[a] Based on analysis of covariance with the screening value as covariate and terms for treatment and stratum (intact uterus versus hysterectomy).

Table 5 shows the analyses of the change from baseline in the mean severity score index of hot flushes for weeks 4 and 12. In the submission, the daily severity score index was determined by calculating a weighted average of hot flush severity (scored as mild = 1, moderate = 2, and severe = 3) with weighting proportional to the number of hot flushes for each severity level. Utilizing the Sponsor's calculation for the daily severity score index, the Estrasorb™ treatment group is effective in reducing the severity of hot flushes at both time points ($p<0.001$ at weeks 4 and 12) as compared with placebo. See Table 5.

Table 5: Change From Screening in the Severity Score Index[a] of Hot Flushes During Treatment, Intent-to-Treat Population, Most Recent Value Carried Forward

Time Point	Placebo	Estrasorb™
Baseline	(N = 100)	(N = 100)
Mean Severity Score per Day (SD)	33.55 (16.11)	33.17 (16.93)
Week 4	(N = 97)	(N = 96)
Mean Severity Score per Day (SD)	19.27 (15.83)	11.77 (15.12)
Mean Change from Baseline (SD)	-15.62 (12.30)	-21.32 (16.55)
p-value versus Placebo[b]	NA	<0.001
Week 12	(N = 90)	(N = 90)
Mean Severity Score per Day (SD)	15.60 (16.63)	5.46 (9.51)
Mean Change from Baseline (SD)	-18.44 (14.52)	-27.95 (19.38)
p-value versus Placebo[b]	NA	<0.001

Source: Adapted for NDA 21-371data submitted June 29, 2001, Volume 25, Tables 10.0 and 10.1, pages 135-141

SD = Standard deviation; NA = Not applicable

[a] The severity score index is a weighted average of hot flush severity (scored as mild = 1, moderate = 2, and severe = 3) with weighting proportional to the number of hot flushes for each severity level.

[b] Based on analysis of covariance with the screening value as covariate and terms for treatment and stratum (intact uterus versus hysterectomy).

Reviewer's Comments

The Agency's proposed 2003 clinical evaluation guidance for industry recommends four independent co-primary endpoints for clinical trials conducted to demonstrate safety and efficacy for the treatment of moderate to severe vasomotor symptoms associated with the menopause:

- **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.**

To demonstrate mean change in severity independent from frequency, it is standard practice in DRUDP to utilize a severity score to demonstrate the mean change in severity of hot flushes between baseline and weeks 4 and 12. The daily severity score is determined by calculating the sum of recorded daily severity (the number of mild hot flushes x 1 added to the number of moderate hot flushes x 2 added to the number of severe hot flushes x 3) and dividing this number by the total number of hot flushes on that day. As previously noted, the Division's Statistical Reviewer recalculated the mean change in severity from baseline to week 4 and week 12 utilizing a severity score as described above. These results show that 3.45 grams of Estrasorb™ containing 8.625 mg of estradiol (2.5 mg of estradiol/gram) is effective in reducing the severity of hot flushes at weeks 4 and 12 as compared to placebo. See Table 6.

Table 6: Change From Screening in the Severity Score[a] of Hot Flushes During Treatment, Intent-to-Treat Population, Most Recent Value Carried Forward

Time Point	Placebo	Estrasorb™
Baseline	**(N = 100)**	**(N = 100)**
Mean Severity Score per Day (SD)	**2.44 (0.37)**	**2.36 (0.36)**
Week 4	**(N = 97)**	**(N = 96)**
Mean Severity Score per Day (SD)	**1.99 (0.81)**	**1.47 (1.03)**
Mean Change from Baseline (SD)	**-0.45 (0.75)**	**-0.89 (1.04)**
p-value versus Placebo[b]	**NA**	**<0.0010**
Week 12	**(N = 90)**	**(N = 90)**
Mean Severity Score per Day (SD)	**1.99 (0.98)**	**0.92 (1.00)**
Mean Change from Baseline (SD)	**-0.55 (0.91)**	**-1.44 (1.04)**
p-value versus Placebo[b]	**NA**	**<0.0001**

Source: Statistical Reviewer's Review
SD = Standard deviation; NA = Not applicable
[a] The severity score per day is determined by calculating the sum of recorded daily severity and dividing this number by the total number of hot flushes on that day.
[b] Based on analysis of covariance with the screening value as covariate and terms for treatment and stratum (intact uterus versus hysterectomy).

Supportive Study E98-2

Study E98-2, a Phase 2/3 study, was a multicenter (6 study sites), double-blind, placebo-controlled clinical trial in which 125 postmenopausal women were randomized to either placebo or 1.15 grams, 2.30 grams, or 3.45 grams of Estrasorb™ containing 2.5 mg of estradiol/gram. Treatment duration was four weeks. Subjects in all four-treatment groups received three 1.15 gram color-coded pouches (green, yellow and white). The three pouches were considered one dose. Subjects randomized to the placebo treatment group applied only placebo to the anterior surface of both thighs and calves (green, yellow, and white pouches all contained placebo). Subjects randomized to the 1.15 gram Estrasorb™ treatment group applied 2.5 mg of estradiol/gram to one anterior thigh from the green pouch, placebo to the opposite anterior thigh from the yellow pouch, and placebo to the right and left calf areas from the white pouch. Subjects randomized to the 2.30 gram Estrasorb™ treatment group applied 2.5 mg of estradiol/gram to one anterior thigh from the green pouch, 2.5 mg of estradiol/gram to the opposite anterior thigh from the yellow pouch, and placebo to the right and left calf areas from the white pouch. Subjects randomized to the 3.45 gram Estrasorb™ treatment group applied 2.5 mg of estradiol/gram to the anterior surface of both thighs and to both calves. Subjects showered or bathed prior to administering a dose of study medication.

The subjects completed a daily diary card as described under Study E99-1. Trough serum estradiol, estrone, estrone sulfate, and FSH serum concentrations were measured on days 1 (end of screening), 8 (end of placebo run-in period), 15, 22, 29, and 36. All blood draws occurred in the morning before dosing.

