CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-166

MEDICAL REVIEW

Team Leader Memorandum

To:	**File for NDA 21-166**
From:	**Theresa H. van der Vlugt, MD, M.P.H.** **Acting Medical Team Leader** **Division of Reproductive and Urologic Drug Products**
Through:	**Daniel Shames, MD** **Director** **Division of Reproductive and Urologic Drug Products**
Date of Memorandum:	**February 9, 2004**

Drug Name:

Trade:	**ESTROGEL®**
Generic:	**Estradiol Gel**
Chemistry:	**Estradiol, USP (estra-1,3,5,-(10)-trenen-3, 17β diol)**
Sponsor:	**Solvay Pharmaceuticals, Inc.** **901 Sawyer Road** **Marietta, Georgia, 30062**
Pharmacologic category:	**Estrogen**
Dosage Form:	**Transdermal gel**
Strength:	**1.25 grams (equivalent to 0.75 mg estradiol, 0.06%)**
Proposed Indications:	**Treatment of moderate to severe vasomotor symptoms associated with the menopause.** **Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause.**
Related Submission:	**IND 29,020**
Related Documents:	**Amendments dated 6/16/03, 8/1/03, 8/13/03, 9/26/03, 10/22/03, 10/23/03, 11/19/03, 12/10/03, 1/7/04, 1/15/04, 1/27/04, 2/2/04, 2/5/04. 2/6/04, Phase IV commitment dated 2/9/04**
Date NDA Submitted:	**April 9, 2003**

Background and Regulatory History

Estradiol gel was first approved for marketing in France in November 1974 under the name Oestrogel® and is currently marketed in 64 countries (marketed in Europe as Oestradose® and Oestracin®). NDA ——— ESTROGEL® was first submitted to the Agency by LaSalle Laboratories, Inc. on April 24, 1989 for a treatment of moderate to severe vasomotor symptoms indication. A not approvable action letter was sent to Schering-Plough Corp. (LaSalle Laboratories was a subsidiary of Schering) on August 17,

1990. [

]

In 1994, Bristol-Myers Squibb acquired ESTROGEL®. At a meeting with Bristol-Myers Squibb on July 25, 1995, the Agency advised Bristol-Myers Squibb that two well-controlled clinical trials for safety and efficacy would be required for approval. Two clinical trials were conducted with Solvay Pharmaceuticals, Inc. and its subsidiary Unimed Pharmaceuticals.

Study CV141-001 was a double-blind, placebo-controlled clinical trial in which 221 healthy postmenopausal women were randomized to one of three treatment groups for a 12-week treatment duration: 1.25 grams of estradiol gel (75 subjects), 2.5 grams of estradiol gel (73 subjects), or placebo (73 subjects). Study CV141-002 was a dose-ranging, comparator-controlled clinical trial in which 361 healthy postmenopausal women were randomized to one of four treatment groups for a 12-week treatment duration: 0.625 grams estradiol gel (92 subjects), 1.25 grams estradiol gel (93 subjects), 2.5 grams estradiol gel (89 subjects) or the 12.5 cm^2 estradiol transdermal system (87 subjects).

NDA 21-166 for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy was first submitted by Unimed Pharmaceuticals (a subsidiary of Solvay Pharmaceuticals, Inc.) for review on August 13, 1999. In May 2000, during the first review cycle of NDA 21-166, Solvay Pharmaceuticals, Inc. was under Application Integrity Policy (AIP). Consequently, reviews of NDA 21-166 were not finalized at that time. In April 2003, the AIP was removed and Solvay Pharmaceuticals, Inc. resubmitted NDA 21-166 for review on April 9, 2003.

NDA 21-166 Data and Analyses

In this submission, Solvay Pharmaceuticals, Inc. has requested consideration of two dosage strengths of ESTROGEL®, 1.25 grams equivalent to 0.75 mg estradiol per day and 2.5 grams equivalent to 1.5 mg estradiol per day, for the treatment of moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. The results of two clinical trials were submitted, one placebo-controlled (Study CV141-001) and one comparator-controlled (Study CV141-002).

Summary of Efficacy

Study CV141-001

Please see the Medical Officer's Review and the Statistical Review for a full description of the data and analyses for Study CV141-001.

Study CV141-001 was a double-blind, placebo-controlled clinical trial in which 221 healthy postmenopausal women were randomly assigned to use placebo (73 subjects) or 1.25 grams of estradiol gel (75 subjects, equivalent to 0.75 mg of estradiol) or 2.5 grams of estradiol gel (73 subjects, equivalent to 1.5 mg of estradiol) daily over a 12-week treatment duration. Eligible subjects were required to experience at least 7 moderate to severe hot flushes per day (or at least 60 per week) at baseline. Daily diary information was collected that recorded the daily number and severity (mild, moderate, or severe) of hot flushes. Acceptable safety evaluations were conducted including physical examination, laboratory evaluations, mammograms, cervical Pap smear and lateral vaginal wall smears for determining the Maturation Index. Two hundred and sixteen (216) subjects (97.7%) took at least one dose of study medication and had at least one post-baseline assessment. One hundred ninety-six (196) subjects (88.7%) completed Study CV141-001. In total, 25 subjects discontinued Study CV141-001 (11.3%). The discontinuation rate in Study CV141-001 raises no safety concerns.

In Study CV141-001, the primary efficacy variables were the number of moderate to severe hot flushes and the mean change from baseline in moderate to severe hot flushes for each of the 12 study weeks. Per the Agency's 2003 draft guidance for industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation", for estrogen alone products intended to treat moderate to severe vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy, the Agency recommends that "the primary efficacy analyses show a clinically and a statistically significant reduction, within 4 weeks of initiation of treatment and maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flushes in the treated groups compared with the control groups". The following four co-primary endpoints are recommended:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4
- Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12

In the protocol for Study CV141-001, the planned analysis was an ANCOVA model with treatment, center and treatment-by-center interaction terms, with baseline frequency of moderate to severe vasomotor symptoms as the covariate. Dunnett's test for multiple comparisons was planned. However, from the data presented in the submission, the residuals from the planned ANCOVA model showed that the normality assumption was questionable. Therefore, the Statistical Reviewer used the van Elteren's non-parametric test as an alternative. Instead of the planned Dunnett's test for multiple comparisons, the Hochberg method was applied to the non-parametric results. These results are shown in Table 1. Both estradiol gel dosage strengths are shown to be statistically significantly different from placebo in the mean change in the number of moderate to severe hot flushes at weeks 4 and 12.

Table 1: Mean Change from Baseline in the Number of Moderate to Severe Hot Flushes Per Day, ITT Population, LOCF

	Placebo N=73	Estradiol Gel 1.25g N=72	Estradiol Gel 2.5g N=71
Baseline			
Mean (SD)	11.01 (5.66)	10.33 (3.07)	10.52 (3.88)
Week 4			
Mean (SD)	5.95 (5.17)	4.43 (4.13)	4.28 (4.37)
Mean Change from Baseline (SD)	-5.06 (4.91)	-5.91 (3.68)	-6.24 (4.40)
Diff. vs. Placebo	-	0.85	1.18
p-value*	-	0.019**	0.020**
Week 12			
Mean (SD)	5.17 (6.52)	2.79 (3.70)	1.96 (4.23)
Mean Change from Baseline (SD)	-5.84 (4.52)	-7.55 (3.52)	-8.56 (5.13)
Diff. vs. Placebo	-	1.71	2.72
p-value*	-	0.043**	<0.001**

Source: Statistical Review of NDA 21-166.

* p=values from Van Elteren's non-parametric test.

** Statistically significantly different from placebo at α=0.049, using Hochberg method to adjust for multiple comparisons at each time point.

However, the magnitude of change (difference versus placebo in reduction of moderate to severe hot flushes) is not as large as would be expected typically for estrogen alone drug products. In the Division's experience, estrogen alone drug products generally produce a difference of at least two hot flushes over placebo at week 4 and maintains or exceeds this difference through week 12. As shown in Table 1, neither the 1.25 gram estradiol gel dosage strength or the 2.5 gram estradiol gel dosage strength achieve at least a two hot flush difference versus placebo at week 4.

From the data presented, the 1.25 gram estradiol gel dosage strength did not achieve a two hot flush difference over placebo throughout the 12 weeks of treatment, although the hot flush difference versus placebo closely approaches the at least two hot flush difference at week 12 (difference versus placebo of 1.71 hot flushes). On the other hand, from the data presented, the 2.5 gram estradiol gel dosage strength approaches a at least two hot flush difference versus placebo at week 5 (difference versus placebo of 1.98 hot flushes at week 5, not shown in Table 1) and exceeds it from week 6 through week 12 (difference versus placebo of 2.72 hot flushes at week 12 as shown in Table 1).

In the submission the severity score of hot flushes was calculated as follows. The numerator of the severity score is a weighted sum of vasomotor symptoms, with mild hot flushes receiving a weight of 1, moderate hot flushes receiving a weight of 2, and severe hot flushes receiving a weight of 3. This sum is divided by the total number of mild, moderate, and severe vasomotor symptoms experienced by the patient. Initially, in the protocol for Study CV141-001 this severity score analysis was a secondary analysis. That was acceptable at the time the protocol was submitted. Currently, however, the Division of Reproductive and Urologic Drug Products (DRUDP) considers severity as a co-primary variable.

The same ANCOVA model (as used for the frequency endpoint) was applied to the severity endpoint. Examination of the residuals showed that the normality assumption was not met. Therefore, a van Elteren's non-parametric test with the Hochberg adjustment approach was used. The analyses used alpha= 0.049 as was used in the analysis of the frequency endpoint. The results of the severity score outcomes in Study CV141-001 are shown in Table 2. Both estradiol gel dosage strengths are shown to be statistically significantly different from placebo in the mean change in the severity of hot flushes at weeks 4 and 12. An expected clinical effect for the severity score endpoint has not been defined by the Division.

Table 2: Mean Change from Baseline in the Severity of Moderate to Severe Hot Flushes Per Day, ITT Population, LOCF

	Placebo N=73	Estradiol Gel 1.25g N=72	Estradiol Gel 2.5g N=71
Baseline			
Mean (SD)	2.30 (0.24)	2.36 (0.29)	2.29 (0.22)
Week 4			
Mean (SD)	2.00 (0.63)	1.73 (0.73)	1.67 (0.85)
Mean Change from Baseline (SD)	-0.31 (0.62)	-0.631 (0.71)	-0.61 (0.85)
Diff. vs. Placebo	-	0.32	0.30
p-value*	-	0.005**	0.053
Week 12			
Mean (SD)	1.76 (0.84)	1.33 (0.97)	0.98 (0.94)
Mean Change from Baseline (SD)	-0.54 (0.84)	-1.03 (0.94)	-1.30 (0.94)
Diff. vs. Placebo	-	0.49	0.76
p-value*	-	<0.001**	<0.001**

Source: Statistical Review of NDA 21-166.

* p=values from Van Elteren's non-parametric test.

** Statistically significantly different from placebo at α=0.049, using Hochberg method to adjust for multiple comparisons at each time point.

Study CV141-002

Please see the Medical Officer's Review and the Statistical Review for a full description of the data and analyses for Study CV141-002.

Study CV141-002 was a dose-ranging, comparator-controlled clinical trial in which 361 healthy postmenopausal women were randomly assigned to use 0.625 grams of estradiol gel (92 subjects, equivalent to 0.375 mg of estradiol), 1.25 grams of estradiol gel (93 subjects, equivalent to 0.75 mg of estradiol), 2.5 grams of estradiol gel (89 subjects, equivalent to 1.5 mg of estradiol), or a 12.5 cm^2 estradiol

transdermal system (87 subjects, 3.9 mg estradiol, 0.05 mg/day) daily over a 12-week treatment duration. In Study CV141-002, a double-blind procedure was used for subjects receiving the three dosage strengths of estradiol gel. The 12.5 cm^2 transdermal system was used as an open-label comparative treatment.

The inclusion and exclusion criteria, study design and implementation, and safety evaluations were similar as noted above for Study CV141-001. Three hundred and fifty-one (351) subjects (97.2%) took at least one dose of study medication and had at least one post-baseline assessment. Three hundred and fifteen (315) subjects (87.2%) completed Study CV141-002. In total, 46 subjects discontinued Study CV141-002 (12.7%). The discontinuation rate in Study CV141-002 raises no safety concerns.

For Study CV141-002, the original statistical analysis compared the 1.25 gram and the 2.5 gram estradiol gel treatment groups to the 0.625 gram estradiol treatment group. No comparisons to the active-control treatment group were done. However, since Study CV141-002 did not have a placebo treatment group, the comparisons of the estradiol gel treatment groups to placebo needed to make conclusions about effectiveness cannot be done. Study CV141-002 is considered as supportive, and no data for Study CV141-002 is considered for efficacy conclusions. The safety outcomes of Study CV141-002 are, however, integrated in the summary of safety for NDA 21-166.

Per the Statistical Reviewer, the results from Study CV141-002 "provide supportive evidence regarding the level of efficacy in terms of the observed effect size", and the treatment effect sizes for both the frequency and severity of moderate to severe hot flushes are similar to Study CV141-001 across all time points.

Efficacy Conclusions and Recommendations

From the data presented in placebo-controlled Study CV141-001, the 1.25 gram estradiol gel dosage strength and the 2.5 gram estradiol dosage strength are both effective in reducing the number and severity of moderate to severe vasomotor symptoms at weeks 4 and 12. A statistically significant difference from placebo in the number of moderate to severe vasomotor symptoms was observed for both dosage strengths at week 4 (p-values of 0.019 and 0.020, respectively) and week 12 (p-values of 0.043 and <0.001, respectively). The same was true for the severity of vasomotor symptoms (p-values of 0.005 and 0.053, respectively at week 4; p-values of <0.001 for both dosage strengths at week 12).

The issue of the magnitude of the reduction in daily hot flushes is of concern for the primary Medical Officer. As previously noted, in the Division's experience, estrogen alone drug products generally produce a difference of at least two hot flushes over placebo at week 4 and maintains or exceeds this difference through week 12. Study CV141-001 demonstrates that this "expected difference" was not observed for the 1.25 gram estradiol gel dosage strength throughout the 12 study weeks (closely approached at week 12, however), but was observed for the 2.5 gram estradiol gel dosage strength beginning at week 6 (closely approached at week 5) and maintained through week 12.

As shown in Table 1 (page 3 of this review), the difference versus placebo in the reduction in the number of moderate to severe hot flushes at week 4 is 0.85 for the 1.25 gram estradiol gel dosage strength and 1.18 for the 2.5 gram estradiol dosage strength. For week 12, the difference versus placebo is 1.71 for the 1.25 gram estradiol gel dosage strength and 2.72 for the 2.5 gram estradiol gel dosage strength. While these differences do not meet the Division's "observed expectations" at week 4 (both less than the "expected difference" of a reduction of at least two hot flushes over placebo), the differences closely approach and exceed the Division's expectations at week 12, respectively. Is the presence of a clinical separation of treatment effect from placebo of at least one moderate to severe hot flushes from baseline to weeks 4 and 12 less clinically meaningful that a separation of two hot flushes?

