to each arm, wrist to shoulder. This will provide us with dosing consistency and the maximum surface area, approximately 750 cm^2, for optimal absorption of the product.

4. **A numerical scale for both frequency and severity of vasomotor symptoms will be required for the patient diaries. Further, the diaries must be kept weekly such that each week can be evaluated separately for symptoms and severity in your NDA submission.**

We will incorporate a numerical scale in the vasomotor symptom diaries. A sample of the diary card is attached (Attachment 5).

5. **Your proposed statistical plan appears acceptable. Please send a desk copy of the final protocol for statistical review when it becomes available.**

A copy of the final draft of Protocol CV141-001 entitled, "Efficacy and Safety Comparison of Estrogel® (17β-estradiol in a topical gel) and Placebo Gel in the Treatment of Menopausal Women with Vasomotor Symptoms" is provided in Attachment 3. Multiple desk copies of this submission are provided; three desk copies are provided to Ms. Kish (FDA) for distribution.

6. **Your proposal to give [ ] to all women with an intact uterus at the end of the study is acceptable provided that an endometrial biopsy be performed at the end of the trial but prior to [ ] treatment. It was noted that the use of [ ] in the pivotal trials will necessitate the inclusion of a [ ] course every three weeks for women with an intact uterus in the labeling of the product.**

All of the references to [ ] have been removed from the protocol. The protocol now reads that all women with an intact uterus will undergo an endometrial biopsy at the end of the trial to evaluate the occurrence of hyperplastic changes. Subjects with evidence of hyperplasia will be prescribed a progestin if the investigator feels that treatment is indicated. The response to progestin will be monitored and any subject with hyperplasia will be followed until the investigator feels that it has satisfactorily resolved. We would propose that the Estrogel® label contain the same information regarding the use of progestins as the current Estrace® and Climara® labels.

7. **Regarding your proposed serum studies, you should note that systemic drug exposure data for the doses to be marketed will be required for the pharmacokinetic section of the package insert. Such information can be obtained from cohorts within the to-be-conducted clinical studies, and/or from separate biopharmaceutical studies. Multiple-dose exposure data to help evaluate intra- as well as inter-subject variability for the product will also be needed. You are requested to assess different covariates as related to systemic drug exposure (e.g., effects of age, weight, etc.) in these studies. In the active control study systemic drug exposure comparisons should be assessed. The Division of Biopharmaceutics also requested copies of your proposed protocols for review prior to your initiation of the studies.**

   The pharmacokinetic study will include all three doses of Estrogel® and the Climara® patch 12.5 sq cm system in a randomized cross-over design. Serial blood samples will be obtained after the first dose and on Days 13 and 14 for measurement of serum estradiol, estrone and estrone sulfate levels. This will give us multiple dose pharmacokinetic information as well as intra-subject variability at steady-state. A summary of the pharmacokinetic study is provided in Attachment 6. The summary is entitled, "Single and Multiple-Dose (Steady-State) Pharmacokinetic Study of Estrogel® (17β-estradiol in a topical gel) and the Climara® Patch in Healthy Post-Menopausal Females." We will also add estradiol, estrone, and estrone sulfate levels to the second pivotal study at each monthly visit.

8. **Fasting insulin levels will not be necessary.**

   Fasting insulin levels will be removed from the protocol.

9. **Finally, it was suggested that the reason for some of the high variability you seem to be getting between subjects may be due to variability of drug application by the study subjects.**

   We are currently examining methods internally to address the variability of dosing.

Memorandum

Bristol-Myers Squibb Company

Pharmaceutical Research Institute
Worldwide Regulatory Affairs - Lawrenceville

To: File

From: J. Bush, M.D.

Date: July 11, 1995

CC: Attendees
J. Bedard
K. Given
M. Loberg
R. Simon

Subject: **Final Minutes: Estrogel Pre-NDA Meeting, June 6, 1995**

Attendees from BMS: Melody Brown, Janice Bush, Karen Reilly, David Upmalis.

Also attending: [redacted], Biostatistician, [redacted] M.D., consultant,

Attendees from FDA: Christina Kish, CSO, Phil Corfmann, Supervisory Medical Officer, Yuan Yuan Chiu, Supervisory Chemist, Greg Cropp, M.D., Medical Reviewer. (Not present: Dr. Phil Price who was attending a premature delivery.)