The primary efficacy endpoint for Study E98-2 was the change from baseline for the average daily count of moderate to severe hot flushes during treatment weeks 3 and 4 combined. However, combined weeks 3 and 4 are not the recommended primary efficacy endpoints for a VMS indication (weeks 4 and 12 are the recommended endpoints). Fortunately, the Sponsor separately reported the observed average daily number of moderate to severe hot flushes and the change from baseline for treatment weeks 1 through 4. The mean change in the number of moderate to severe hot flushes from baseline to week 4 is the subject of this review of Study E98-2. For Study E98-2, the secondary efficacy analyses consisted of evaluations of treatment groups for clinical response (defined as the absence of moderate to severe hot flushes during a seven-day interval) and trough serum concentrations of estradiol, estrone, estrone sulfate, and FSH.

There were 125 subjects randomized to participate in Study E98-2 (32 in placebo, 32 at 1.15 grams, 30 at 2.30 grams, and 31 at 3.45 grams of Estrasorb™). All 125 randomized subjects were included in the ITT population.

A total of 8 subjects discontinued the study early (3 in the placebo treatment group, and 5 in the combined Estrasorb™ treatment groups). Three of the 8 early discontinuations were due to enrollment violations (two not meeting the FSH and/or estradiol entry criteria, and one abnormal mammogram). Two subjects discontinued due to the development of an adverse event (1 for mild dyspareunia and uterine spasm in the placebo group, and 1 for pain and myasthenia in the 1.15 gram Estrasorb™ treatment group). Two subjects voluntarily withdrew consent, and one subject was non-compliant after she stopped treatment after getting a cold.

The demographic and background characteristics of subjects in Study E98-2 were similar to Study E99-1. The mean age at study entry was 51.2 years, 80% of subjects were white (100 of 125 subjects) and 18% of subjects were black (23 of 125 subjects). A total of 31 subjects had protocol violations (7 in the placebo treatment group, and 24 in the combined Estrasorb™ treatment groups). One of the most common protocol violations was that 10 subjects (8%, 10 of 125 subjects) had less than seven moderate to severe hot flushes per day or 60 per week at baseline (1 in the placebo treatment group and 9 in the combined Estrasorb™ treatment groups). In addition, 10 subjects (8%, 10 of 125 subjects) had final blood draws that were not within 24 hours of their last visit.

The mean duration of exposure to study medication during the active treatment period in Study E98-2 was 27.2 days in all treatment groups combined.

The results of Study E98-2 show that the mean average daily moderate to severe hot flush count at baseline was similar for the placebo treatment group (11.50/day) and the three Estrasorb™ treatment groups (ranged from 9.59 to 11.20/day). Relative to the placebo treatment group, all three of the Estrasorb™ treatment groups showed a greater reduction in the mean number of moderate to severe hot flushes throughout the 4-week treatment period. The largest reduction in the mean number and mean change of moderate to severe hot flushes from baseline to week 4 was seen in the 3.45 gram Estrasorb™ treatment group (decreased from a mean baseline number of 9.93/day to 1.71/day at week 4, mean change of –8.12/day). The 2.30 gram and 1.15 gram Estrasorb™ treatment groups showed slightly lower, yet similar results. The 2.30 gram Estrasorb™ treatment group decreased from a mean baseline number of 11.20/day to 3.66/day at week 4 with a mean change at week 4 of –6.62 per day. The 1.15 gram Estrasorb™ treatment group decreased from a mean baseline number of 9.59/day to 3.18/day at week 4 with a mean change at week 4 of –6.32 hot flushes per day. The placebo treatment group decreased from a mean baseline number of 11.50/day to a mean number of 6.24/day at week 4 with a mean change at week 4 of –5.06 hot flushes per day. See Table 7. Based on these results, the 3.45 gram Estrasorb™ treatment group (containing 2.5 mg of estradiol/gram) showed the most clinically significant reduction in mean number of hot flushes versus placebo per day followed by the 2.30 grams Estrasorb™ treatment group and the 1.15 gram Estrasorb™ treatment group (reduction of 3.06 hot flushes per day for the 3.45 gram dose, 1.56 hot flushes per day for the 2.30 gram dose, and 1.26 hot flushes per day for the 1.15 gram dose).

Table 7: Change in the Mean Daily Number of Moderate to Severe Hot Flushes in Study E98-2, Intent Intent-to-Treat Population

Time Point	Treatment Group			
		Estrasorb™		
	Placebo (N = 32)	1.15 Grams (N = 32)	2.30 Grams (N = 30)	3.45 Grams (N = 31)
Baseline Mean Number per Day (SD)	11.50 (4.83)	9.59 (4.24)	11.20 (5.63)	9.93 (4.11)
Week 4	(N = 29)	(N = 31)	(N = 27)	(N = 29)
Mean Number per Day (SD)	6.24 (5.58)	3.18 (4.55)	3.66 (4.99)	1.71 (2.56)
Mean Change from Baseline (SD)	-5.06 (7.30)	-6.32 (4.41)	-6.62 (3.77)	-8.12 (5.27)
p-value versus Placebo[a]	NA	0.024	0.188	<0.001

Source: Adapted from NDA 21-371 data submitted June 29, 2001, Volume 43, Panel 11B, pages 79-80 and Panel 11C, pages 82-83.

SD = Standard deviation, NA = Not applicable

[a] P-value for the treatment group comparisons are obtained from a ranked ANCOVA model including effects for treatment, baseline average daily count of moderate to severe hot flushes, BMI, and stratum (intact uterus versus hysterectomy).

In addition, the number and percent of subjects in Study E98-2 who reported no moderate to severe hot flushes at week 4 showed a 3 to 5 times more favorable response for the 3.45 gram Estrasorb™ treatment group. Forty-five percent (45%) of subjects (14 of 31 subjects) in the 3.45 gram Estrasorb™ treatment group reported no moderate to severe hot flushes at week 4 compared with 9% for placebo (3 of 32 subjects at week 4). However, 17% of subjects in the 2.30 gram Estrasorb™ treatment group (5 of 30 subjects) and 22% of subjects in the 1.15 gram Estrasorb™ treatment group (7 of 32 subjects) also reported no moderate to severe hot flushes at week 4. Based on these findings, the 2.30 gram Estrasorb™ treatment group and the 1.15 gram Estrasorb™ treatment group produced similar results that were greatly exceeded by the 3.45 gram Estrasorb™ treatment group.