To more fully explore the reduction in the number of moderate to severe hot flushes versus placebo in Study CV141-001, the Statistical Reviewer prepared, for descriptive purposes only, an analysis of the data submitted for Study CV141-001 using a greater than or equal to 50% reduction in the frequency and severity of moderate to severe hot flushes as the definition of a responder. The results of this analysis are shown in Table 3.

Table 3: Subjects with 50% or Greater Reduction in the Frequency and Severity of Moderate-to-Severe Hot Flushes Per Day, Intent-to-Treat Population, LOCF

Study Week	Number of Hot Flushes/Day			Severity Score/Day		
	Placebo N=73	Estradiol Gel 1.25g n=73	Estradiol Gel 2.5g n=71	Placebo N=73	Estradiol Gel 1.25g n=73	Estradiol Gel 2.5g n=71
Week 4	32 (44%)	47 (65%)	46 (65%)	8 (11%)	11 (15%)	20 (28%)
Week 5	38 (52%)	51 (71%)	56 (79%)	9 (12%)	15 (21%)	25 (35%)
Week 12	44 (60%)	59 (82%)	61 (86%)	13 (18%)	29 (40%)	41 (58%)

LOCF = Last Observation Carried Forward

Table 3 provides supportive data to indicate that the 1.25 gram and the 2.5 gram estradiol gel treatment groups show similar proportions of subjects with 50% or more improvement in the number of hot flushes at weeks 4 (65% of subjects for both dosage strengths) and that this proportion of subjects exceeds the placebo effect (44%). Similar results are demonstrated for week 12 (82% and 86%, respectively compared with 60% in the placebo treatment group). This reviewer believes that an important proportion of women improve on treatment with both the 1.25 gram and 2.5 gram estradiol gel dosage strengths at week 4 and that this proportion increases through week 12.

We recommend that a second 12-week adequately powered, placebo-controlled safety and efficacy study be conducted as a Phase 4 commitment to determine the lowest effective dose of ESTROGEL® for the treatment of moderate to severe vasomotor symptoms(VMS) and moderate to severe symptoms of vulvar and vaginal atrophy (VVA) associated with the menopause per the following timeline: protocol submission within 6 months of the date of receipt of the ESTROGEL® approval letter from the Division of Reproductive and Urologic Drug Products (DRUDP), study start within 6 months of the protocol agreement with DRUDP, and a final study report submitted within 6 months of the study completion.

Summary of Safety

Please see the Medical Officer's Review of NDA 21-166, dated February 9, 2004, for a full description of the safety data submitted in Study CV141-001 and Study CV141-002.

No deaths were reported for Study CV141-001 and Study CV141-002.

Endometrial Hyperplasia

In Study CV141-001, 2 cases of endometrial hyperplasia were diagnosed in this 12-week study. One of the two cases of endometrial hyperplasia diagnosed in Study CV141-001 showed endometrial hyperplasia with atypia, considered to be a prognostic marker for endometrial cancer. Both cases of endometrial hyperplasia occurred in the 2.5 gram estradiol gel treatment group at week 12. In contrast, no cases of endometrial hyperplasia were diagnosed in the 1.25 gram estradiol gel treatment group or in the placebo treatment group. In addition, four cases of disordered proliferative endometrium (the endometrial lesion most confused with endometrial hyperplasia) were reported in Study CV141-001 at week 12; three cases were reported in the 2.5 gram estradiol gel treatment group and one case was reported in the placebo treatment group.

During the review process for NDA 21-166, the primary Medical Officer and a second Medical Officer (a board-certified pathologist) reviewed the actual reports of the examining pathologists (provided by the Sponsor upon request) for the two reported cases of endometrial hyperplasia and the four reported cases of disordered proliferative endometrium. The "review team" (the primary Medical Officer and a second Medical Officer) concurred with the diagnoses of endometrial hyperplasia in Subjects 2S02 and 6S08 and with the four reported cases of disordered proliferative endometrium (three cases in the 2.5 gram estradiol gel treatment group and one case in the placebo treatment group). Although disordered proliferative endometrium in the placebo group is an unexpected finding, the finding in placebo Subject 3S48 is probably representative of chance since a review of the baseline biopsy for this subject revealed

Clinical Pharmacology and Biopharmaceutics

Please see the Clinical Pharmacology and Biopharmaceutics Review of NDA 21-166.

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II finds NDA 21-166 acceptable. The Sponsor is encouraged to develop an in vitro estradiol release test and define the estradiol release specifications for ESTROGEL® to evaluate potential post-approval changes.

Pharmacology and Toxicology

Please see the Pharmacology/Toxicology Review of NDA 21-166.

Final Product Labeling

Final product labeling is in accordance with the Agency's 2003 draft labeling guidance. The **DOSAGE AND ADMINISTRATION** section of labeling has been modified to indicate that the lowest effective dose of ESTROGEL® for the treatment of moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar and vaginal atrophy has not been determined.

The following table titled, "Mean change from Baseline in the Number and Severity of Moderate to Severe Hot Flushes Per day, ITT Population LOCF" appears in final product labeling under **Clinical Studies,** ***Effect on vasomotor symptoms***.

Table 1: Mean Change from Baseline in the Number and Severity of Moderate to Severe Hot Flushes Per Day, ITT Population, LOCF

	No. of Hot Flushes/Day		Severity Score/Day	
	Placebo n=73	ESTROGEL 1.25g n=72	Placebo n=73	ESTROGEL 1.25g n=72
Baseline Mean (SD)	11.01 (5.66)	10.33 (3.07)	2.30 (0.24)	2.36 (0.29)
Week 4 ◊				
Mean (SD)	5.95 (5.17)	4.43 (4.13)	2.00 (0.63)	1.73 (0.73)
Mean Change from baseline (SD)	-5.06 (4.91)	-5.91 (3.68)	-0.31 (0.62)	-0.63 (0.71)
Diff. vs Placebo		0.85		0.32
p-value *				0.005 **
Week 8				
Mean (SD)	5.36 (5.78)	3.44 (4.40)	1.89 (0.77)	1.44 (0.90)
Mean Change from baseline (SD)	-5.65 (4.11)	-6.89 (3.80)	-0.41 (0.78)	-0.92 (0.89)
Diff. vs Placebo		1.24		0.51
Week 12 ◊				
Mean (SD)	5.17 (6.52)	2.79 (3.70)	1.76 (0.84)	1.33 (0.97)
Mean Change from baseline (SD)	-5.84 (4.52)	-7.55 (3.52)	-0.54 (0.84)	-1.03 (0.94)
Diff. vs Placebo		1.71		0.49
p-value *		0.043 **		<0.001 **

* p-values from Van Elteren's non-parametric test
** Statistically significantly different from placebo.
◊ Primary Timepoint

NDA 21-166 Conclusions and Recommendations

The safety and efficacy data presented in NDA 21-166 support the approval of ESTROGEL® 1.25 grams for the treatment of moderate to severe vasomotor symptoms (VMS) and moderate to severe symptoms of vulvar and vaginal atrophy (VVA) associated with the menopause. I concur with final ESTROGEL® labeling. We recommend that the Sponsor conduct a Phase IV clinical trial to determine the lowest effective dose of ESTROGEL® for VMS and VVA indications. A Phase IV commitment was received from the Sponsor on February 9, 2004.

Theresa H. van der Vlugt, MD, M.P.H.
Acting Medical Team Leader

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

/s/

Theresa Van Der Vlugt
2/9/04 05:18:48 PM
MEDICAL OFFICER
Team Leader Memorandum for ESTROGEL 1.25 grams for VMS and VVA indications.

Daniel A. Shames
2/9/04 05:52:33 PM
MEDICAL OFFICER

Medical Officer's Original Summary of NDA 21-166

1. NDA 21-166 — Submission Date: August 13, 1999
M.O. Review #1 — Review Completed: May 2000
M.O. Review #2 — Review Completed February 2, 2004

Drug name: 17 Beta Estradiol USP

Generic Name: 17 • •Estradiol Gel

Proposed Trade Name: Estrogel® and 0.06%

Chemical Name: Estradiol USP (estra-1,3,5,-(10)-trenen-3, 17• •diol

Sponsor: Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, Georgia, 30062

Pharmacologic Category: Estrogen

Proposed Clinical Indication: [redacted]

Dosages and Route of Administration: 1.25g (equivalent to 0.75mg estradiol, or 0.03%) [redacted] applied topically to the arm

NDA Drug Class: 3S

Related Drugs: There is one approved topical estrogen therapy product, Estrasorb®, approved in the U.S. on October 9, 2003. Other approved products that rely on the stratum corneum of the skin for absorption are transdermal products for estrogen therapy (ET).

Summary/Issues: In the late 1980s, Besins Iscovesco (France) submitted through its US agent, LaSalle Laboratories, Inc. an IND #29,020 and an NDA [redacted] for Estrogel. This NDA was not approvable based upon lack of efficacy in the treated population. Later in 1990, the product was licensed for US registration to Schering-Plough Corp. In 1994, Bristol-Myers Squibb (BMS) acquired Estrogel and Phase 3 studies were initiated. By protocol amendment, BMS transferred all obligations to LaSalle Laboratories which subsequently completed Phase 3 studies with Solvay laboratories and its subsidiary Unimed Pharmaceuticals.

Unimed originally supplied all chemistry and clinical studies submitted under this NDA. This is because its parent company, Solvay, was under an Application Integrity Policy (AIP) since May 12, 1997 and was not legally allowed to sponsor or submit an NDA. Previously, it was unclear whether Unimed was a wholly independent subsidiary of Solvay; presently, Urimed is a subsidiary of Solvay. In this review cycle, data has been submitted by Solvay.

Related Reviews:

Initial IND 29,020
Initial NDA [ ]
Statistical reviews dated May 8, 2002 and January 23, 2004
Biopharmaceutics review dated: February 5, 2004

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I Recommendations

A. [redacted]

B. [redacted]

I Summary of Clinical Findings

The sponsor has demonstrated efficacy of Estrogel® 2.5g in Study CV141-001 but safety was not demonstrated in Study CV-141-001. This study was a double blind, randomized, placebo-controlled, multicenter study that enrolled 225 postmenopausal women at 11 investigational sites. One hundred ninety-six (196) patients completed this study. The sponsor demonstrated both clinical and statistical effectiveness of Estrogel® 2.5g at week 5 through week 12 of treatment. In the same study the clinical effectiveness of Estrogel® 1.25g was not demonstrated during 12 weeks of treatment; statistical efficacy was demonstrated at weeks 4 through 12.

Safety is a significant problem with the 2.5 g dosage strength. Three cases of endometrial hyperplasia and 5 cases of disordered proliferative endometrium were diagnosed on submitted endometrium specimens in 2 controlled studies. High levels of exogenous estradiol have been shown to produce hyperplasia and disordered proliferative endometrium and serum estradiol levels drawn at 12 weeks of treatment confirm high levels of serum estradiol concentrations (≥ 100pg/ml above baseline).

Overview of Clinical Program

Estrogel® was first approved for marketing in France in November 1974 under the name Oestrogel® and is currently marketed in 64 countries. This product is marketed in Europe as Oestradose® and Oestracin®. Estrogel® (1.25 g and 2.5g) was first submitted to the Agency on April 24, 1989 and a not approvable letter was sent to Schering (LaSalle Laboratories was a subsidiary of Schering) on August 17, 1990. In the not approval letter several approvability issues were presented. Most importantly, safety was felt to be the primary concern, in that, high serum levels of estradiol were produced by the 1.5g dose and the sponsor provided no endometrial safety data to support relative endometrial safety. At that time the 1.5g dosage produced serum levels in the range of 50-100pg/ml above baseline; this level was much higher than those produced by Estraderm®, a transdermal product approved in 1984 and is comparable to that produced by oral dosages in Premarin® 2.5m g and Estrace® 2mg. In addition, a small placebo controlled study did demonstrate efficacy, but safety could not be documented. At an in-house meeting with Schering on August 22, 1990, FDA stated it would require a dose-ranging study to find the lowest effective dose and FDA suggested that Schering provide safety and efficacy data for a lower dose, e.g. Estrogel® 0.625g.

At a meeting with Bristol-Myers Squibb on July 25, 1995, FDA (HFD-510) told the sponsor that two well-controlled studies for safety and efficacy would be required for approval. The first study was to be a double-blind placebo controlled study and the second study was to be against an active control such as Climara® patch. HFD-510 also required that the site of application be specific to the inner aspect of the upper arm and that a numerical scale for both frequency and severity of VMS would be required from patient's daily diaries. The double-blind, placebo-controlled study was started on February 14, 1996 and was completed on July 20, 1998.

NDA 21-166 underwent a first cycle of review (sponsored by Unimed) that was completed in May 2000, but reviews were not finalized because Solvay, the sponsor of this NDA, was under Application Integrity Policy (AIP). Once the AIP was removed on April 9, 2003 the review clock restarted and review of NDA 21-166 ensued.

Efficacy

Overall, the efficacy of Estrogel® 2.5g was demonstrated in Study CV-141-001. Clinically significant improvement, *a reduction of at least 2 hot flushes per day,* was shown with the 2.5 g dose at week 5 and a statistically significant reduction in symptoms was demonstrated at weeks 4 through 12. The statistical methodology use was a van Elteren's non parametric test with a Hochberg adjustment for multiple comparisons. The 1.25g per day dosage strength did not demonstrate a clinically significant reduction (at least 2 hot flushes per day) at any time period during 12 weeks of treatment; a statistically significant reduction was, however, demonstrated at weeks 4 through 12. Study CV-141-002 was a randomized, dose-ranging, active control, multicenter study. A double-blind procedure was used for patients receiving three dosages of Estrogel®. The Climara® patch system (12.5cm^2, 0.05 mg/day estradiol) was used as an open-label comparative treatment. Although not a placebo controlled study, this study appeared to demonstrate that the 1.25g dose was not as effective as Climara® 0.05 mg per day at

any time point from the 2nd to the 12th treatment week. Comparability was shown for the 2.5g dose to Climara® 0.05 mg/day during this study.

Safety

Safety of Estrogel® 2.5g dosage strength in Study CV-141-001 is problematical and this dose appears unsafe for its intended use. In 12 weeks of treatment 2 patients in the 2.5g treatment group developed endometrial hyperplasia. This clinical presentation is correlated with high serum levels of estradiol in these patients (Subjects 02S02-114, 06S08175, peak levels of estradiol of 120, 100, above baseline, respectively). Three patients (02S16-122, 03-S47-311 and 07-S08-152) developed disordered proliferative endometrium, a pathological diagnosis that is most often confused with endometrial hyperplasia. In two of 3 patients with disordered proliferative endometrium estradiol levels greater than 100 pg/ml above baseline was demonstrated. In addition, two patients who developed proliferative endometrium were also found to have serum levels of estradiol in excess of 100 pg/ml above baseline.