After a brief description of the regulatory history of Estrogel, a short presentation on CMC information to acclimate the reviewers was made. The two clinical trials that BMS proposes to conduct were presented and endorsement from the Division was requested. Specific CMC issues and our plans for pK studies were not discussed at this meeting since separate meetings will be set up with the supervisory chemist and the Biopharmaceutics group respectively.

The following were discussed during the course of the meeting:

- [redacted]

- There has been no change in the drug product manufacturing process. The only difference between the Schering-Plough NDA and the one that we propose is that the manufacturing site has been moved to the BMS facility in Buffalo, N.Y. The formulation was discussed and was also physically shown to the attendees. Using the placebo and the accompanying paddle, a simulated application of the gel was also demonstrated. The FDA questioned the potential variability in the amount of gel dispensed. BMS responded that a study of twenty women indicated that there is about a 4% variability among users in the amount of Estrogel that is placed on the paddle for application to the skin.

- BMS proposes to meet the new HRT Guidelines by conducting two pivotal studies to compare the efficacy and safety of two strengths of Estrogel to a placebo gel for the relief of vasomotor symptoms in postmenopausal women.

- Safety data will include previous data from the Schering-Plough NDA, and data from both the BMS pivotal studies will be pooled to perform the safety analysis. Dr. Upmalis stated that BMS intends to repeat the pK studies, but we believe that previous data have established that [redacted] We propose that an additional level of 1.25 g of Estrogel as the lowest dose should also be evaluated. [redacted]

- The labeling that will be sought in our NDA will be class labeling for symptomatic indications. We would expect to start with the lowest dose (1.25 g) and titrate up if needed for a relief of symptoms.

- The issues of "lowest effective dose" was discussed, and this may be difficult to delineate. There is no "no effect" dose, so it is not clear that adding another lower dose level will be useful [redacted], but the statistical power of the current studies will only be sufficient to evaluate the difference between Estrogel and placebo. Each trial has a 108 patients with 43 patients on 2.5g, 43 patients on 1.25 g, and 22 placebo patients. There will be two such studies, and the safety analysis will be done on an aggregate of the two studies. **The FDA reviewers were concerned about the proposed size of the studies and will need to evaluate this further internally.**

- Patients will be qualified based on physical and biochemical parameters. Symptoms will be graded according to what is in the guidance. There will be no visual analog scale; patient diary cards will be used.

- Lab tests: a patient will qualify by estradiol and FSH as per the HRT Guidelines. There will also be lipid assessments and fasting blood glucose. In addition, coagulation labs will be obtained (fibrinogen, Factor VII, and a PAI 1). **The FDA agreed to get back to BMS as to whether fasting insulin would be necessary to be obtained.**

- At the end of the study, BMS plans to administer [redacted] to everyone who has a uterus whether they have been on active drug or not. **The FDA stated that they would discuss that at an internal meeting and let BMS know as to whether that was acceptable or not.**

- [redacted]

- There was also a study presented which evaluated effects of rubbing of the skin on estradiol absorption. The results indicate that the estradiol which is available to be absorbed will be absorbed rapidly, and that even wiping the skin after 1-5 minutes has little effect on the amount of estradiol that is absorbed. While a majority of the estradiol in Estrogel remains on the skin, this estrogen is not available since it must be in the wet alcohol vehicle to be absorbed. Therefore, there should be no concern about casual contact either with children or adults. Oral contact with the Estrogel should result in no Estrogel absorbed given the fact that it is not soluble in water or orally absorbed. **It was agreed that the FDA would need to evaluate these data further.**

Summary:

The FDA stated that they would have a further internal meeting that would include Dr. Price. They would look at the [redacted] Schering-Plough to see if there were additional issues to discuss. It was noted that such issues as: 1) dosing and whether the Agency wants to insist on an "ineffective" dose, 2) issues that came up during the discussion of the use of [redacted] in women who have been on placebo, and 3) sample size would all need to be discussed specifically. The FDA indicated that they would include John Hunt from Biopharmaceutics and would also get input from Dan Marticello in Biometrics. It was agreed that this internal meeting would proceed as soon as it could possibly be scheduled so that BMS could receive input in order to meet a goal of starting the clinical trials up in early fall. BMS stated that a separate chemistry meeting and a separate Biopharm meeting would be scheduled, but it was agreed that the internal meeting would not need to wait on these.