However, Study E98-2 showed a statistically significant decrease in the mean number of moderate to severe hot flushes from baseline to end-of-study for the 1.15 gram and 3.45 gram Estrasorb™ treatment groups compared to the placebo treatment group at week 4 ($p=0.024$ and $p<0.001$, respectively). There was no statistically significant difference observed between the 2.30 gram Estrasorb™ treatment group and placebo at week 4 ($p=0.188$) even though the mean change in average daily moderate to severe hot flushes for the 2.30 gram dose is comparable to the mean change for the 1.15 gram dose (–6.62 and –6.32 at week 4, respectively).

In Study E98-2, the average trough estradiol serum concentrations increased from baseline through week 3 and then decreased slightly through the last clinic visit for the Estrasorb™ treatment groups. At end-of-study, the trough estradiol serum concentrations were highest in the 3.45 gram Estrasorb™ treatment group (40 pg/ml), followed by the 2.30 gram Estrasorb™ treatment group (34 pg/ml), and the 1.15 gram Estrasorb™ treatment group (23 pg/ml). The pattern of average trough serum estrone concentrations was similar to the pattern observed for the trough serum estradiol concentrations.

No deaths occurred in Study E98-2. Among the 125 subjects in the safety population, treatment-emergent adverse events were experienced by 53% of subjects in the placebo treatment group (17 of 32 subjects), 47% in the 1.15 gram Estrasorb™ treatment group (15 of 32 subjects), 37% in the 2.30 gram Estrasorb™ treatment group (11 of 30 subjects), and 68% of the 3.45 gram Estrasorb™ treatment group (21 of 31 subjects). Headache was the most frequently reported adverse event in the four treatment groups (range of 6% to 16%).

Reviewer's Comments

Study E98-2 is considered supportive because the study treatment duration was only 4 weeks. However, Study E98-2 does provide dose response data for three Estrasorb™ treatment groups versus placebo for the first primary efficacy endpoint for VMS at week 4. For a VMS indication, the primary efficacy analysis should show both a clinically and statistically significant reduction in the frequency and severity of hot flushes within 4 weeks of initiation of treatment that should be maintained throughout 12 weeks of treatment.

A dose response gradient was not clearly observed in Study E98-2 (e.g., more response to treatment as the dosage strength increases from 1.15 grams to 3.45 grams). Both the 1.15 gram and 3.45 gram Estrasorb™ treatment groups showed a statistically significant reduction in the number of hot flushes compared to placebo at week 4 ($p=0.024$ and $p<0.001$, respectively). The 2.30 gram Estrasorb™ treatment group did not ($p=0.188$) even though the mean change in average daily moderate to severe hot flushes for the 2.30 gram dose is comparable to the mean change for the 1.15 gram dose (-6.62 and -6.32, respectively). This lack of a linear reduction in vasomotor symptoms relief is unexplained given the trough serum estradiol concentrations reported for Study E98-2 (23 pg/ml for the 1.15 gram dose, 34 pg/ml for the 2.30 gram dose, and 40 pg/ml for the 3.45 gram dose of Estrasorb™). In the Division's experience from reviews of other clinical trial data for a VMS indication, efficacious drug products produce serum estradiol concentrations that are increased at least 25 to 30 pg/ml above baseline.

Also, in the Division's experience from reviews of other clinical trial data for a VMS indication, efficacious drug products produce a reduction of at least 2 hot flushes per day above placebo. In Study E98-2, the 3.45 gram Estrasorb™ treatment group (containing 2.5 mg of estradiol/gram) showed the most clinically significant reduction in mean numbers of hot flushes versus placebo per day (reduction of 3.06 hot flushes per day for the 3.45 gram dose) followed by the 2.30 gram Estrasorb™ treatment group (reduction of 1.56 hot flushes per day), and lastly by the 1.15 gram Estrasorb™ treatment group (1.26 hot flushes per day).

Overall, the 3.45 gram Estrasorb™ treatment group demonstrated a stronger clinical and statistical response than the 2.30 gram and 1.15 gram Estrasorb™ treatment groups, and produced a larger reduction in the mean number of moderate to severe hot flushes from baseline to week 4. Nonetheless, the statistically significant results demonstrated for the 1.15 gram Estrasorb™ treatment group combined with the trough serum estradiol concentrations reported for Study E98-2 leave doubt that the lowest effective dose of Estrasorb™ has been determined.

We recommend that a second full 12-week adequately powered safety and efficacy study be conducted as a Phase 4 commitment to determine if lower doses of Estrasorb™ are effective for the treatment of moderate to severe vasomotor symptoms associated with the menopause. We recommend that the Sponsor consider the inclusion of one or more lower doses of Estrasorb™ than the 3.48 gram dose submitted for consideration in this submission.

6.4. Efficacy Conclusions

Data from a total of 200 subjects in Study E99-1 was presented in this submission for the treatment of moderate to severe vasomotor symptoms associated with the menopause. From the data presented in Study E99-1, 3.45 grams of Estrasorb™ containing 8.625 mg of estradiol (2.5 mg of estradiol/gram), applied daily, shows a significantly lower number and severity of hot flushes compared with placebo. These differences are clinically and statistically significantly different from placebo at weeks 4 and 12 ($p<0.001$).

The results of the pouch expression study confirmed a mean 0.07 gram increase in pouch content expressed from two 1.74 gram foil-laminated pouches (packaging proposed in this submission) as compared with three 1.15 gram foil-laminated pouches (packaging used in Phase 3 Study E99-1). The difference in daily systemic delivery of estradiol may be considered small (0.57 mg of estradiol/day versus 0.50 mg of estradiol/day, respectively).

The reviewer recommends approval of 3.48 grams of Estrasorb™ containing 8.7 mg of estradiol (2.5 mg of estradiol/gram), applied daily, delivered in two 1.74 gram foil-laminated pouches, for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

7. INTEGRATED REVIEW OF SAFETY

7.1 Brief Statement of Findings

The integrated data presented in the submission for the 335 subjects in Phase 1 Study E98-1and placebo-controlled Studies E98-2, and E99-1 shows that the overall safety profile of 3.45 grams of Estrasorb™ topical emulsion applied daily is acceptable. No deaths occurred during the conduct of any of these studies. Seven serious adverse events that occurred in 6 subjects (4 in placebo treatment group and 3 in the 3.45 gram Estrasorb™ treatment group), were reported during 60.3 mean days of exposure (range of 1 to 99 days of exposure) to placebo or 1.15 grams, 2.30 grams, 3.45 grams of Estrasorb™. Seven subjects discontinued due to treatment-emergent adverse events. Application site reaction was the most common adverse event that led to discontinuation (29%, 2 of the 7 discontinuations).