In Study CV 141-002 there was 1 reported case of endometrial hyperplasia in the 2.5g treatment group and 2 cases of disordered proliferative endometrium. There were no cases of either pathological diagnosis reported in the 0.625g and 1.5g dosages.

Dosing

In study CV 141-001 the 2.5g dose appears to be too high for its intended use and the 1.25g dose appears to have delayed clinical efficacy up to 12 weeks of treatment. In comparative study CV141-002 Estrogel® 0.625g dose compared to Climara® 0.05mg/day appears to be ineffective.

Clinical Review

I. Introduction and Background

Drug name: 17 Beta Estradiol USP

Generic Name: 17 • •Estradiol Gel

Proposed Trade Name: Estrogel® and 0.06% formulations

Chemical Name: Estradiol USP (estra-1,3,5,-(10)-trenen-3, 17• •diol

Sponsor: Solvay Pharmaceuticals, Inc.
901 Sawyer Road
Marietta, Georgia 30062

Pharmacologic Category: Estrogen

Proposed Clinical Indication:

Dosages and Route of Administration: 1.25g (equivalent to 0.75mg of estradiol. or 0.03%) applied topically to the arm

NDA Drug Class: 3S

Related Drugs: There is one approved topical estrogen therapy product, Estrasorb®, approved in the U.S. on October 9, 2003. Other approved products that rely on the stratum corneum of the skin for absorption are transdermal products for estrogen therapy (ET).

Clinical Background:

Estradiol is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. By direct action, it causes growth and development of the vagina, uterus, and fallopian tubes. With other hormones, such as pituitary hormones and progesterone, estradiol can cause enlargement of the breast through promotion of ductal growth, stromal development, and accretion of fat. Estrogens contribute to the shaping of the skeleton, to the maintenance of tone and elasticity or urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and the pigmentation of the nipples and genitals.

Loss of ovarian estradiol secretion after menopause can result inability of thermoregulation causing hot flushes, associated with sleep disturbances and excessive sweating, and urogenital atrophy, causing dyspareunia and urinary incontinence. Estradiol therapy alleviates many of symptoms associated with estradiol deficiency in the postmenopausal woman.

Orally administered estradiol is rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrone than estradiol. In contrast, the skin metabolizes estradiol only to small extent. Percutaneous administration, like transdermal administration, produces therapeutic serum levels of estradiol with lower circulating levels of estrone and estrone conjugates translating to smaller doses than those seen in oral therapy.

Relevant human experience

Estrogel® was first approved for marketing in France in November 1974 under the name Oestrogel® and is currently marketed in 64 countries. This product is marketed in Europe as Oestradose® and Oestraclin®.

Important information from related INDs

Protocol CV141-001 and CV141-002 were initially sponsored by Bristol-Myers Squibb and La Salle Laboratories Inc. and later by Solvay Pharmaceutical. ——— was contracted to perform and oversee both trials and ——— was retained by both Bristol-Myers Squibb and Solvay during the course of the clinical trial phase.

Unimed Pharmaceutics attempted to obtain information regarding the financial interest of investigators through the previous sponsors and ——— There remains a number of investigators for which there is no documentation of there financial interest.

The original IND 29,020 was submitted by Besins Pharmaceuticals. An NDA for Estrogel® was first submitted to the Agency on April 24, 1989 and a not approvable letter was sent to Schering Corporation on August 17, 1990. [

An additional meeting was held on July 25, 1995 with Bristol-Myers Squibb and the sponsor was again told two well-controlled studies for safety and efficacy would be required for approval. The first study should be a double-blind, placebo-controlled study as the sponsor proposed. The second study should be an active control study against one of the patches currently marketed. HFD-510 also required that the site of application be specific to the inner aspect of the upper arm (right or left side depending upon the study participant's handedness). The sponsor was told that a numerical scale for both frequency and severity of VMS would be required from patient's diaries. Furthermore, diaries must be kept such that during the review period for this NDA each week would be evaluated separately for frequency and severity.

Foreign experience

Estrogel® was first approved for marketing in France in November 1974 under the name Oestrogel® and is currently marketed in 64 countries. This product is marketed in Europe as Oestradose® and Oestraclin®. There is an approved patent (May 20, 1997) for the manual pump for dispensing individual metered amounts of Estrogel®.

II. Chemistry, Animal Pharmacology and Toxicology, Microbiolgy: See Pharmacologist Review –See CMC Review

III. Human Pharmacokinetics and Pharmcodynamics: See Biopharmaceutics review for detailed Pharmacokinetics and Pharmacodynamic review

The delivery of estradiol in a pecutaneous gel, as opposed to oral administration, allows the estradiol to reach the circulation without undergoing first pass metabolism during intestinal absorption and in the liver to less active metabolites such as estrone and estriol. This permits the use of lower doses of estradiol to achieve the same physiological result as an orally administered drug. Estradiol in blood is distributed between free estradiol, albumin bound estradiol, and sex hormone binding globulin (SHBG) bound estradiol.

Estradiol is transported across intact skin and into the systemic circulation by a passive diffusion process, the rate of diffusion across the stratum corneum being the principle controlling factor. Estrogel is absorbed rapidly from the skin within 5 minutes and requires no rubbing.

In one multiple-dose pharmacokinetics study, 23 evaluable postmenopausal women received 2.5g Estrogel® gel on their arms, forearms and shoulders once daily for 11 consecutive days. The serum concentrations of estradiol following 2.5g Estrogel® gel applications appeared to reach steady state after the third daily application. During the four days of dosing, the C_{max} of estradiol and free estrone were 209.2 pg/mL and 74.1 pg/mL, respectively; C_{min} was 23.6 pg/mL and 35.1 pg/mL, respectively; and C_{aver} was 66.1 pg/mL and 50.8 pg/mL, respectively. Based upon this study, the mean daily delivery rate of estradiol is approximately 96 µg per day from the Estrogel® 2.5g dose.

In another study, 12 postmenopausal women received Estrogel® 2.5g gel on their arms from wrist to shoulder once daily for six consecutive days. After the last dose on Day 6, the estradiol C_{max} and free estrone was 193.3 pg/mL and 121.8 pg/mL, respectively; C_{aver} over the dosing interval was 109 pg/mL for estradiol and 90.3 pg/mL for estrone, respectively.

Comment: Serum levels of estradiol achieved at 12 weeks appear to be in the range of estradiol transdermal patches at the 0.05mg to 0.075 mg dosages. This

range is 40 to 80 pg/mL above baseline for treated patients. The C_{aver} in this *multiple* dose study is in the range of 66.1 pg/mL above baseline. The C_{aver} of *daily* dosing appears to be quite high (109 pg/ml) and this value will be correlated with clinical study values.

IV. Description of Clinical Data and Sources

The sponsor submitted two well-controlled studies to support this NDA. The first study, Protocol CV141-001, was a double-blind, randomized, placebo-controlled, multicenter study in a total of 225 menopausal women at 11 investigational sites. One hundred ninety- six (196) patients completed this study. Study CV141-002 was a randomized, double-blind, active control, multicenter study in a total of 361 menopausal women. Women received either Estrogel® 1.25g, or Estrogel 2.5g® daily or a Climara® transdermal patch which was administered every 7 days. Three hundred fifteen (315) patients completed this study. Of note, FDA requirements for the VMS indication can now be met by a single placebo-controlled study.

Before reviewing Study CV141-001 in detail, 5 protocol amendments will briefly be discussed:

Amendment 1 was mandated to increase the size of the patient population in study CV141-001. Symptomatic women who were amenorrheic after undergoing hysterectomy and bilateral oophorectomy were included into the study. Inclusion criteria were amended to reflect the minimum daily number of hot flushes specified by HFD-510 to conform to the March 1995 Guidance for Industry, entitled "Guidance for Clinical Evaluation of Combination Estrogen/Progestin Containing Drug Products Used For Hormone Replacement Therapy of Postmenopausal Women" (HRT Guidance). Patients who were diabetic and were on diet alone would not be excluded and specific laboratory standards of thyroid patients were adopted.

Amendment 2 reflected the change in study sponsorship from Bristol-Myers Squibb Company to LaSalle Laboratories.

Amendment 3 involves the transfer to Solvay Phamaceuticals and its responsible parties.

Amendment 4 revised the statistical analysis section of the protocol to address multiple statistical issues. Daily VMS frequency calculations were to be based on the frequency during the one-week period preceding each visit; the previous frequency week interval did not allow for separate evaluation of weekly symptom frequency and severity. This change prompted a reduction in the minimum duration of therapy from 4 weeks to 12 so as to define the Intent-to-Treat (ITT) sample size for the analysis. Dunnett's test was substituted for the Bonferroni procedure. Finally, an interim analysis of the primary efficacy outcomes was permitted based on the likelihood that the ongoing studies would detect the lowest effective study drug dose. This analysis was not meant to terminate or modify the original protocol.

Amendment 5 provided for early study termination, after consultation with the HFD-510. It was determined that any data collected from patients enrolled subsequent to April 1998 would not likely provide further demonstration of safety. HFD-510 also advised that the primary endpoint for the study should include only moderate-to-severe VMS *instead of all* VMS symptoms. In addition, the ITT population was expanded to include as many patients as possible with this amendment. Finally, serious adverse events were modified to comply with the revised Title 21 (CFR, Part 312) guidelines promulgated by the International Conference of Harmonization (ICH) guideline for Good Clinical Practice.

V. Clinical Reviews

The sponsor submitted two well-controlled studies to support this NDA. The first study is CV141-001, which was a double-blind, randomized, placebo controlled, multicenter study with a total of 225 menopausal women enrolled at 11 investigational sites who received placebo, 1.25g or 2.5g Estrogel®. One hundred ninety-six (196) patients completed this study. The second study, Study CV-141-002 was a randomized, double-blind, active control, multicenter study with a total of 361 menopausal women. Women received either Estrogel® 0.625g, 1.25g, 2.5g or a Climara® transdermal patch which was administered every 7 days. Three hundred-fifteen (315) women completed this study. *Of note, at the time of these studies FDA required two studies for approval of a VMS indication. Today, approval can be obtained with a single well-designed placebo- controlled study for a molecular entity that is not defined as new.*

PROTOCOL CV-141-001

The primary objective of this study was to compare the efficacy of transdermal estrogen-therapy (ET) using two dosage strengths of Estrogel® with topically applied placebo for the treatment of VMS in menopausal women.

Design

This was a twelve week, double-blind, multiple dose, randomized, placebo-controlled, parallel multi-center study.

Source and number

The study plan called for enrolling a total of 225 menopausal women at 10-12 investigational sites. There were 221 patients enrolled in the study, 75 were randomly assigned to receive 1.25g Estrogel®, 73 were randomly assigned to receive 2.5 g of Estrogel®, and 73 were randomly assigned to receive the placebo gel. The number of patients who completed the study was 196.

Inclusion Criteria:

Patients were enrolled in the study if they satisfied the following criteria:

1. patients were of female sex;

2. patients were required to be in good stable, general state of health as determined by medical history, clinical laboratory tests, baseline mammography, and physical and gynecologic examinations;

3. patients were required to be amenorrheic, either naturally (for at least 12 months) or surgically (hysterectomy with bilateral oophorectomy). If patients had undergone a hysterectomy without bilateral oophorectomy prior to menopause, they were eligible for study entry if they were aged 45 years or older and met the criteria defined in criterion Number 5;

4. patients were required to have serum estradiol concentrations of less than or equal to 20 pg/mL and serum follicle stimulating hormone (FSH) levels of at least 40 mIU/mL;

5. patients were required to experience a minimum of 7 moderate-to severe hot flushes per day or at least 60 moderate-to-severe hot flushes weekly, defined as

hot flushes that interfered with daily activities, disrupted sleep, or were associated with perspiration (moderate-to-sever). During the period, the severity of episode was quantified from daily recording for the first 2 weeks;

6. patients who had previously received estrogen therapy were to have abstained from such therapy for at least 8 weeks prior to the first screening visit (Week –3); and

7. patients were required to give voluntary, written informed consent and to agree to observe all study requirements.

Exclusion Criteria:

Patients who met any of the following exclusion criteria were excluded from participating in this study:

1. treatment with oral, transdermal, or vaginal steroid hormones (estrogens, progestins, androgens, or corticosteroids) at any time during 8 weeks prior to first screening visit (Week –3) or treatment with injectable or implanted steroid hormones at any time during the 6-month period prior to the first screening visit;

2. allergy to estradiol therapy;

3. reactions to transdermally administered medications;

4. estrogen-dependent neoplasia;

5. vascular disease, thrombotic disorders, or angina, active hepatic or gall bladder disease (a history of asymptomatic gall stones was acceptable) during the 6 months prior to study entry;

6. undiagnosed vaginal/uterine bleeding during the 6 months prior to study entry;

7. clinically significant abnormalities in the medical history, physical examination, or mammography;

8. use of any investigational new drug within 30 days of the first screening visit;

9. any prior evidence of malignant changes detected on mammography;

10. serious renal [serum creatinine 1.5 x upper limit of normal (ULN), cardiac, or hepatic disease (alanine aminotransferase [ALT] or aspartate transaminase [AST] >2 x ULN);

11. endocrine disease (with the exception of diet-controlled diabetes and controlled thyroid disease, as evidence by a normal TSH within 3 months of study entry);

12. any malignancy, with the exception of cervical cancer graded lower than stage 1A, unless treated with no evidence of recurrence in the last 5 years;

13. malignant melanoma or other skin cancers of stage T3 or greater;

14. history of substance abuse during the 6 months prior to study entry;

15. dementia or evidence of mental incapacity that would preclude compliance with the protocol;

16. inability to provide informed consent or be available for chose follow-up;

17. elevated sitting blood pressure (systolic > 165 mm Hg and/or diastolic >95 mm Hg) on two readings taken at least 5 minutes apart during the screening visit at Week –3;

18. Pap smear at screening showing any degree of dysplasia;

19. endometrial biopsy at screening showing any degree of hyperplasia;

20. inability to have an endometrial biopsy as a result of urogenital atrophy, small introitus, or stenotic cervical os;

21. body weight exceeding 130% of ideal range for weight and height; and

22. any condition that the investigator deemed would make the individual unsuitable to participation in the trial.

Specific reasons for patient discontinuation prior to completing 12 weeks of therapy included withdrawn consent, investigator discretion, and the occurrence of one or more adverse events, death, lost to follow-up or other reasons. An outcome page in the CRF was to be completed for all patients who discontinued prematurely from the study.

Comment: Inclusion and exclusion criteria are appropriate for this study.

Study Procedures:

Eligibility for study entry was determined by the inclusion and exclusion criteria and the diary card assessment at screening. All patients who qualified for enrollment in the study based on their daily or cumulative weekly number of hot flushes provided blood samples from which clinical laboratory analyses could be performed. Eligible patients were randomly assigned to therapy approximately one week later, when all of the laboratory test, mammography, endometrial biopsies and Pap smears were available to the investigator.