7.2 Materials Utilized in the Review

Studies E98-1, E98-2, and E99-1 were integrated because all of these controlled studies used the [ ] formulation of Estrasorb™. Studies N95-3, N96-1 and N97-3 were reviewed but were not included in the integrated safety database because these studies were performed using the "old" [ ] formulation of Estrasorb™ containing only [ ] water. Three additional studies, Study E2000-1 (Phase 1 single-dose, residual estradiol study submitted 9/12/02), Study E2002-1 (Phase 1 partner transfer study submitted 5/19/03), and Study E2002-2 (Phase 1 sunscreen and photosensitivity study submitted July 11, 2003) that did use the "new' [ ] formulation were reviewed as individual studies. The safety population was defined as all randomized subjects who received at least one application of study medication including the placebo run-in period in Studies E99-1 and E98-2.

7.3 Description of Patient Exposure

A total of 335 subjects were randomized across Studies E98-1, E98-2, and E99-1and included in the integrated safety database. One hundred thirty four (134) subjects received placebo (40%, 134 of 335 subjects). A total of 201 subjects received Estrasorb™ with 139 of these Estrasorb™ subjects receiving the 3.45 gram Estrasorb™ dose containing 2.5 mg of estradiol/gram (41% 139 of 335 subjects), the dosage strength that is the subject of this NDA. The remaining 62 subjects received either 1.15 grams of Estrasorb™ (32 subjects) or 2.30 grams of Estrasorb™ (30 subjects).

A total of 90 additional subjects received treatment in non-integrated studies. Fifty (50) of 90 subjects received the Estrasorb™ formulation that contained [redacted] water (Studies N95-3, N96-1, and N97-3). The other 40 subjects received the [ ] formulation containing [redacted] water (Studies E2000-1, E2002-1 and E2002-2).

Due to the varying periods of treatment in each of the three studies in the ISS (8 days for Study E98-1, 4 weeks for Study E98-1, and 12 weeks for Study E99-1), the mean duration of exposure to active study medication was higher in the placebo treatment group (67.7 days) than in the overall Estrasorb™ treatment groups (53.0 days). This difference is due to the fact that about half of the subjects in the overall Estrasorb™ treatment groups (93 of 201) participating in Study E98-2 had only a 4 week treatment period. When one considers the 12-week Study E99-1alone, the mean duration of exposure to active study medication in the ITT population was 81.1 days for the placebo treatment group and 80.5 for the Estrasorb™ treatment group.

Baseline demographics were similar between the placebo and the overall Estrasorb™ treatment groups for the three integrated studies in the ISS. See Table 8 for a summary of demographic information for combined Studies E98-1, E98-2, and E99-1.

Table 8: Summary of Demographic Information for Studies E98-1, E98-2, and E99-1, Combined Safety Population

	Treatment Groups	
Parameter	Placebo N (%)	Estrasorb™ N (%)
Subjects in the ISS Population	134 (40%)	201 (60%)
Mean Age (years) (SD)	51.6 (6.2)	51.9 (6.1)
< 50 years (%)	40 (30)	64 (32)
50 - 59 years (%)	82 (61)	117 (58)
> 59 years (%)	12 (9)	2 (10)
Race		
White	100 (75)	160 (80)
Black	28 (21)	34 (17)
Asian	1 (<1)	0
Hispanic	4 (3)	4 (2)
Other	1 (<1)	3 (1)

BMI (kg/m^2)		
Mean (SD)	26.75 (5.31)	28.04 (5.65)
< 24 kg/m^2	45 (34)	46 (23)
24 – 27 kg/m^2	40 (30)	54 (27)
> 27 kg/m^2	49 (37)	98 (49)
Spontaneous Amenorrhea		
Yes	62 (46)	99 (49)
No	72 (54)	102 (51)
Hysterectomy		
Yes	72 (54)	102 (51)
No	62 (46)	99 (49)

Source: Adapted from Panel 8.8.3.1 and Table 3.0.0, NDA 21-371 data submitted June 29, 2001, Volume 26, pages 68, 146-148.

7.4 Safety Findings from Clinical Studies

In total, 425 subjects were included in the nine study conducted during the development of Estrasorb™ (335 subjects in the ISS and 90 subjects in non-integrated studies). All nine studies were conducted in the US.

There were no deaths reported during any of the clinical trials with Estrasorb™. Seven serious adverse events (SAEs) that occurred in 6 subjects (3 subjects in the placebo treatment group and 3 subjects in the 7.5 mg Estrasorb™ treatment group) were reported in the three integrated studies (Studies E98-1, E98-2, and E99-1). All 6 subjects were hospitalized. All serious adverse events resolved except for Subject 13001 (chronic cervical pain, cervical diskectomy), and none required discontinuation from the study. No SAEs were reported in the four non-integrated studies. See Table 9 for a listing of SAEs reported in Studies E98-1, E98-2, and E99-1.

Table 9: Serious Adverse events by Treatment group for Studies E98-1, E98-2, and E99-1

Protocol	Treatment Group	Subject	Preferred Term
E98-2	2.45 g Estrasorb™	01110	Depression
E99-1	Placebo	10017	Cholecystitis and cholecystectomy
	Placebo	11002	Eye (vitreal) hemorrhage, retinal tear
	Placebo	18002*	Benign mucinous cystadenoma of ovary Enlarged uterine fibroids
	3.45 g Estrasorb™	03379	Lumbar pain, laminectomy performed
	3.45 g Estrasorb™	13001	Cervical pain, cervical diskectomy performed

Source: Adapted from Panel 8.8.6.1 and Table 8.0.0, NDA 21-371 data submitted June 29, 2001, Volume 26, page 74.

* Ovarian cyst on TVUS at end-of-study. Subject 18002 underwent total abdominal hysterectomy and bilateral oophorectomy.

Reviewers Comments

The incidence of serious adverse events requiring hospitalization in the ISS is small (2%, 7 of 335 subjects). Cholecystitis with cholecystectomy and ovarian cyst and uterine fibroids are associated with estrogen use and have been reported in other clinical trials with estrogens.

Three hundred ten subjects (93%, 310 of 335 subjects) completed Studies E98-1, E98-2, and E99-1, and 25 subjects (7%, 25 of 335 subjects) discontinued from the studies. The most common reasons for discontinuation across all subjects were adverse events (2%, 7 of 335 subjects) and withdrawal of consent (2%, 7 of 335 subjects). The percentage of subjects who withdrew due to an adverse event was higher in the placebo treatment group (3%, 4 of 134 subjects) than in the overall Estrasorb™ treatment groups (1%, 3 of 201 subjects). Two of the 7 subjects who discontinued due to an adverse event did so during the placebo run-in period before the start of active study medication:

- Subject 05505 in Study E98-2 due to dyspareunia,

- Subject 15017 in Study E99-1 due to an application site reaction.

Two of the remaining 5 subjects were assigned to the placebo treatment group:

- Subject 13008 in Study E99-1 was bitten by a dog on day 54,
- Subject 15018 in Study E99-1 with left breast pain/fibrocystic breast on day 15.

The final 3 subjects were assigned to the Estrasorb™ treatment groups:

- Subject 04423 in Study E98-2 due to myasthenia on day 11 (1.15 grams Estrasorb™),
- Subject 03360 in Study E99-1 due to an application site reaction on day 27 (3.45 grams Estrasorb™),
- Subject 07709 in Study E99-1 due to an application site reaction on day 34 (3.45 grams Estrasorb™).

Other reasons for withdrawal included lost to follow-up, non-compliance, and other. There were no subjects in the four non-integrated studies that discontinued due to an adverse event. See Table 10 for a summary of subject disposition by combined treatment group for Studies E98-1, E98-2, and E99-1.

Table 10: Summary of Subject Disposition by Treatment Group for Combined Studies E98-1, E98-2, and E99-1

		Treatment Group				
		Estrasorb™				
	Placebo	1.15 g	2.30 g	3.45 g	Overall	Total
Total Number of Subjects	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Enrolled/Randomized	134	32	30	139	201	335
Safety Population	134 (100)	32 (100)	30 (100)	139 (100)	201 (100)	335 (100)
Who Completed Study	124 (93)	31 (97)	27 (90)	128 (92)	186 (93)	310 (93)
Who discontinued Study	10 (7)	1 (3)	3 (10)	11 (8)	15 (7)	25 (7)
Reason for Discontinuing						
Adverse Event	4 (3)	1 (3)	0	2 (1)	3 (1)	7 (2)
Lost to Follow-Up	1 (<1)	0	0	0	0	1 (<1)
Withdrawal of Consent	2 (1)	0	1 (3)	4 (3)	5 (2)	7 (2)
Non-Compliant	2 (1)	0	0	3 (2)	3 (1)	5 (1)
Other	1 (<1)	0	2 (7)	2 (1)	4 (2)	5 (1)

Source: Adapted from Panel 8.8.2.1, NDA 21-371 data submitted June 29, 2001, Volume 26, page 63.

Reviewer's Comments

Overall, a high percentage of subjects (93%, 310 of 335 subjects) completed the three integrated studies in the ISS. Likewise, a high percentage of subjects were compliant with daily applications of Estrasorb™ (99%, 330 of 335 subjects).

A total of 203 subjects (60%, 203 of 335 subjects) in the integrated safety database experienced at least one treatment-emergent adverse event (TEAE). A TEAE was defined as any adverse event that started on or after day 1 and within 30 days after the last application of study medication, or started prior to day 1 but increased in severity on or after day 1 and within 30 days after the last application of active study medication.

The incidence of TEAEs was similar between the placebo treatment group (61%, 82 of 134 subjects) and the overall Estrasorb™ treatment groups (60%, 121 of 201 subjects) as reported in the ISS. A few exceptions are noted:

- The incidence of headache was higher in the placebo treatment group (13%, 17 on 134 subjects) than in the overall Estrasorb™ treatment groups (7%, 15 of 201 subjects).
- The incidence of pruritus was higher in the overall Estrasorb™ treatment groups (4%, 8 of 201 subjects) than in the placebo treatment group (0%, 0 subjects).
- The incidence of breast pain was higher in the overall Estrasorb™ treatment groups (8%, 16 of 201 subjects) than in the placebo treatment group (3%, 4 of 134 subjects).

- The incidence of endometrial disorder (preferred term for TVUS > 4 mm) was higher in the 7.5 mg Estrasorb™ treatment group in Study E99-1 (48%, 24 of 50 subjects with uteri) than in the placebo treatment group (27%, 14 of 51 subjects with uteri).

See Table 11 for the number and percent of subjects reporting treatment-emergent adverse events that occurred at a rate ≥ 2% in combined Studies E98-1, E98-2, and E99-1for the placebo and 3.45 gram Estrasorb™ treatment groups.

Table 11: All Treatment Emergent Adverse Events Regardless of Drug Relationship Reported at a Frequency ≥ 2% for Placebo and 3.45 Gram Estrasorb™ Treatment Groups in the ISS.

Body System/Preferred Term	Placebo N (%)	3.45 g Estrasorb™ N (%)
Selected Safety Population	134 (40)	139 (41)
Subjects with at Least 1 TEAE*	82 (61)	95 (68)
Body As a Whole		
Abdominal pain	6 (4)	6 (4)
Accidental Injury	4 (3)	4 (3)
Back Pain	6 (4)	6 (4)
Fever	3 (2)	3 (2)
Flu Syndrome	4 (3)	4 (3)
Headache	17 (13)	12 (9)
Infection	10 (7)	16 (12)
Pain	4 (30	4 (3)
Digestive System		
Dyspepsia	3 (2)	1 (<1)
Flatulence	1 (<1)	5 (4)
Nausea	4 (3)	2 (1)
Abscess Periodontal	4 (3)	1 (<1)

Metabolic/Nutritional Disorders		
Peripheral Edema	1 (<1)	3 (2)
Weight Gain	0	4 (3)
Musculoskeletal System		
Arthralgia	3 (2)	4 (3)
Leg Cramps	2 (1)	3 (2)
Nervous System		
Depression	3 (2)	1 (<1)
Dizziness	3 (2)	1 (<1)
Respiratory system		
Cough Increased	4 (3)	1 (<1)
Pharyngitis	2 (1)	4 (3)
Rhinitis	3 (2)	4 (3)
Sinusitis	6 (4)	9 (6)
Skin and Appendages		
Acne	0	3 (2)
Application Site Reaction	4 (3)	6 (4)
Pruritis	0	5 (4)
Urogenital		
Breast Pain	4 (3)	14 (10)
Endometrial Disorders	11 (8)	21 (10)
Urinary Tract Infection	1 (<1)	3 (2)
Uterine Fibroids Enlarged	3 (2)	2 (1)
Vaginal Hemorrhage	0	6 (4)
Vaginal Moniliasis	0	6 (4)

Source: Adapted from NDA 21-371 data submitted June 29, 2001, Volume 26, Table 10.0.0, Page 157.