Patients were required to attend 2 screening visits at Week –3 and Week –1. The major objective of the first screening visit was to assure that all patients entering the study met the inclusion criteria. Assessments included a complete medical history including gynecologic history; date of last natural menstrual period; history of hormone therapy (HT); review of hormone drug therapy taken within 2 months of the first screening visit; review of concomitant medications and measurements of blood pressure.

Patients were scheduled to return in approximately 14 days in the fasted state (no food or alcohol consumed for 12 hours). Patients were given two pre-study, 7day diary cards for the purpose of recording the number and severity of hot flushes each day. The prestudy diary cards were to be completed daily for 14 consecutive days beginning on the day following the first screening visit. The completed diary cards were to be returned to the investigator at the second screening visit (Week –1). Of note, in the actual conduct of the study, there was some variability in timing between visits.

During the second screening visit (Week –1), procedures were to be performed if a patient experienced at least 7 hot flushes per day or at least 60 hot flushes per week, which were considered to be of moderate-to-severe intensity. A complete gynecologic examination and physical examination including vital signs, height, and weight measurements were preformed. Other procedures included a mammogram taken no

longer than 9 months prior to study entry; phlebotomy for the screening fasting laboratory profile; urinalysis by diptstick; cervical Pap smear; vaginal smears (from both lateral vaginal walls using standard procedure) for determination of maturation index (MI); and an endometrial biopsy from non-hysterectomized women. Patients were scheduled to return for a baseline visit (day 0).

At the baseline visit (Day 0), results of laboratory test, histology reports, and mammograms were reviewed to assure compliance with the protocol. Blood pressure measurements, adverse events, and use of concomitant medications were recorded. Study medications, gel applicators, and diary cards were dispensed to eligible patients according to randomization numbers. Patients were scheduled to return at intervals of approximately 4 weeks corresponding to visits at Weeks 4, 8, and 12.

During the treatment period, patients were required to attend visits at the end of Week 4, Week 8, and Week 12. Diary cards for the screening and treatment periods were issued to assess the frequency and severity of VMS and the occurrence of adverse events. Daily assessments on the diary cards were completed for Weeks 1 through 12. During each scheduled visit, menopausal symptoms recorded on the diary cards were evaluated. Also, during each visit, blood pressure was measured, application sites were examined, adverse events were reviewed and recorded, and unused medication was collected and weighed.

At Week –1 and 12, serum chemistry, hematologic test, and urinalysis by dipstick were preformed. Blood samples were collected for measurements of serum concentrations of estrone and estradiol at Weeks –1 and 12. Patients were instructed to withhold food and alcohol for 12 hours prior to Week 12.

At Week 12, a general physical examination that included a pelvic examination with Pap smear, breast examination, and mammogram was performed. Vaginal smears from both lateral vaginal walls using standard procedures were taken for determination of maturation index (MI). An endometrial biopsy was obtained from all non-hysterectomized women. Unused gel study medication was accounted for by collecting and weighing remaining study medication.

A post-treatment phase was conducted. Patients with evidence of endometrial hyperplasia, based on the results of an endometrial biopsy, were prescribed a progestin. In addition, investigators could also prescribe a progestin to any patient at their discretion. Following the final visit (15 to 30 days after Week 12), the investigator conducted follow-up telephone calls to all patients who were prescribed a progestin. During the telephone interview, the investigator was to confirm that the patient was compliant with the progestin therapy.

Efficacy

The sample size for this study was calculated to assure that both safety and efficacy objectives could be assessed. The incidence of breast pain or breast tenderness among patients who received 2.0 mg Estrace® (approximately equivalent to 2.5 mg of Estrogel®) was estimated to be 22% from the previously reported study. Hypothesizing a 5% incidence among placebo-treated patients, a total of 225 patients consisting of 75 patients in each treatment group, was considered sufficient to show a difference between the active gel dose groups and the placebo gel with at least 80% power at the 5% significance level. These calculations were based on an attrition rate of 15% among enrolled patients.

The sample size of 225 patients was also deemed sufficient to show a difference in change from baseline to Week 12 in the daily frequency of vasomotor symptoms between Estrace® 1.0 and 2.0 mg (approximately equivalent to 1.25 g and 2.5 g Estrogel®, respectively) and the placebo gel that was reported in the same study.
According, a total of 99 enrolled patients (33 in each active gel group and 33 in the placebo gel group) would be adequate to show a difference in efficacy.

The primary efficacy variable was an analysis of covariance (ANCOVA) and Dunnett's test for multiple comparisons. In this analysis, the model had fixed factors: treatment, center, and treatment by center interaction; baseline value was a covariate, and the dependent variable was the change from baseline in measured mean daily frequency of moderate-to-severe flushes. The Estrogel® treatment groups were compared with placebo by the ANCOVA model at each evaluation week. The results were summarized in tabular form showing the pairwise comparisons of the response to Estrogel® and placebo.

Mean frequency of moderate-to-severe flushes was based on the number of flushes averaged from Day 1 through Day 7 for each week. Baseline means were calculated from the average frequencies reported at Screening Visits (Week –3) and 2 (Week –1).

Two types of analyses were performed: last observation carried forward (LOCF) and visit-wise. The LOCF analysis allows data from a preceding week to be carried forward in the analysis of any time point after week 1. Data for subjects who discontinued were carried forward in the analysis for all subsequent time points. Visit-wise analysis at each time point included only those subjects for whom data was available for that specified time point.

The primary efficacy outcome measure was based on the change in the frequency of moderate-to-severe flushes from baseline through Week 12. The mean daily frequency of moderate-to-severe flushes was determined from each week based on the data recorded on each subject's diary card that was collected at each visit.

The mean daily frequency of moderate-to–severe flushes was to be analyzed in a repeated measure analysis of covariance. The baseline response, defined as the average of the two screening visit daily averages, will be used as the covariate. The analysis for the covariance model was to include study site as a random effect, treatment group, subject within treatment group as the between error term, evaluation week, treatment-by-week interaction and baseline, baseline by treatment, baseline by week, baseline by treatment by week covariate adjustments, and residual error. The Estrogel® treatment groups were to be compared with placebo through the analysis of covariance model at each evaluation week. The results were to be displayed by constructing a 95% confidence band about the response of placebo based on the difference in response between the Estrogel® dose groups and placebo.

Pooling of centers data was allowed in the descending order by the number of subjects in the ITT efficacy sample (center size). Data from the first center with fewer than five subjects per treatment group, having primary efficacy measurements in any treatment group, were pooled with that of centers having the fewest number of subjects. Pooling was to be continued until the "meta-center" contained data for at least five subjects in each treatment group. (There were 3 centers with less than 5 subjects per treatment group).

Comment: See statistical comments and reviews by the Biometric team. Note in this review cycle a recheck of the residuals from the planned ANCOVA model showed that the normality assumption was not satisfied. Therefore, van Elteren's non-parametric test was used as an alternative. Instead of the planned Dunnett's

test for multiple comparisons, the Hochberg method was applied to the non-parametric results.

Safety

The safety analyses were based on all subjects who were randomized to treatment in the ITT safety analyses. The primary safety outcome was the incidence of breast pain or breast tenderness during the treatment period. As appropriate, the incidence of breast pain or breast tenderness among treatment groups was compared using Fisher's exact test. Similarly, these analyses were conducted for treatment-emergent adverse events (TEAE) that occurred with high incidence, as deemed appropriate. The results of these analyses are presented along with the selected menopause-specific events.

TEAEs were tabulated by body system and categorized according to the Coding Symbols for the Thesaurus of Adverse Reactions Terms (COSTART). The incidence of all TEAEs, TEAEs leading to premature discontinuation from this study, and the incidence of serious TEAEs are displayed by number and percent. Adverse events were presented according to frequency, severity, and attribution to study medication, and selected subgroups, if deemed appropriate.

Interim Analysis

An interim analysis of Protocol CV141-001 was performed to enable preliminary comparison of the efficacy of Estrogel® in strengths of 1.25 g and 2.5 g per day with that of the placebo gel. The purpose of the interim analysis was to ascertain the lowest strength of Estrogel® effective in the treatment of menopausal VMS in conjunction with a companion study under Protocol CV141-002. Secondly, this study evaluated the frequency of hot flushes in patients treated with increasing strengths of Estrogel® compared with that of the placebo gel. At the cutoff date of September 22, 1997, for the interim analysis, 136 menopausal women were randomly assigned to receive medication at 11 investigational sites. The results of the interim analysis showed Estrogel® to be effective in reducing the VMS compared to placebo gel by Dunnett's multiple comparisons test at Week 12.

Comment: The use of an interim analysis to ascertain the lowest effective dose is unusual and inappropriate for a VMS pivotal study. A statistical penalty was assesses against the sponsor in the final analyses.

Table 1 (sponsor's table 10.1.2) shows the disposition of all patients included in the analyses of safety and efficacy:

Table 1

Modified Sponsor's Table 10.1.2

CHARACTERISTIC	PLACEBO	ESTROGEL® 1.25 g n (%)[1]	ESTROGEL 2.5g n (%)[1]
Randomized to treatment	73 (100.0)	75 (100.0)	73 (100.0)
Intent-to-Treat (ITT) efficacy[3]	73 (100.0)	72 (96.0)	71 (97.3)
Completed study[2]	65 (89.0)	65 (86.7)	66 (90.4)
Discontinued prematurely	8 (11.0)	10 (13.3)	7 (9.6)
Withdrew consent	0 (0)	3 (4.0)	0 (0.0)
Lost to follow-up	4 (5.5)	2 (2.7)	3 (4.1)
Withdrawn by investigator	1 (1.4)	0 (0.0)	0 (0.0)
Adverse event	0 (0.0)	2 (2.7)	2 (2.7)
Other	3 (4.1)	3 (4.0)	2 (2.7)

[1] Percentages are based on subjects randomly assigned to treatment
[2] Based on Cochran-Mantel-Haenszel test comparing the numbers of subjects who completed and discontinued prematurely across treatment groups.
[3] Subjects who were randomized to treatment and had at least one post-baseline efficacy assessment.

Note: Overall 50 (22.4%) of enrolled patients discontinued from this study prematurely. Five patients (3 in the 1.25g dosage and 2 in the 2.5g dosage) were excluded from the efficacy analysis because they did not have at least one post-baseline efficacy assessment. A total of 11 (4.9%) were lost to follow-up with approximately the same number from each treatment group.

The sponsor presented baseline demographic information for all patients in table 10.2.1. Due to the size of this table, information will be summarized. The mean age was approximately 50.8 years of age for all treatment groups with the largest majority 144 (48%) of patients in the 45-54 age group. Ethnic origin in this study showed 180 of 221 (81.4%) of patients to be White, 35 of 221 (15.8%) of patients to be Black, 4 of 221 to be Asian/Pacific Island (1.8%) 5 of 221 (2.2%) to be Hispanic and Other to be <1%. The groups were fairly comparable as to height and weight with mean height ranging from 64.1 to 64.9 inches tall (p=0.093), weight ranged from 154.2 lbs. to 166.2 lbs. p=0.019) and a mean Body Mass Index of ranging from 26.4m^3 to 27.8 m^3 (p=0.144). Sixty-one point nine (61.9%) had use prior hormone drug therapy and 84 of 221 (38.1) had used no prior hormone drug therapy. The mean time since the last menses ranged from 9.8 years to 11.0 years. Natural menopause had occurred in 76.9% of patients while (23.1%) had a surgical menopause. Overall, the Estrogel® 1.25g group appeared to be heavier, to have a greater Body Mass Index, and to have used a greater percentage of prior hormone therapy than the other groups.

The majority of patients (191 of 221 (86.4%) in this study took some type of concomitant medication during the treatment. The most common medications consisted of over-the counter analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), anti-sinus medications, antacids such as Tums, antibiotics such as Amoxicillin and multivitamin combinations. The most common analgesics include acetaminophen by used by 29.4% of all patients, ibuprofen used by 24.4%, and aspirin used by 12.7%. No single treatment groups used more concomitant medications than the other. Importantly, the overall use of the most common analgesics and NSAIDs was comparable among the treatment groups.

Comment: Over-the-counter medications use is consistent with other studies seeking a hormone therapy indication.

Most patients complied with the study treatments. Patients were deemed compliant provided they used at least 80% of the gel that was expected to be used during the treatment period. Hence, compliance was evaluated on the basis of recovered gel mass average for both Tubes 1 and 2. Compliance was fairly comparable among the treatment groups, slightly fewer patients were at least 80% compliant in the Estrogel® dosage 2.5g group (71.4%) compared with the Estrogel® 1.25g dosage group (83.1%) and the placebo group (79.2%). Compliance could not be determined for 8 patients whose gel mass data were missing: 1 in the placebo group, 4 in the Estrogel® 1.25 dosage group, and 3 in the Estrogel® 2.5 dosage group. Of note, with the exception of Week 12, more than 80% of patients in each treatment group completed at least 7 days of diary data at each week. At Week 12, approximately 30% of patients in each treatment group did not complete 7 days of diary data; however, most did complete 5 to 6 days of diary data.

Comment: Compliance is consistent with other VMS studies with roughly 80% of patients taking study medication. There was decreased compliance in diary data entry toward the end of the study.

The frequency and severity of hot flushes among patients in the ITT efficacy population during each screening visit (Week –1 and Week –3) and averaged over both screening visits are presented in the following table:

Table 2

Mean (±SD) Frequency and Severity of Hot Flushes During Screening for the Intent-To-Treat (ITT) Efficacy Population[1] of Protocol CV141-001

Sponsor's Table 12 Vol.2

Characteristic	Placebo N = 73	Estrogel® 1.25g N =72	Estrogel® 2.5g N = 71	P-Value[2]
Frequency of moderate-to-severe hot flushes[3] average of Screening Weeks –3 and –1	11.0 ± 5.67	10.3 ± 3.07	10.5 ± 3.88	0.673
Frequency of all hot flushes,[4] average of Screening weeks –3 and –1	12.5 ± 5.83	11.7 ± 3.64	12.1 ± 4.24	0.612
Severity of all hot flushes, [5] average of Screening Weeks –3 and –1	2.3 ± 0.23	2.4 ± 0.29	2.3 ± 0.22	0.244

[1] Based on the total number of patients in each category who were in the ITT efficacy population. The ITT efficacy population was defined as patients who were randomly assigned to receive study medication and had at least one postbaseline efficacy assessment.
[2] Based on analysis of variance
[3] Based on the number of moderate-to-severe hot flushes averaged from Day 1 through Day 7 of each week. When daily frequencies were missing, the mean was based on the days for which moderate-to-severe frequencies were recorded.
[4] Based on the total number of hot flushes averaged from Day 1 through Day 7 for each week. When daily frequencies were missing, the mean was based on those days on which frequencies were recorded.
[5] The severity of hot flushes was categorized by patients as none, mild, moderate, or severe. Severity ratings (0, 1, 2, and 3, respectively) were assigned, and these ratings were used as multipliers for the reported number of daily hot flushes, which were averaged from Day 1 through Day 7 for each week to obtain a weekly severity score.