* Treatment Emergent Adverse Event

Reviewer's Comments

The reported treatment-emergent adverse events are not unexpected.

In Study E99-1 endometrial biopsies were performed during screening and at the end-of-study for all subjects with an intact uterus. At the completion of Study E99-1, subjects with an intact uterus were provided with 14 days of treatment with medroxyprogesterone acetate (MPA). Seven days later, study investigators contacted the subjects to record if bleeding occurred. A transvaginal ultrasound (TVUS) was then completed. If the TVUS showed a double-wall endometrial thickness > 4 mm an endometrial biopsy was performed after which the subjects were provided with a second course of MPA for 14 days.

One hundred and one (101) of 200 subjects had an intact uterus (51 placebo subjects and 50 Estrasorb™ subjects). Ninety-seven subjects received MPA treatment (48 placebo subjects, 94%; and 49 Estrasorb™ subjects, 98%). The four subjects who did not receive MPA all discontinued from the clinical trial early. Thirty-five (35) of the 49 subjects, who received MPA in the 3.45 gram Estrasorb™ treatment group (71%), had withdrawal bleeding following the administration of MPA, 14 did not bleed (29%). This demonstrates the endometrial stimulation of estradiol during 12 weeks of unopposed Estrasorb™ in subjects with uteri. This finding is expected in clinical trials utilizing an estradiol alone treatment group.

Ten (10) out of 48 subjects in the placebo treatment group who received MPA had withdrawal bleeding (21%), 38 did not bleed (79%). This finding is expected in clinical trials utilizing a placebo treatment group and post-treatment MPA administration.

The Sponsor complied with the Division's recommendation that a TVUS be conducted in all subjects following the administration of MPA, and that an endometrial biopsy be performed if the TVUS double-wall thickness was reported as > 4 mm. Per protocol, the endometrial biopsy was to be performed at week 16. Two subjects in the Estrasorb™ treatment group refused to have a TVUS and also refused to have an endometrial biopsy. Twenty-four of the remaining 48 subjects in the Estrasorb™ treatment group had a post-MPA treatment TVUS > 4 mm (48%), 14 subjects in the placebo treatment group did also (27%). These numbers (24 for Estrasorb™ and 14 for placebo) differ from the numbers listed under Urogenital Body System, Endometrial Disorders in Table 9 (given as 21 and 11, respectively). The Sponsor excluded adverse events that started more than 30 days after the last application of active study medication as treatment emergent. This reviewer, however, has included all subjects with a TVUS > 4 mm following the administration of MPA in this discussion.

Ten subjects in the Estrasorb™ treatment group with a TVUS > 4 mm at the end-of-study refused to have an endometrial biopsy performed; 14 subjects agreed to have an endometrial biopsy performed. Eleven (11) of the 14 subjects in the placebo treatment group with a TVUS > 4 mm underwent an endometrial biopsy. The Agency's 2003 draft clinical evaluation guidance document recommends that all women with uteri have an endometrial biopsy at baseline and at the end-of-study. The routine administration of MPA at the end-of-study to all subjects with uteri is no longer recommended. Nonetheless, several points of interest are noted from the findings submitted.

For the placebo treatment group:

- 1 subject (Subject 17005) had an endometrial biopsy diagnosis of hyperplasia without atypical cells at baseline and a TVUS of < 4 mm at end-of-study, therefore, no endometrial biopsy was conducted at end-of-study. The 1995 HRT Guidance recommends that subjects with endometrial hyperplasia or cancer should be excluded from study participation.
- 8 subjects with double-wall endometrial thickness reports of > 4 mm at end-of-study had diagnoses of atrophic endometrium on biopsy.
- 3 subjects with double-wall endometrial thickness TVUS reports of > 4 mm refused to have an endometrial biopsy performed and did not receive a second course of MPA treatment, per protocol-specified procedure.
- 2 subjects had an endometrial biopsy diagnosis of atrophic endometrium at baseline, a TVUS > 4 mm at end-of-study, and diagnoses of proliferative endometrium on endometrial biopsy at end-of-study; 1 subject had a diagnosis of "other" endometrium at baseline, a TVUS > 4 mm, and a diagnosis of proliferative endometrium at end-of-study. Two of these three subjects received a second course of MPA, per protocol-specified procedure, and bleed. One subject did not receive a second course of MPA.

For the Estrasorb™ treatment group:

- 1 subject (Subject 10021) with an endometrial biopsy diagnosis of secretory endometrium at baseline had an endometrial biopsy diagnosis of hyperplasia without atypical cells at end-of-study. The subject reported no bleeding after MPA and had an end-of-study TVUS double-wall endometrial thickness of 13 mm. This subject did receive a second course of treatment with MPA but did not bleed. The Sponsor did not consider this adverse event related to study medication use as the diagnosis was made more than 30 days post treatment. As stated previously, per the protocol for Study E99-1, an endometrial biopsy was scheduled to be performed during week 16 (4 weeks post-treatment) if the TVUS was reported as > 4mm. For Subject 10021 treatment stopped on 5/20/00. Her post-MPA ultrasound and endometrial biopsy were not performed until [redacted] Although Subject 10021 did not have her endometrial biopsy performed on week 16 per protocol, this case of endometrial hyperplasia should be considered a treatment emergent adverse event.
- 9 subjects with double-wall endometrial thickness TVUS reports of > 4 mm refused to have an endometrial biopsy performed, 2 of these subjects had TVUS reports of 16 mm following withdrawal

bleeding after 14 days of MPA. Only 1 of these 9 subjects received a second course of MPA treatment.

- **3 subjects with diagnoses of atrophic endometrium at baseline had diagnoses of proliferative endometrium at end-of-study. Two of these three subjects received a second course of MPA, per protocol-specified procedure.**

These finding demonstrate inconsistencies in implementation of the study design for Study E99-1 regarding safety monitoring. Every effort should be undertaken to encourage study participants in estrogen alone and estrogen/progestin treatment groups in clinical trials to comply with the recommendation for a baseline and end-of-study endometrial biopsy with appropriate referral for definitive management, when necessary. However, a double-wall endometrial thickness > 4 mm is not unexpected during 12 weeks of unopposed Estrasorb™ in subjects with uteri.

The case of endometrial hyperplasia that was confirmed in Subject 10021 should be considered a treatment-emergent adverse event.

Studies N95-3, N96-1, and N97-3

There were no clinically notable differences seen between the placebo treatment group and the overall ESTRASORB™ treatment groups with respect to baseline demographics and background information in these studies. No deaths were reported. There were no serious adverse events reported and no subjects discontinued due to an adverse event.

The incidence of TEAEs in these 3 studies ranged from 35% in Study N97-3 to 50% in Study N95-3. The most commonly reported TEAE were similar in these studies and the integrated studies with the exception of peripheral edema in Study N97-3.

Study E2000-1

The objective of Study E2000-1 was to assess the amount of residual estradiol on the skin surface at 2 and 8 hours after application of 1.15 grams of Estrasorb™ containing 2.5 mg of estradiol per gram (equivalent to 2.87 mg or 2875 micrograms of estradiol) to the anterior surface of the left and right thigh for 2 minutes (a 6 x 8 inch area was delineated using waterproof adhesive tape). Twelve postmenopausal women participated. The study nurse observed the application and the subject remained in the clinical site for 8 hours. Residual estradiol determinations were performed using a [redacted] test developed by Novavax, Inc. The application areas were sampled prior to dosing and at 2 and 8 hours post-dosing. No subjects had detectable residual estradiol on the skin surface prior to application (LOQ, amounts [redacted]). At 2 hours post-dosing all 12 subjects had detectable residual estradiol on their left thighs. The amounts of estradiol detected at two hours post-application ranged from 220 micrograms (7.6% of 2875 micrograms applied) to 803 micrograms (28% of 2875 micrograms applied). At 8 hours post-dosing, all 12 subjects had detectable residual estradiol on their right thighs. The amounts detected at 8 hours post-application ranged from 74 micrograms (2.6% of 2875 micrograms applied) to 582 micrograms (20.2% of 2875 micrograms applied). Both thighs were then washed with soap and water and rinsed with water (8 hours post dosing) and again swiped for residual estradiol. Four of the 12 subjects (25%) still had detectable quantities of estradiol after washing that ranged from 17.8 micrograms (0.6% of 2875 micrograms applied) to 38.3 micrograms (1.3% of 2875 micrograms applied).

No deaths occurred during this study. No subjects experienced a serious adverse event or no subjects discontinued due to an adverse event. Four of the 12 subjects experienced treatment-emergent adverse events (1 case each of mild headache, moderate intermittent mid back pain, mild razor burn prior to dosing and mild erythema after removal of the adhesive tape delineating the application areas). All four adverse events resolved and were judged by the investigator to be unrelated to study drug medication.

Reviewer's Comments

The results of Study E2000-1 indicate that the percent of residual estradiol detected varied between the 12 subjects at both time points, from 7.6% (220 micrograms) to 28% (803 micrograms) at 2 hours post-application and 2.6% (74 micrograms) to 20% (582 micrograms) at 8 hours post-application. After washing, these amounts were further reduced to none (< LOQ in 8 subjects) and 0.6% (17.8 micrograms) to 1.3% (38.3 micrograms) in 4 subjects.

However, if the correlate is considered based on the amount of estradiol applied to the skin surface (equivalent of 2875 micrograms applied to each thigh), the percent of estradiol no longer available for detection (i.e., "absorbed") on the skin surface also varied between the 12 subjects, from 72% to 92.4% at 2 hours post-application to 80% to 97.4% at 8 hours after application. Therefore, it appears from the available information that at least 72% of the applied dose at 2 hours and at least 80% at 8 hours was no longer detectable on the skin surface. In addition, washing after 8 hours appears to remove any remaining estradiol on the skin surface in the majority of subjects.

The variability in the amounts of estradiol detected on the skin surface 2 and 8 hours post-application in 12 subjects is not unexpected. Skin permeability, vigor of rubbing, the amount of drug products remaining on the hands after application, and clothing contact are but a few of the possible contributing factors. To better understand the safety issues of residual estradiol on the skin surface, the Sponsor was requested to conduct the following transfer potential study (Study E2002-1).

Study E2002-1

The primary objective of Study E2002-1was to determine if systemic absorption of estradiol occurred in a male subject after intentional contact exposure to the primary Estrasorb™ application sites of postmenopausal women. Study E2002-1 was an open-label Phase 1 study, conducted in 1 US center, in which 14 postmenopausal women (mean age 57.6 ± 8.7 SD) applied approximately 1.74 grams of Estrasorb™ containing 2.5 mg of estradiol/gram (equivalent of 4.35 mg or 4350 micrograms of estradiol) to each thigh and calf daily for two days. The contents of one 1.74 gram pouch was applied to the anterior left thigh and left calf areas for 3 minutes until thoroughly absorbed, and the contents of a second 1.74 gram pouch was applied to the anterior right thigh and right calf areas for 3 minutes until thoroughly absorbed. Any excess material remaining on the hands was rubbed on the buttocks. On completion of application, both hands were washed with soap and water. The pouches were weighed prior to and after application to determine the amount of product expressed by each subject.

Fourteen male partners (mean BMI of 28) attempted to transfer estradiol to his forearm by vigorously rubbing them against his female partner's thigh for 2 minutes, left forearm to left thigh at 2 hours and right forearm to right thigh at 8 hours. In female subjects, trough serum estradiol, estrone, estrone sulfate, FSH, total testosterone, free testosterone, and dihydrotestosterone (DHT) were measured prior to initial dosing (screening day –24) and at 1, 2 and 8 hours after dosing on days 0 and 1. The same serum hormone levels were measured in male subjects prior to initial attempted transfer (screening day –24 and day -10) and at 1, 2, 4, 8, 12, 18 and 24 hours post dosing on days 0 and 1.