Comment: Suprascripts 1, 3, and 5 are most pertinent to this review.

The primary efficacy variable is the mean change from baseline in moderate to severe vasomotor symptoms. Mean changes from baseline are presented in the following table. This table uses the van Elteren's non-parametric test and Hochberg's adjustment for multiple comparisons.

Table 3

Sponsor's Table 13 Vol 45 Unmodified

Mean Changes From Baseline (±SD) In Frequency of Moderate-To Severe Hot Flushes At Each Week For The Intent-To-Treat Efficacy Population[1] In Protocol CV141-001			
Time Point[2]	Placebo	Estrogel Gel® 1.25g	Estrogel® 2.5g
Baseline	11.0 ± 5.67	10.3 ± 3.07	10.5 ± 3.88
Week 1	-2.9 ± 3.43	-2.7 ± 3.33	-2.8 ± 3.86
Week 2	-4.6 ± 4.56	-4.2 ± 3.58	-4.7 ± 4.32
Week 3	-4.9 ± 4.52	-5.5 ± 3.57	-5.9 ± 4.68
Week 4	-5.1 ± 4.91	-5.9 ± 3.68	-6.2 ± 4.40
Week 5	-5.3 ± 4.43	-6.3 ± 3.71	-7.3 ± 4.56
Week 6	-5.4 ± 4.12	-6.7 ± 3.68	-7.8 ± 4.55
Week 7	-5.7 ± 4.29	-6.8 ± 3.63	-7.7 ± 6.19
Week 8	-5.6 ± 4.11	-6.9 ± 3.80	-8.2 ± 5.07
Week 9	-5.8 ± 4.25	-7.4 ± 3.50	-8.4 ± 4.52
Week 10	-5.8 ± 4.13	-7.4 ± 3.47	-8.7 ± 4.45
Week 11	-5.9 ± 4.52	-7.4 ± 3.59	-8.7 ± 4.65
Week 12	-5.7 ± 4.52	-7.5 ± 3.52	-8.6 ± 5.13

[1]Based on the number of moderate-to-severe hot flushes averaged from Day 1 through Day 7 for each week. When daily frequencies were missing, the mean was based on the days for which moderate-to-severe frequencies were recorded. Baseline means were obtained from the average number of moderate-to-severe hot flushes reported at Screening Visits 1 and 2.

[2] Method of last observation carried forward was used for patients who discontinued after Week 1.

Note that the Estrogel® groups showed significant improvement over placebo from baseline ($p = 0.0001$). Note the high standard deviations associated with this treatment. Most importantly, note at Week 4 there is improvement over baseline of 0.8 moderate to severe hot flushes (5.6 per week) for the Estrogel® 1.25g dosage group; a 1.1 [7.7 per week] moderate to severe hot flushes for the Estrogel® 2.5g dosage group. In previous approved products for this indication, the mean change from baseline in moderate-to-severe hot flushes is improved by at least 2 per day (14 per week) over that of placebo at week 4, and for some products this changes is noted by week 2. *Therefore, from a clinical viewpoint this is not significant.* Note that by week 12 hot flushes in the Estrogel® 1.25 dosage group have shown a reduction of 1.8 over that of placebo. Again, this is not clinically significant since this product never meets a decrease of 2 per day (14 per week) relative to placebo that is commonly seen with approved estrogen products used for a reduction in moderate-to-severe hot flushes. At week 5, the Estrogel® 2.5 dosage group has a mean change from baseline that is 2 per day (14 per week) hot flushes better than placebo and this trend continues through week 12 of treatment. Note that the Estrogel® 2.5 dosage group does not demonstrate a clinically significant change relative to placebo at week 4, but is clinically significant by the usual methods for evaluating estrogen products for the reduction in moderate to severe vasomotor symptoms from week 5 through week 12.

Comment: Estrogel 1.25g per day does not show clinical efficacy in the treatment of moderate-to- severe hot flushes at any time during 12 weeks of treatment. Estrogel® 2.5g per day does show efficacy beginning at week 5 for moderate-to-severe hot flushes and

this efficacy continues to week 12 of treatment. It appears that a significant number of patients are not absorbing sufficient amounts estradiol from the skin to ameliorate a clinically significant number of vasomotor symptoms, although statistically significance is demonstrated. Since publication of the 1995 HRT Guidance sponsors have been required to demonstrate a clinically and statistically significant reduction in both frequency and severity of hot flushes. Estrogel® 1.25mg does not meet these criteria.

Table 4

Table 4 (sponsor's table 22) is the primary efficacy table for severity of vasomotor ®symptoms. Table 4 is based on van Elteren's non parametric test and Hochberg's adjustment for multiple comparisons at Week 4 and 12.

Sponsor's Table 22 Vol 45 Modified

Mean (±SD) Severity of Hot Flushes At Each Week For The Intent-To-Treat Efficacy Population[1] In Protocol CV141-001			
Time Point[2]	Placebo	Estrogel® 1.25g	Estrogel® 2.5g
Baseline	2.3 ± 0.23	2.4 ± 0.29	2.3 ± 0.22
Week 1	2.2 ± 0.33	2.2 ± 0.43	2.3 ± 0.43
Week 2	2.0 ± 0.56	2.1 ± 0.50	1.9 ± 0.67
Week 3	2.0 ± 0.53	1.9 ± 0.64	1.7 ± 0.80
Week 4	2.0 ± 0.63	1.7 ± 0.73	1.7 ± 0.85
Week 5	1.9 ± 0.68	1.7 ± 0.78	1.4 ± 0.89
Week 6	1.9 ± 0.70	1.6 ± 0.83	1.3 ± 0.92
Week 7	1.9 ± 0.72	1.5 ± 0.88	1.2 ± 0.90
Week 8	1.9 ± 0.77	1.4 ± 0.90	1.2 ± 0.94
Week 9	1.8 ± 0.74	1.4 ± 0.91	1.1 ± 0.94
Week 10	1.8 ± 0.78	1.5 ± 0.91	1.0 ± 0.94
Week 11	1.8 ± 0.78	1.4 ± 0.95	1.0 ± 0.96
Week 12	1.8 ± 0.84	1.3 ± 0.97	1.0 ± 0.94

[1]Severity was rate as 0 (none), 1 (mild), 2 (moderate), or 3 (severe). These rating were used as multipliers for the reported number of daily hot flushes, which were then averaged from Day 1 through Day 7 for each week to obtain a severity score. When daily frequencies were missing, the mean was based on the day for which severity was recorded. Baseline means were obtained from the average severity reported at Screening Visits 1.

[2]Method of last observation carried forward was used for patients who discontinued after Week 1.

At Week 4 severity of symptoms in the Estrogel ®1.25g dosage group is statistically significantly improved vs. placebo (p= 0.0045); but this is not the case with the Estrogel ®2.5 g dosage group (p=0.0532). At Week 5, severity of both the Estrogel® 1.25g and the 2.5g dosage groups is statistically significantly different from placebo, p = 0.0399 and 0.0034, respectively. From a clinical viewpoint the above data does not make clinical sense and is contradictory to the frequency data that showed a greater degree of reduction in the Estrogel® 2.5g dosage compared to the 1.25g dosage group. In previous reviews of products to treat VMS, if a drug product was being consistently absorbed then severity of symptoms followed frequency, that is, as the frequency of symptoms decreased, the severity of symptoms decreased. Therefore, there appears to be some inconsistency in this data that will be discussed later.

As an objective parameter, the sponsor studied the vaginal maturation index. The maturation index is the relative ratio of basal/parabasal cells, intermediate cells, and superficial cells evaluated from vaginal smears taken at screening (baseline) and at week 12 (final visit). The results of sponsor's table 10.7.1 (Vol. 42) showed that the percentage of vaginal superficial cells increased significantly from screening values and the percentage of vaginal basal/parabasal cells decreased from screening in both treatment groups. In the Estrogel® 1.25g dosage group basal/parabasal cells decreased from 12.4 subjects at baseline to 2.8 subjects at the final visit and superficial cells increased from 8.0 subjects at baseline to 19.0 subjects at the final visit. In the Estroge® 2.5g dosage group basal/parabasal cells decreased from 18.9 subjects at baseline to 0.1 subjects at the final visit and superficial cells increased from 5.4 subjects to 18.3 subjects at the final visit. There was *no* change in the basal/parabasal ratio and superficial cells ratio in the placebo group.

Comment: These findings support the biologic effect that varying dosages of estrogens alter the vaginal epithelium and transform it to a less atrophic epithelium.

The sponsor supplied Table 10.9.1.1 (See page 34, Table 7). This is a table showing mean estradiol and estrone levels for the Intent-to-Treat (ITT) safety sample for Study CV-141-001. This table shows baseline and Week 12 mean levels of estradiol and estrone at baseline and week 12. Additionally median, standard deviations (SD), and minimum/maximal levels of estradiol and estrone are supplied. Review of this table reveals essentially normal levels of estradiol and estrone for postmenopausal women at baseline. At week 12 *mean* levels of estradiol in the placebo group (SD), Estrogel® 1.25g and Estrogel® 2.5g dosage groups are 14.4 (31.9), 106 (243.74), and 123.2 (151.10) pg/mL above baseline respectively. Mean estrone levels, Estrogel® 1.25g and Estrogel® 2.5g are 32.5 (32.90), 58.5 (40.98) and 75 (58.98) pg/mL, respectively. At Week 12 *median* estradiol levels were 5.0, 33.5, and 65 pg/mL in the placebo and Estrogel 1.25g and 2.5g dosage groups, respectively. Minimal/Maximal levels of estradiol from 0.00 to 170.00 pg/mL in the placebo group, 0.00 to 1520 pg/mL in the Estrogel® 1.25g dosage group, and 5.00 to 890.00 pg/mL in the Estrogel® 2.5g dosage group. For estrone the minimal/maximal levels are 5.00 to 210 pg/mL in the placebo group, 15.00 to 250 pg/mL in the Estrogel® 1.25g group and 16.66 to 320pg/mL in the Estrogel® 2.5g group.

Comment: These findings demonstrated the tremendous variation in Estrogel® levels achieved by this product. At first glance, the initial levels of estradiol at week 12 appear to show the drug is being absorbed, however, the standard deviations are greater than the serum mean levels achieved. The minimal/maximal levels of estradiol are extraordinarily high and confirm wide variations in the absorption of this product. It appears that the stratum corneum, which is the rate-limiting surface for absorption, is highly variable in studied patients and provides insight into why this product is incompletely effective. Theoretically, with a product that is — alcoholic base and a small surface area, significantly large amounts of the alcohol evaporate so that the skin is unable to absorb a sufficient amount of this product.

Safety

All adverse events were recorded. Adverse experiences were classified into a standardized terminology using the COSTART (Coding Symbols for Thesaurus Reactions Terms) version 4.0, by body system. Percentages are based on the number of patients in the ITT safety population for each study group. Patients may have reported

multiple adverse events that are coded to the same preferred term and body system; thus, totals do not necessarily reflect the sum of individual adverse events.

All patients who took medication were analyzed in the safety analysis. A total of 221 patients were included in the analysis of treatment emergent signs and symptoms (TESS). Seventy-five (75) were in the Estrogel ®1.25g dosage group, 73 were in the Estrogel® 2.5g dosage and 73 were in the placebo group. A total of 171 patients (77.4%) experienced one or more TESS during the study: 59 (78.7%) in the Estrogel ®1.25g dosage group, 61 (83.6%) in the Estrogel ®2.5g dosage group and 51 (69.9%) in the placebo group. The incidence of TESS showed a slight increase with increasing dose. Specifically, in incidence of TESS were 8.8% in the Estogel® 1.25g dosage group and 13.7 in the Estrogel® 2.5g dosage group.

Sponsor's table 10 (Vol. 1.41 of the NDA submission) reported TESS of 5% or more by any treatment group. The TESS are grouped by body system. As stated earlier, the body system totals are not necessarily the sum of the individual study events since a patient could report two or more different study events in the same body system. Table 27 will now be summarized in a descriptive fashion due the size of this table. **Under Body as a Whole:** Headache was the most common adverse event reported. It was reported in 13 (17.8%) of placebo patients, and in 13 (17.3%) and 14 (19.2%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. Infection was reported in 5 (6.8%) of placebo patients and 12 (16.0%) and 5 (6.8%) of Estrogel® 1.25 and 2.5g dosage groups, respectively. Pain was reported in 8 (11.0%) of placebo patients and 5 (6.7%) and 4 (5.5%) of patients in the Estrogel® 1.25g and 2.5 g dosage groups, respectively. Abdominal pain was reported in 1 (1.4%) of patients in the placebo group and in 6 (8.0%) and 2 (2.7%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. Accidental injury was reported in 1 (1.4%) of patients in the placebo group and in 4 (5.3%) and 3 (4.1%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. Asthenia was reported in 3 (4.1%) of patients in the placebo group and in 4 (5.3%) and 1 (1.45) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. Flu syndrome was reported in 1 (1.4%) of patients in the placebo group and in 3 (4.0%) and 5 (6.8%) of patients in the Estrogel® 1.25g and 2.5 g dosage groups, respectively.

Under Cardiovascular system: AEs were reported in 3 (4.1%) of placebo patients and in 5 (6.7%) and 5 (6.8%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. **Under Digestive system:** Nausea was reported in 3 (4.1% of placebo patients and in 4 (5.3%) and 9 (12.3%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. Flatulence was reported in 4 (5.5%) of patients in the placebo group, and in 3 (4.0%) and 1(1.4%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. **Under musculoskeletal system:** arthralgia was reported in 0 (0%) of placebo patients and in 4 (5.3%) and 2 (2.7%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. **Under nervous system:** nervousness was reported in 1 (1.4%) of placebo patients and in 0 (0.0%) and 4 (5.5%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. **Under respiratory system:** pharyngitis was reported in 3 (4.1%) of placebo patients and in 2 (2.7%) and 6 (8.2%) of patients in the Estrogel® 1.25 and 2.5g dosage groups, respectively. Sinusitis was reported in 1 (1.4%) of placebo patients and in 5 (6.7%) and 5 (6.8%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. Rhinitis was reported in 5 (6.8%) of placebo patients and in 2 (2.7%) and 1 (1.4%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. **Under Skin and Appendages:** rash was reported in 4 (5.55) of patients in the placebo group and in 4 (5.3%) and 4 (5.5%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. **Under Urogenital system:** breast pain was reported in 7 (9.6%) of patients in the placebo group and in 8 (10.7) and 8 (11.05) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. Vaginitis was reported in 3 (4.1%) of patients in the placebo group and in 8 (10.7%) and 1

(1.4%) of patients in the Estrogel® 1.25 and 2.5g dosage groups, respectively. Endometrial disorder was reported in 1 (1.4%) of patients in the placebo group and in 1 (1.3%) and 6 (8.2%) of patients in the Estrogel ®1.25g and 2.5g dosage groups, respectively. Dysmenorrhea was reported in 1 (1.4%) of placebo patients and in 1 (1.3%) and 5 (6.8%) of patients in the Estrogel® 1.25g and 2.5g dosage groups, respectively. Metorrhagia was reported in 0 (0.0%) of patients in the placebo group and in 0 (0.0%) and 5 (6.6%) of patients in the Estrogel®1.25g and 2.5g dosage groups, respectively.

Under urogenital system: Table 10.15.5 (V0l. 1.42) reported the total number of nonhysterectomized patients reporting selected TESS in a subset of the ITT safety sample. Endometrial disorder was reported in 1 (3.2%) of patients in the placebo group and in 1 (4.0%) and 6 (14.3%) of patients in the 1.25g and 2.5g Estrogel® dosage groups, respectively. Endometrial hyperplasia was reported in 0 (0.0%) in the placebo and Estrogel® 1.25g dosage group and in 2 (4.8%) of patients in the 2.5g Estrogel® dosage dosage group. Menorrhagia was reported in 0 (0.0%) of patients in the placebo and 1.25g Estrogel® dosage group and in 1 (2.4%) of patients in the Estrogel® 2.5g dosage group. Metorrhagia was reported in 0 (0.0%) of patients in the placebo and Estrogel® 1.25g dosage group and in 5 (11.9%) of patients in the Estrogel® 2.5g dosage group. Uterine hemorrhage was reported in 0 (0.0%) of patients in the placebo and Estrogel® 1.25g dosage group and in 1 (2.4%) of patients in the Estrogel® 2.5g dosage group. Vaginal hemorrhage was reported in 0 (0.0%) of patients in the placebo and the Estrogel® 1.25 g dosage group and in 2 (4.8%) of patients in the Estrogel® 2.5g dosage group. Overall, there were 15 (35.7%) distinct patients reported in this subgroup with severe bleeding/hemorrhage and an endometrial disorder/endometrial hyperplasia.

Comment: The incidence of TESS is consistent with other studies in which there is estrogen replacement or a combination with a progestin. Breast pain, headache, nausea and vaginal bleeding are reported with similar percentages of AEs as reported in this study. Bleeding disorders were similar between the placebo group and the Estrogel® 1.25g group. This is consistent with a lower amount of estradiol being absorbed with the Estrogel® 1.25g group.

Endometrial hyperplasia is significant in this study. Two cases of treatment of this disorder have not been seen within twelve weeks of treatment with other approved products and with 3 additional cases of disordered proliferative endometrium a significant concern arises for the approvability of the 2.5g dosage due to safety concerns.

There were no deaths in this study.

Two cases of endometrial hyperplasia (2S02, 6S08) in the Estrogel® 2.5g dosage group were reported. In addition, 4 cases of disordered proliferative endometrium (the endometrial lesion most confused with endometrial hyperplasia) were reported. Of these cases, 1 was in the placebo group and 3 were in the Estrogel® 2.5g dosage group. Endometrial hyperplasia in the placebo patient (3S48) is clearly unexpected but is probably representative of chance since the baseline biopsy revealed proliferation with breakdown, while the 3 cases in patents treated with Estrogel® patients are probably related to increase amounts of estradiol being absorbed since baseline biopsy revealed atrophy in 2 cases and surface epithelium in the third case. Of interest, at week 12 the sponsor drew serum samples of estradiol on these patients. In the two Estrogel® treated patients with endometrial hyperplasia the estradiol levels were recorded as 100pg/mL and 120pg/mL, respectively; in the patients with disordered proliferative endometrium the serum levels of estradiol were 310pg/ml, 74 and 120pg/mL, respectively. These levels are clearly high and would be consistent with long-term studies showing levels of 100 pg/mL of estradiol or greater as being associated with a higher incidence of endometrial hyperplasia, e.g. estradiol pellets. In addition, three patients (2S45, 3S65, and 6S45) who

had serum levels in excess of 100 pg/mL had a diagnosis of proliferative endometrium on endometrial biopsy at week 12.

Five (5) patients were withdrawn from the study because of adverse medical events and all were receiving active treatment. Two (2[2.7%]) patients were in the Estrogel® 1.25g dosage group and 3([4.1%]) patients were in the 2.5g dosage group. One patient (001-06-18) in the 1.25g Estrogel® discontinued due to kidney stones and a myocardial infarction; the other patient in the 1.25g group discontinued due to exposure to poison ivy for which she developed dermatitis on the arms, legs, and abdomen. In the Estrogel® 2.5 dosage group, 3 patients discontinued due to an adverse event. One patient (001-02-35) discontinued do to a malignant tumor of her left optic nerve. This was not seen as being related to the treatment. The second patient in the Estrogel® 2.5g dosage group discontinued due to the development of cholelithiasis 29 days after starting Estrogel® 2.5g. She subsequently underwent a cholecystectomy. The serious event was considered unlikely to be related to study medication, but this is debatable. The third patient in the Estrogel® 2.5 g dosage group discontinued due to headaches and nausea 14 days after starting Estrogel® 2.5g. This was probably related to the study medication.

The sponsor reported the percent of clinical laboratory data based on the ITT population in Tables 10.14.1.1 and 10.14.1.2. Although there were a few outliers, most of the abnormal values during the therapy were considered by the investigators to be of no clinical importance. The sponsor also reported in Table 29 (in the NDA submission), the markedly abnormal values for the ITT population for all treatment groups. No significant or worrisome trends were noted in any of the treatment groups. Of interest, and as a follow-up to elevated estradiol levels, in the safety evaluation, the sponsor reports 18/221 (8.1%) of patients had one or more elevated serum estradiol levels that exceeded a serum concentration of 200 pg/mL. A number of explanations were given as to the "seemingly implausible" estradiol levels, but these levels are probably factual when viewed in the context of endometrial effects in patients reviewed earlier.

Reviewer's comments/conclusions of study results:

In this randomized, twelve week, placebo-controlled study, the 1.25g dose of Estrogel® was statistically significantly different from placebo at the 4th treatment week and remained statistically significant to the 12th treatment week. At no time during the 12 weeks of treatment was the Estrogel® 1.25g dosage group *clinically different* from placebo that is, *there is no clinical separation of treatment effect from placebo of at least 2 moderate to severe hot flushes from baseline to the end of 12 weeks of treatment.* This is very unusual and has not been seen in this division in my 20 plus years of reviewing products for HT. To this reviewer, it implies variable absorption in individual subjects of estradiol from the skin. Effective transdermal products produce a statistically and clinically significant reduction in vasomotor symptoms by the 4th treatment week and this treatment effect continues through 12 weeks of treatment.

The results from the Estrogel® 2.5g dosage group are statistically different from placebo from the 4th treatment week until week twelve of treatment; however, it does not become clinically significantly different from placebo until week 5 and this clinically significant difference from placebo remains until the 12th week of treatment. This is slightly delayed efficacy when compared to approved transdermal and most oral products. Safety appears to be a significant problem for the 2.5g dosage. *The occurrence of 2 cases of endometrial hyperplasia in 71 treated patients is a substantial safety issue.* Furthermore, although the sponsor states that the reported high serum levels of estradiol in these patients may be the result of some type of contamination the fact remains that the hyperplasia rate is unacceptably high for such a short 12-week study and contamination of serum estradiol samples does not result in endometrial hyperplasia. Additionally, 4 cases of disordered proliferative endometrium were reported, In 3 of 4 cases the serum

estradiol levels ranged between 100 and 1140 pg/ml above baseline further supporting the concept of high serum estradiol levels having a negative effective upon the endometrium in some patients being treated.

Study CV141-002

The primary objective of this study was to compare the safety and efficacy of three strength of Estrogel® gel for the relief of menopausal symptoms and the efficacy of Estrogel® 1.25g to that of the Climara ® 12.5-sq cm system to these symptoms. Secondary endpoints were to include 1) changes in other menopausal symptoms, including sweating and sleep disturbance, 2) subjective measurements of well-being, 3) maintenance of vaginal epithelium and vaginal bleeding, and 4) reduction in vaginal atrophy.

This was a randomized, dose-ranging, active control, multicenter study. A double-blind procedure was used for patients receiving the three dosages of Estrogel® gel (give 3 dosage strengths). The Climara® patch system was used as an *open-label* comparative treatment.

The study plan called for enrolling 392 patients at approximately 20 investigational centers. Data from 361 enrolled at 22 centers were included in the ITT safety analysis, and data from 351 patients were included in the ITT efficacy analysis.

Inclusion criteria:

Inclusion criteria are identical to study Protocol CV141-001

Exclusion criteria:

Exclusion criteria are identical to study Protocol CV141-001.

Study Procedures:

Study procedures were consistent with Study protocol CV141-001 except for the use of the active control patch Climara®, which is manufactured by Berlex.

Study analysis was based on data from two population samples: intent-to-treat (ITT) efficacy and ITT safety. The ITT efficacy sample included all patients who were randomly assigned to receive study medication had at least one post-baseline efficacy assessment. The ITT safety sample included all patients who were randomly assigned to receive one of the dosages of Estrogel® or the open-label patch. In Protocol Amendments 3 and 4, the definition of ITT was expanded to include as many patients as possible.

The primary efficacy outcome measure was based on the change in the frequency of moderate-to-severe hot flushes from baseline through Week 12 as modified by Protocol Amendment 4. Each week of treatment was compared with the baseline. Analysis consisted of a one-way analysis of covariance (ANCOVA) and Dunnett's test for multiple comparison with the 0.625g dosage. The model has fixed factors: treatment, center, and treatment-by-center interaction; baseline value was the covariate, and the dependent variable was the mean change from baseline of the daily frequency of moderate-to-severe hot flushes. The change in the frequency of moderate-to-severe hot flushes achieved with the Estrogel® 0.75g dosage group was compared with that of the Estrogel® 1.25g and 2.5g groups and the open-label patch group by the ANCOVA model at each evaluation week using a Dunnett's test. The Estrogel® 1.25 dosage group was compared to the open-label patch group using a pair-wise comparison test. In addition,

the Estrogel® 2.5g dosage group was also compared with the open-label patch group by the ANCOVA model at each evaluation week.

Mean frequency of moderate-to-severe flushes was based on the number of flushes averaged from Day 1 through Day 7 for each week. Baseline means were calculated from the average frequencies reported at Screening Visits (Week –3) and 2 (Week –1).

Two types of analyses were performed: last observation carried forward (LOCF) and visit-wise. The LOCF analysis allows data from a preceding week to be carried forward in the analysis of any time point after week 1. Data for subjects who discontinued were carried forward in the analysis for all subsequent time points. Visit-wise analysis at each time point included only those subjects for whom data was available for that specified time point. Since efficacy conclusions are not based on visit wise analyses, I would not include any of this data in the review and state that only the ITT analysis with LOCF will be considered.

Pooling of center data was allowed in the descending order by the number of subjects in the ITT efficacy sample (center size). Data from the first center with fewer than five subjects per treatment group, having primary efficacy measurements in any treatment group, were pooled with that of centers having the fewest number of subjects. Pooling was to be continued until the "meta-center" contained data for at least five subjects in each treatment group.

Comment: See statistical comments and reviews by the Biometric team. Note in this review cycle a recheck of the residuals from the planned ANCOVA model showed that the normality assumption was not satisfied. Therefore, van Elteren's non-parametric was used as an alternative. Instead of the planned Dunnett's test for multiple comparisons, the Hochberg method was applied to the non-parametric results.

Safety

The safety analyses were based on all subjects who were randomized to treatment in the ITT safety analyses. The primary safety outcome will be the incidence of breast pain or beast tenderness during the treatment period. As appropriate, the incidence of breast pain or breast tenderness among treatment groups was compared using Fisher's exact test. Similarly, these analyses are conducted for treatment-emergent adverse events (TEAE) that occurred with high incidence, as deemed appropriate. The results of these analyses are presented along with the selected menopause-specific events.

TEAEs were tabulated by body system and categorized according to the Coding Symbols for the Thesaurus of Adverse Reactions Terms (COSTART). The incidence of all TEAEs, TEAEs leading to premature discontinuation from the study and the incidence of serious TEAEs are displayed by number and percent. Adverse events are presented according to frequency, severity, and attribution to study medication, and selected subgroups, if deemed appropriate.

The sample size for this study was calculated to assure that both safety and efficacy objectives could be assessed. Based on an estimated standard deviation of 4 for the change from baseline in the daily number of hot flushes reported in previous studies, a total of 392 patients, consisting of approximately 98 patients in each treatment group, was considered sufficient to show a difference between the Estrogel® dosage groups and the open-label patch group. A power of at least 80% at the 5% significance level was needed to detect a clinically meaningful difference in the change from baseline to Week 12 in the mean frequency of vasomotor symptoms in the Estrogel® 1.25g dosage group compared with that in the open-label patch group. This sample size also provided

sufficient power to detect a trend in the mean daily frequency of VMS across dosage levels of Estrogel®. *A clinically meaningful change from baseline in the daily number of hot flushes experienced by patients from baseline was defined as a reduction by 2 in the number of hot flushes per day compared with that reported at baseline.*

A Bonferroni adjustment was used (alpha =0.025) for comparison of 1) the changes in the frequency of VMS observed between the Estrogel® 1.25g dose and the open-label 12.5-sq cm patch, and (2) the trend in frequency for VMS across the 0.625g, 1.25g, and 2.5g doses of Estrogel® to maintain an overall 5% significance level. The sample size estimations above are based on an attrition rate of 20%.

Results

Table 5 (sponsor's table 10.1.2) shows the disposition of all patients in the analyses of safety and efficacy:

Table 5

Sponsor's Table 10.1.2 Vol.54

CHARACTERISTIC	Estrogel® 0.625g n (%)[1]	Estrogel® 1.25g n (%)[1]	Estrogel® 2.50g n (%)[1]	Climara® Patch N (%)[1]
Randomized to treatment	92 (100.0)	93 (100.0)	89 (100.0)	87 (100.0)
Intent-to-Treat (ITT) efficacy[2]	91 (98.9)	90 (96.8)	84 (94.4)	86 (98.9)
Completed Study[3]	78 (84.8)	80 (86.0)	75 (84.3)	82 (94.3)
Discontinued prematurely	14 (15.2)	13 (14.0)	14 (15.7)	5 (5.7)
Lost to follow-up	1 (1.1)	1 (1.1)	5 (5.6)	1 (1.1)
Withdrew consent	4 (4.3)	5 (5.4)	1 (1.1)	1 (1.1)
Withdrawn by investigator	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)
Adverse event	5 (5.4)	4 (4.3)	2 (2.2)	1 (1.1)
Other	3 (3.3)	2 (2.2)	5 (5.6)	1 (1.1)

[1] Percentages are based on subjects randomly assigned to treatment
[2] Subjects who were randomized to treatment and had at least one post-dateline efficacy assessment.
[3] The P-Value is 0.160 for patients who completed and discontinued prematurely across treatment groups based on Cochran-Mantel-Haenszel test.

Note: Overall, 46 patients discontinued prematurely from the study, with the lowest percentage being in the Climara® group. AEs were the most common reason for patients not completing the study. Patients withdrawing consent was the second most common reason for not completing the study. Protocol violation (compliance or presence of exclusion criterion) was the most commonly cited "other" reason for study discontinuation.

The sponsor presented baseline demographic information for all patients in table 10.2.2, Vol. 54. Due to the size of this table, information will be summarized. The mean age was approximately 51, with a range of age 23 to 79 years. The largest majority of patients were in the age range of 45 to 54 years for the 4 treatment groups. Ethnic origin in this study showed 294/361 (81.4%) of patients were White, 62/361 (17.1%) were Black, 21/361 (5.8%) were Hispanic, 3/361 (.083%) were Asian/Pacific Island, and 2/361 (.55%) were other. The mean height for the four treatment groups was approximately 64 inches. The mean weight for the four treatment groups was 159.2 lbs., which was not significantly different between groups, p=0.601. The mean Body mass index was 26.8kg/m^2, with no significant difference between treatment groups. Prior hormone use was reported in 57.3% of patients and 42.7 reported no prior drug therapy. The reported time since the

last menses was approximately 9.7 years. Eighty percent (80%) of patients had a natural menopause and 20% were reported to have had a surgical menopause (bilateral oophorectomy). Overall, there were no significant differences between treatment groups.

The majority of patients 301/361 (83.4%) of patients in this study took some type of concomitant medications during the study. The most common medications (those used by 10% or more of all patients) during the study are presented in table 10.2.3. This table is not reproduced, but the most common medications consisted of analgesics, nonsteroidal anti-inflammatory drugs, vitamins, and mineral supplements, all of which were over-the-counter. Medications used by patients included acetaminophen (23.5%) ibuprofen (27.1%), multivitamins (19.4%), aspirin (15.2%), calcium carbonate (10.8%), and vitamin E (10.8%).

Comment: Over-the-counter medications are consistent with other studies seeking ERT/HRT indications.

Most patients complied with the study treatments. Patients were deemed compliant provided they used at least 80% of the gel or patches dispensed to them. Compliance was comparable among the treatment groups with treatment groups demonstrating compliance of greater than 90%. Compliance could not be determined for 6 patients in the Estrogel® gel treatment groups (3 in the Estrogel® 1.25g group and 3 in the Estrogel® 2.5g group) because their gel mass data was missing. Compliance could not be determined in one patient in the open-label patch group. At week 12, 54/91 (59.3%), 60/90 (66.6%), 56/84 (66.6%) of patients in the Estrogel® 0.75, 1.25g and 2.5g groups, respectively had completed 7 days of diary data; in the Climara® patch group 62/86 (72%) had completed 7 days of diary data.

Comment: Compliance is consistent with other VMS studies with roughly 80-90% of study drug being taken, and less full compliance of diary data as the study progresses.

Efficacy

The mean frequency and severity of hot flushes among patients in the ITT efficacy population during each screening visit (Week –1 and Week –3) and averaged over the screening visits are presented in the following table:

Table 6

Mean (± SD) Frequency and Severity of Hot Flushes During Screening for the Intent-To-Treat Efficacy Population[1] of Protocol CV141-002

Sponsor's Table 12 Vol.54 (Unmodified)

Characteristic	Estrogel® 0.625g N = 91	Estrogel® 1.25g N = 90	Estrogel® 2.5g N = 84	Climara® Patch N = 88
Frequency of moderate-to-severe hot flushes[3] average of Screening Weeks –3 and –1	12.5 ± 11.11	11.7 ± 5.37	11.8 ± 4.74	10.9±4.62
Frequency of all hot flushes,[4] average of Screening weeks –3 and –1	13.7 ± 11.40	13.1 ± 5.83	13.4 ± 4.79	12.6±5.73
Severity of all hot flushes, [5] average of Screening Weeks –3 and –1	2.3 ± 0.27	2.4 ± 0.35	2.3 ± 0.32	2.3±0.30

[1] Based on the total number of patients in each category who were in the ITT efficacy population. The ITT efficacy population was defined as patients who were randomly assigned to receive study medication and had at least one postbaseline efficacy assessment.
[2] Based on analysis of variance
[3] Based on the number of moderate-to-severe hot flushes averaged from Day 1 through Day 7 of each week. When daily frequencies were missing, the mean was based on the days for which moderate-to-severe frequencies were recorded.
[4] Based on the total number of hot flushes averaged from Day 1 through Day 7 for each week. When daily frequencies were missing, the mean was based on those days on which frequencies were recorded.
[5] The severity of hot flushes was categorized by patients as none, mild, moderate, or severe. Severity ratings (0, 1,2, and 3, respectively) were assigned, and these ratings were used as multipliers for the reported number of daily hot flushes, which were averaged from Day 1 through Day 7 for each week to obtain a weekly severity score.

Sponsor's Addendum table 1.2.1 submitted on April 21, 2000 is the primary efficacy table in this review (Addendum table 1.2.1 is very similar to table 10.4.2.1 in Vol.54 except this table does not report data in quartiles). Addendum Table 1.2.1 is based on Dunnett's 2-sided test for multiple comparisons with Estrogel® 0.625g as the control. This model is based on: treatment, center, and treatment by center as fixed factors; baseline value as the covariate; and change from baseline in measured mean daily frequency of moderate-to-severe flushes as the dependent variable. Review of this table reveals the following points:

- At week 2, the Climara® patch is statistically different from Estrogel® 0.625g.
- The Climara® patch remains statistically different from Estrogel® 0.625g from week 2 through week 6; no statistical differences are noted from week 7 through week 12.
- At all treatment weeks the absolute reduction in number of hot flushes is greater in the Climara® patch.
- There appears to be no statistical difference between any of the three Estrogel® treatment groups; dose response was not demonstrated.

Comment: In this active control trial, Climara® 12.5 cm^2 demonstrated statistically significant greater decreases from baseline than did Estrogel® 0.625g group from Weeks 2 through 6. This is not surprising since Climara® 12.5 cm^2 is compared to

the lowest dose of Estrogel® 0.625g and this dose was deemed by the sponsor to be a non-effect dose. What is surprising is that there is no dose response demonstrated between all Estrogel® dosages and there appears to be no statistical trend or difference in efficacy between the 0.625 and the 1.25g dosages. Additionally, interpretation of the data relative to Climara® suffers from the fact that the Climara® patch was identifiable (open-label) in this study.

Table 22 (also table 10.6.4.1) is the primary efficacy table for severity of vasomotor symptoms in this review. Table 22 will be summarized. Severity was graded as none, mild, moderate, and severe as in the CV141-001 study. Results of mean severity showed a steady decrease in all treatment groups. The severity of hot flushes was reduced most in the Climara® treatment group, followed by the Estrogel® 2.5g group. It should be noted for each treatment week severity was reduced to a greater extent in the Climara® 12.5 cm^2 group compared to the Estrogel® 2.5g group. *It is also worth noting there is no difference between the 0.625g group and the 1.25g Estrogel® treatment groups in any of the 12 treatment weeks.*

Comment: Reduction in the severity of hot flushes is supportive of the mean change in frequency data. There appears to be little if any difference between the Estogel® 0.625g and the 1.25g dosage. A statistical trend favors the Climara® patch 12.5 cm^2 over Estrogel® 2.5g.

As an objective parameter, the sponsor studied the vaginal maturation index. The maturation index is the relative ratio of basal/parabasal cells, intermediate cells, and superficial cell evaluated from vaginal smears taken at screening (baseline) and at week 12. The results of sponsor's table 23 (and table10.7.2) in the NDA submission show that there were significant shifts from baseline to higher maturation at the final visit for the Climara group $p < 0.001$, Estrogel® 2.5g $p < 0.013$ and Estrogel® 0.625 $p < 0.003$. There was no significant shift in the Estrogel® 1.25g group, $p = 0.189$.

Comment: It is unclear in this study why Estrogel® 1.25g dose should not be comparable to the other regimens, especially at a targeted site such as the vagina.

The sponsor supplied Table 10.9.1.1 which displays the mean estradiol and estrone levels for the ITT safety sample. This table shows baseline and Week 12 mean levels of estradiol and estrone. Additionally median, standard deviation (SD), and minimum/maximal levels of estradiol and estrone were supplied. Review of this table shows normal levels of estradiol and estrone for the postmenopausal women at baseline. At 12 weeks, mean levels of estradiol are 93.9 (203.64), 67.1 (87.07), 180.7 (532.25), and 45.8 (39.93) pg/mL above baseline in the Estrogel® 0.625g,1.25g, 2.5g, and Climara® treatment groups, respectively. Median values of estradiol were 25, 32, 60, and 38.5 pg/mL above baseline for the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Mean estrone levels were 46.0 (30.52), 35.90 (41.0), 60 (62.5), and 45.8 (38.5) pg/mL in the Estroge® 0.625g, 1.25g. 2.5g and Climara® treatment groups, respectively. Minimal/Maximal levels of estradiol were 0.00-1130, 0.00-560.00, 0.00-4570, and 0.00-260 pg/mL in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® groups, respectively.

Comment: These results show the tremendous variation in estrogen levels achieved by this product. Standard deviations are greater than some serum mean levels achieved by Estrogel®. The minimal/maximal levels of estradiol are extraordinarily high and confirm wide variations in intersubject absorption of this product. Of interest, the serum levels achieved by Climara® are very close to those reported in the literature. See Pharmacokinetic (PK) review for additional information regarding levels of estradiol variations in the PK studies.

Safety

All adverse events were recorded. Adverse experiences were classified into a standardized terminology using the COSTART (Coding Symbols for Thesarus ReactionsTerms) version 4.0, by body system. Percentages are based on the number of patients in the ITT safety population for each study group. Patients may have reported multiple adverse events that coded to the same preferred term and body system; thus, totals do not necessarily reflect the sum of individual adverse events.

All patients who took medication were analyzed in the safety analysis. A total of 361 patients were included in the analysis of treatment emergent signs and symptoms (TESS). Ninety-two (92) were in the Estrogel® 0.625g dosage group, 93 were in the Estrogel® 1.25g dosage group, 89 were in the Estrogel® 2.5g dosage group, and 87 were in the Climara® treatment group. A total of 291 patients (80.6%) experienced one or more TESS during the study: 76 in the Estrogel® 0.625g group, 76 in the Estrogel® 1.25g group, 68 in the Estroge® 2.5g group, and 71 in the Climara® group.

Sponsor's table 27 (Vol. 1.54) reported TESS of 5% or more by any treatment group. The TESS is grouped by body system. As stated earlier, the body system total were not necessarily the sum of the individual study events since a patient could report two or more different study events in the same body system. Table 27 will now be summarized in a descriptive fashion due to the size of this table. **Under Body as a Whole:** headache was the most common adverse event. Headache was reported in 17 (18.5%), 21 (22.6%), 12 (13.5%) and 16 (18.4%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Infection was reported in 9 (9.8%), 17 (18.3%), 8 (9%), and 10 (11.5%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Abdominal pain was reported in 9 (9.8%), 7 (7.5%), 10 (11.2%), and 10 (11.5%) of patients in the Estroge® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Pain was reported in 5 (5.4%), 7 (7.5%), 9 (10.1%), and 8 (9.2%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Flu syndrome was reported in 5 (5.4%), 6 (6.5%), 2 (2.2%) and 8 (9.2%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups respectively. Asthenia was reported in 7 (7.6%),-4 (4.3%), 3 93.4%), and 6 (6.9%) of patients in the 0.625g,-1.25g, 2.5g and Climara® treatment groups, respectively. Back pain was reported in 4 (4.3%), 5 (5.4%), 5 (5.6%), and 3 (3.4%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups respectively.

Under Cardiovascular System: palpitations was reported in 5 (5.4%). 1 (1.1%), 1 (1.1%), and 2 (2.3%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. **Under Digestive system:** nausea was the most common adverse event. It was reported in 8 (8.7%), 6 (6.5%), 6 (6,7%) and 8 (9.2%) of patients in the Estrogel® 0.625g, 1.25g,-2.5g and Climara® treatment groups, respectively. Flatulence was reported in 4 (4.3%), 8 (8.6%), 10 (11.2%) and 6 (6.9%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Diarrhea was reported in 1 (1.1%), 4 (4.3%), 5 (5.6%), and 5 (5.7%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. **Under Nutritional disorders:** weight gain was reported in 5 (5.4%), 3 (3.2%), 2 (2.2%), and 1 (1.1%) of patients in the Estrogel® 0.625,-1.25, 2.5g and Climara® treatment groups, respectively. **In the Musculoskeletal system:** 10 (10.9%), 13 (14.0), 9 (10.1), and 4 (4.6%) of patients reported an adverse event. No specific symptoms such as arthritis, arthralgia, bone pain, etc. reached a 5% level. **Under Nervous system:** depression was reported in 7 (7.6%), 3 (3.2%), 2 (2.2%), and 5 (5.7%) of patients in the 0.625g,-1.25g, 2.5g, and Climara® treatment groups, respectively. Insomnia was reported in 2 (2.2%), 6 (6.55), 4 (4.5%),-and 4 (4.6%) of patients in the 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Nervousness was reported in 5 (5.4%), 4 (4.3%), 3 (3.4%) and 3 (3.4% of patients in the 0.615g,-1.25g, 2.5g and Climara® treatment groups, respectively.

Anxiety was reported in 5 (5.4%), 2 (2.2%), 0 (0.0%) and 4 (4.6%) of patients in the Estrogel ® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively.

Under Respiratory system: pharyngitis was reported in 3 (3.3%), 5 (5.45), 1 (1.1%), and 3 (3.4%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g, and Climara® treatment groups, respectively. Sinusitis was reported in 5 (5.4%), 1(1.1%), 0 (0.0%) and 1 (1.1%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g, and Climara® treatment groups, respectively. **Under Skin and Appendages:** rash was reported in 2 (2.2%), 8 (8.6%), 7 &.9%) and 4 (4.6%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g, and Climara® treatment groups, respectively. Application site reaction was reported in 0 (0.0%), 1 (1.1%), 0 (0.0%) and 18 (20.7%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. **Under Urogenital system:** breast pain was reported in 8 (7%), 13 (14.0), 22 (24.9%), and 16 (18.4%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Vaginitis was reported in 2 (2.2%), 7 (7.5%), 8 (9.0%), and 14 (16.1%) of patients in the Estroge® 0.625g, 1.25g, 2.5g, and Climara® treatment groups, respectively. Metrorrhagia was reported in 3 (3.3%), 5 (5.4%), 7 (7.9%), and 3 (3.4%) of patients in the 0.625g, 1.25g, 2.5g, and Climara® treatment groups, respectively. Endometrial disorder was reported in 4 (4.35), 2 (2.2%), 4 (4.5%), and 4 (4.6%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Leukorrhea was reported in 1 (1.1%), 5 (5.4%), 5 (5.6%), and 2 (2.3%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Suspicious Papanicolaou smear was reported in 4 (4.3%), 7 (7.5%), 0 (0.0%), and 2 (2.3%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Vaginal hemorrhage was reported in 1 (1.1%), 2 (2.2%), 1 (1.1%) and 5 (5.7%) of patients in the Estrogel® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively.

Comment: The incidence of TESS is consistent with other studies in which there is estrogen replacement or a combination of estrogen plus a progestin. Breast pain, headache, nausea and forms of vaginal bleeding are usually reported with similar percentages seen in this study. There is a slight dose respond effect noted in the Estrogel® groups related to bleeding (metrorrhagia), but not to vaginal hemorrhage. Interesting, the highest percentage of vaginal hemorrhage was noted in the Climara® group, which is not consistent with reported serum estradiol levels.

There were no deaths reported in this study.

Of additional interest, there were 9 reported cases of breast neoplasm. Breast neoplasm was reported in 2 (2.2%), 1 (1.1%), 3 (3.3%) and 3 (3.3%) patients in the Estroge® 0.625g, 1.25g, 2.5g and Climara® treatment groups respectively. Review of these cases revealed no carcinomas. Fibrocyctic disease of the breast was reported in 1 (1.1%), 1 (1.15), 2 (2.2%), and 2 (2.35) of patients in the Estroge® 0.625g, 1.25g, 2.5g and Climara® treatment groups, respectively. Uterine hemorrhage was reported in 0 (0.0%), 1 (1.1%), 2 (2.2%), and 0 (0.0%) of patients in the Estrogel® 0.625g. 1.25g, 2.5g, and Climara® treatment groups, respectively. *Endometrial hyperplasia* was reported in 0 (0.0%), 0 (0.0%), 1 (1.1%) and 2 (2.3%) of patients in the Estroge® 0.625g, 1.25g, 2.5g, and Climara® treatment groups, respectively.

Comment: One case of endometrial hyperplasia in the Estrogel ®2.5g dose and 2 cases of hyperplasia in the Climara® group are of concern. High levels of estradiol were shown in one Climara® patient.

Four (4) patients were withdrawn from the study because of adverse medical events in this study: I each in the 1.25g and 0.625g Estrogel® treatment groups (1.1%) and 2 in the Estrogel® 2.5g treatment group. Patient 002-15-07 in the 0.625g Estrogel® group

withdrew within 2 weeks of randomization due to idiopathic pancreatitis. Patient 002-01-14 in the Estrogel® 1.25g group withdrew within one month due to severe chest pain. Patient 002-20-04 in the Estrogel® 2.5g group withdrew because of severe abdominal pain secondary to an ovarian mass and previous diagnosed endometriosis. At surgery, extensive endometriosis was noted and the patient underwent a total abdominal hysterectomy and bilateral salpinoophorectomy. Patient 002-03-05 in the Estrogel® 2.5g group withdrew due to carpel tunnel syndrome for which she underwent carpel tunnel release surgery. All four cases were classified by the investigators as being unrelated to study medications; however, this is questionable since exacerbation of endometriosis by estrogens is not an unusual adverse event.

The sponsor reported the percent of clinical laboratory data based on the ITT population in tables 10.14.1.1 and Table 10.14.1.2. Although there were a few outliers, most of the abnormal values during therapy were considered by the investigators to be of no clinical importance. The incidence of markedly abnormal serum chemistry values at week 12 were reported for fasting glucose, triglycerides and LDL-C; however, the incidence of these abnormalities was fairly similar among the treatment groups. In addition, blood pressure measurements remained normal in over 90% of patients who had normal blood pressures at baseline.

8.1.4 Reviewer's comments/conclusions of study results:

In this randomized, dose-ranging, active control, multicenter study 3 dosages of Estrogel® were studied in a double blind manner against the active drug, Climara 12cm^2 patch. *This was not studied in a double-blind manner for various dosages of Estroge® but against the comparator.* Estrogel® 0.625g was the comparator arm in all analyses. The comparison of the 0.625g dose with the 1.25g and 2.5g dosages were not significantly different at any time point during this 12- week study. In addition, no dose response was demonstrated among the 3 Estrogel® dosages. Climara® was statistically significant different in the reduction of moderate-to-severe VMS from the Estroge® 0.625g dose at weeks 2, 3, 4, and 5. Release rates of estradiol from Estroge®l are highly variable among patients in all treatments groups and may account for the less than robust results seen in this trial of 3 dosages of Estroge®.

VI Integrated Review of Efficacy

The sponsor performed two randomized trials, a placebo-controlled study and a comparative study against an approved transdermal patch, Climara®. In the placebo controlled study, Estrogel® 1.25g and 2.5g doses were compared to placebo. Results in the ITT analyses when compared to placebo demonstrate Estrogel® 2.5g is statistically different from placebo by week 4 (p= 0.0201) and this is maintained through 12 weeks of treatment. However, a clinically meaningful reduction of at least 2 hot flushes per day was not demonstrated until the 5th treatment week; this treatment effect continued through the remaining weeks of treatment. Results of the Estrogel® 1.25g dose demonstrate statistical efficacy at week 4 (p=0.0189) and this continued to week 12. However, a clinically meaningful reduction of at least 2 hot flushes per day compared to placebo was *never* achieved during 12 weeks of treatment. Importantly, there is no consistency between clinical data and statistical data demonstrated in this trial compared to what is usually seen in the review of approved estrogen products used to treat VMS. Statistical and clinical efficacy data are usually consistent for estrogen products and follow a pattern of decreasing frequency and severity of VMS; both frequency and severity are decreased by treatment week 4 and this treatment effect continues through the remaining weeks of treatment.

Estrogel® 0.625g was the comparator arm against Estrogel® 1.25g, Estrogel® 2.5g and Climara® 12.5 cm^2. The comparisons of Estrogel® 0.625g are not statistically different from the 1.25g and 2.5g dosages at any time period in this 12-week trial. In addition, at week 2 through 5, Climara® is statistically different from the Estrogel® 0.625g dose. Of interest, when a second statistical review was utilized using van Eltern's non-parametric method with the Hochberg adjustment for multiple comparisons, the treatment effect for both frequency and severity of moderate to severe VMS were shown to be similar to those seen in the CV141-001 study for the Estrogel®1.25g and 2.5g dosages. In summary, reviewed data in study CV141-002 only add to the concern about effectiveness of multiple dosages of Estrogel®. Data in this study are neither robust nor suggestive of a minimally effective dose.

As an objective parameter of effectiveness, the sponsor studied the vaginal maturation index. In both studies the 2.5g dose showed a statistically significant increased in the basal/parabasal versus superficial cell ratio. A statistical difference was shown for the 1.25g dose in the placebo trial but not in the comparative trial. In the comparative trial both the Estrogel ®0.625g and Climara® showed statistically significant differences from baseline.

VII Integrated Review of Safety

The sponsor included 582 US patients in the integrated summary of safety for studies CV-141-001 and CV-141-002. There were 4 human Pharmacokinetics and Bioavailability studies of 108 women, and 14 other studies of approximately 1240 women, most conducted in Europe, that evaluated Estrogel® in the relief of vasomotor symptoms and other estrogen-related indications. Retrieved safety data was classified into a standardized terminology using the COSTART system. Safety data from studies CV141-001 and CV141-002 were pooled.

Deaths

No deaths were reported in this clinical program.

Significant/Potential Significant Events

In studies CV-141-001 and CV-141-002 approximately 15 patients discontinued treatment due to a treatment emergent signs and symptoms (TESS), 5 (5.4%), 6 (3.6%), 4 (2.5%) in the Estrogel® 0.625, 1.25g, 2.5g group respectively. One (1.1%) withdrew in the Climara® treated group. Of this total, 7 has a serious TESS 1 (1.1%), 2 (1.2%), and 4 (2.5%) in the Estrogel® treatment groups, respectively. Of the 7 serious TESS, 5 of 7 were probably not related to the drug. Two serious TESS patients developed idiopathic pancreatitis and exacerbation of endometriosis symptoms that required surgery. Adverse events reported by > 5% in each treatment group include the following: headache 77 (18.2%), nausea 33 (7.8%), rash 25 (5.9%), breast pain 59 (14%), menorrhagia/metrorrhagia 21 (5.0%) and vaginitis 26 (6.2%). In addition, application site reactions was reported in 18 (20.7%) of patients with Climara®. Endometrial hyperplasia was reported in 3 Estrogel® patients (1 with atypia), 2 in the placebo-controlled study and 1 in the comparative study. Of interest, 2 patients in the Climara® 12.5 cm^2 group developed endometrial hyperplasia in the CV141-002 study. As stated earlier in the previous section, 3 cases of endometrial hyperplasia are an approvability issue.

Laboratory Findings/Vital Signs

Based on laboratory data available in these studies, no laboratory abnormality was directly attributable to Estrogel®. Additionally, no clinically important vital sign

abnormalities were identified. Abnormalities in all study groups occurred inconsistently and generally were not associated with adverse events.

Safety Update

On December 8, 1999, the sponsor submitted a letter stating that all available safety information had been reported in the original NDA. There are no on-going clinical studies; all studies were completed prior to the time of this NDA submission. Therefore, there is no safety information to report.

VIII Dosing and Administrative Issues

In general, the proposed label, dated January, 2004 corresponds to the Labeling Guidance for Non-Contraceptive Estrogen Drug Products dated April 1999. This label will not be reviewed in detail since it is the recommendation of this reviewer that this product not be approved.

IX Use in Special Populations

The sponsor conducted no studies in special populations.

X Conclusions and Recommendations

The sponsor has not demonstrated through two adequate and well-controlled clinical trials the effectiveness of Estrogel®. Estrogel® 2.5g demonstrated statistical effectiveness at week 4 of treatment and this continued through week 12; however, clinical effectiveness was delayed until week 5 of treatment. Importantly, this product does not appear to be safe when compared to other HT products in clinical trials. Overall, in studies CV141-001 and CV141-002 there were 3 cases of endometrial hyperplasia (1 with atypia), which appear to be confirmed by high serum levels of estradiol, and 5 cases of disordered proliferative endometrium, suggesting that some patients are absorbing substantially greater amounts of estradiol that produce untoward effects upon the endometrium. Supporting this are pharamacokinetic studies that demonstrate, in some subjects, estradiol levels exceeding 100 pg/ml above baseline, with wide standard deviations, further suggesting pharmacological, not physiological amounts of estrogen are being absorbed in some patients. Therefore, this reviewer can not recommend approval of Estrogel® 2.5g.

Estrogel® 1.25g did demonstrate statistical effectiveness at week 4 through 12, but never demonstrated clinical effectiveness during the 12 weeks of treatment. At stated earlier, this is very unusual and is not seen with transdermal products. In the opinion of this reviewer, the problem can be summarized by variant amounts of estradiol being absorbed over the entire arm by individual patients. Clinically, it appears some patients absorb sufficient amount of estradiol to decrease vasomotor symptoms while other patients do not absorb enough estradiol to demonstrate efficacy. This concept is supported by pharmacokinetic studies that demonstrate mean levels of estradiol in a therapeutic range, but standard deviations that are greater than the mean levels with a net effect that some patients absorb too much Estrogel® and some patients absorb too little. Therefore, this reviewer can not recommend approval of the 1.25g dose because clinical effectiveness, *as previously defined in HFD-580*, has not been demonstrated.

The sponsor should institute another clinical trial using the 1.25g dosage pump (sponsor's preferred method of dosage) rather than the spatula technique which was used in studies. To improve absorption the dosage should be applied on a specified area on the outer surface of the arm. This study should be adequately powered to demonstrate a clinical and statistical difference in effectiveness. A pre-study statistical plan should be approved with HFD-580 prior to initiation of this study.

1.0 The Approach to Evaluation of Drugs for the Treatment of Menopausal Symptom Therapy (MST) After Publication of Data from the Women's Health Initiative (WHI) Study

In the Agency's January 2003 Draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" it states, for estrogen alone products intended to treat moderate to severe vasomotor symptoms, that "the primary efficacy analyses show a clinically and a statistically significant reduction, within 4 weeks of initiation of treatment and maintained throughout 12 weeks of treatment, in both the frequency and severity of hot flushes in the treated groups compared with the control groups." The following four co-primary endpoints were recommended in the Draft Guidance.

1. Mean change in frequency of moderate to severe vasomotor symptoms (MSVMS) from baseline to week 4
2. Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 12
3. Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 4
4. Mean change in severity of moderate to severe vasomotor symptoms from baseline to week 12

Since the publication of multiple articles related to the WHI studies (beginning July 2002), the Division has been reexamining its approach to regulating hormonal and other products for MST. This reevaluation has been taking place in consultation with CDER officials at all levels. The reevaluation continues as of the date of this memorandum and includes an intensive internal examination of issues discussed in the draft January 2003 Guidance.

The Division is evaluating products for MST in various phases of both the IND and NDA process. In addition, the Division is tasked with continuous evaluation of products currently on the market. Although there are many issues to be examined surrounding the safe and efficacious use of products for MST, there is general consensus in medical practice that many adverse events and risks are dose-related. Therefore, postmenopausal women should have access to the lowest doses that are effective for a particular indication. The Division Director has became concerned that strict adherence to the efficacy endpoints, as presented in the January 2003 Draft Guidance, may have the unintended consequence of limiting availability of a lower dose of a particular product that may be effective in some meaningful proportion of women.

2.0 ESTROGEL 1.25mg (NDA 21-166), Evidence and Conclusions

The data presented in NDA 21-166 (Study CV141-001), demonstrate that ESTROGEL 1.25G statistically meets the recommended endpoints (as described in the 2003 Draft Clinical Evaluation Guidance) for efficacy compared to placebo as measured by mean change from baseline for frequency of moderate to severe vasomotor symptoms at weeks 4 and 12 and also for severity of moderate to severe vasomotor symptoms at weeks 4 and 12.

The primary reviewer maintains, however, that the difference between the mean changes from baseline for frequency at weeks 4 and 12 between the drug product and placebo is not clinically significant. The reviewer defines clinically significant as a mean difference of two hot flushes per day. The primary reviewer has no such definition of clinical significance regarding severity of hot flushes.

The Medical Team Leader believes (see Team Leader memo) and I agree that the change from baseline data in study CV141-001 does support the effectiveness of ESTROGEL 1.25G. I believe that post-WHI the definition of what is clinically significant by traditional standards should be a reexamined because rigorous application of these standards may have the unintended consequence of preventing women access to lower doses of drug (that are reasonably effective) that may have improved safety.

Additionally, ESTROGEL 1.25G may not be the lowest effective dose for the vasomotor symptom (VMS) and vulvar and vaginal atrophy (VVA) indications and, therefore, a lower dose should be studied.

3.0 Regulatory Recommendations

I recommend that NDA 21-166, ESTROGEL 1.25 G, be approved for the treatment of moderate to severe vasomotor symptoms (MSVMS) and moderate to severe symptoms of vulvar and vaginal atrophy (MSVVA) associated with the menopause.

I further recommend that the Sponsor conduct a study to determine the lowest effective dose of ESTROGEL for MSVMS and MSVVA

Daniel A. Shames

Director, Division of Reproductive and Urologic Drug Products

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