In the 14 postmenopausal female subjects, the results from Study E2002-1 show 2 to 3-fold increases in serum estradiol, estrone, and estrone sulfate concentrations, and an 8% decrease in serum FSH concentration, all statistically significant after 2 days of dosing. See the reported findings below:

	Estradiol (ng/dL) (Mean ± SD)	Estrone (ng/dL) (Mean ± SD)	Estrone Sulfate (ng/dL) (Mean ± SD)	FSH (mIU/mL) (Mean ± SD)
Day –24	0.29 ± 0.15	1.60 ± 1.34	52.79 ± 40.12	73.29 ± 18.11
Day 0:				
1 hr. post-dose	0.75 ± 1.23	1.87 ± 1.30	39.29 ± 24.46	64.21 ± 15.74
2 hrs. post-dose	0.94 ± 1.35	1.71 ± 1.56	39.57 ± 23.53	66.00 ± 18.34
8 hrs. post-dose	2.35 ± 2.11	1.93 ± 1.08	62.71 ± 37.02	64.50 ± 18.71
Day 1:				

1 hr. post-dose	2.05 ± 1.97	3.84 ± 2.36	124.43 ± 73.70	60.57 ± 15.90
2 hrs. post-dose	2.21 ± 2.02	3.84 ± 2.46	125.07 ± 73.32	60.71 ± 14.91
8 hrs. post-dose	3.41 ± 2.95	4.46 ± 2.87	156.57 ± 93.05	58.00 ± 13.67

For estradiol PK parameters for female subjects, the mean AUC $_{(1\text{-}8h)}$ on days 0 and 1 were 10.70 ± 10.39 and 19.34 ± 15.91 ng-h/dL, respectively. The mean C_{max} on days 0 and 1 were 2.35 ± 2.11 and 3.54 ± 2.89 ng-h/dL, respectively.

Reviewer's Comments

Study E2002-1 is the first study conducted using the package configuration of two 1.74 gram foil-laminated pouches of Estrasorb™. The two 1.74 gram package configuration is proposed in labeling in this submission. However, the primary Phase 3 safety and efficacy Study E99-1 utilized a 3 package configuration (three 1.15 gram pouches) and while Study E2002-1 does not provide any efficacy information it does provide limited PK information.

Although two days of application of Estrasorb™ are a brief time to see changes in serum estradiol, estrone, estrone sulfate, and FSH concentrations, the 14 female subjects in Study E2002-1experienced statistically significant changes in serum hormone concentrations in the desired direction – increases in estradiol, estrone, and estrone sulfate and a decrease in FSH concentration over the two dosing days.

In males, the normal range of serum estradiol concentration is reported as 0.8-3.5 ng/dL. At screening for Study E2002-1, only one male subject had a serum estradiol concentration above the normal range (Subject 15M, 4.3 ng/dL). During the two days of attempted estradiol transfer, 4 serum estradiol concentration measurements were reported above the upper bounds of the normal range: Subject 07M at 2 and 18 hours on day 0 (3.60 and 5.10 ng/dL, respectively) and at 18 hours on day 1 (4.90 ng/dL), and Subject 15M at 18 hours on day 1 (3.80 ng/dL). All other reported serum estradiol concentration measurements were within the normal range. Results of the mean serum concentrations of estradiol, estrone, and estrone sulfate (mean ± SD) for the 14 male subjects are as follows:

	Estradiol (ng/dL) (Mean ± SD)	Estrone (ng/dL) (Mean ± SD)	Estrone Sulfate (ng/dL) (Mean ± SD)
Day -24	1.94 ± 0.92	2.27 ± 0.77	109.43 ± 42.32
Day -10:			
0 hour	1.76 ± 0.51	2.11 ± 1.15	89.50 ± 44.69
1 hr. post-dose	1.74 ± 0.54	2.20 ± 0.92	86.86 ± 42.48
2 hrs. post-dose	1.91 ± 0.70	2.11 ± 0.97	84.29 ± 37.48
4 hrs. post-dose	1.71 ± 0.52	1.97 ± 0.96	88.36 ± 41.02
8 hrs. post-dose	1.79 ± 0.64	2.00 ± 1.03	92.36 ± 50.57
12 hrs. post-dose	1.59 ± 0.41	1.89 ± 1.06	89.79 ± 41.45
18 hrs. post-dose	1.76 ± 0.51	2.60 ± 0.92	80.71 ± 40.54
24 hrs. post-dose	1.54 ± 0.36	2.18 ± 1.09	88.21 ± 35.94
Day 0:			
0 hour	1.76 ± 0.47	2.30 ± 0.79	91.00 ± 42.38
1 hr. post-dose	1.97 ± 0.47	2.60 ± 0.80	96.79 ± 46.28
2 hrs. post-dose	2.11 ± 0.65	2.46 ± 0.77	98.71 ± 54.94
4 hrs. post-dose	1.84 ± 0.59	2.36 ± 0.77	94.71 ± 50.32
8 hrs. post-dose	1.80 ± 0.48	2.32 ± 0.75	100.71 ± 46.52
12 hrs. post-dose	1.61 ± 0.37	2.21 ± 0.75	110.29 ± 48.18
18 hrs. post-dose	2.41 ± 0.94	3.09 ± 0.62	100.21 ± 43.23
24 hrs. post-dose	1.79 ± 0.37	2.63 ± 0.75	92.07 ± 31.11
Day 1:			
0 hour	1.79 ± 0.37	2.63 ± 0.75	92.07 ± 31.11
1 hr. post-dose	2.29 ± 0.59	2.91 ± 0.78	108.57 ± 42.00
2 hrs. post-dose	1.74 ± 0.50	2.43 ± 0.84	105.86 ± 37.89
4 hrs. post-dose	1.86 ± 0.56	2.44 ± 0.58	101.00 ± 37.49
8 hrs. post-dose	1.73 ± 0.36	2.68 ± 0.65	114.36 ± 45.17

12 hrs. post-dose	1.96 ± 0.44	2.11 ± 0.42	90.64 ± 31.69
18 hrs. post-dose	2.80 ± 0.82	3.18 ± 0.96	80.43 ± 19.79
24 hrs. post-dose	1.99 ± 0.40	2.84 ± 0.54	98.57 ± 23.32

For estradiol PK parameters, the mean $AUC_{(0\text{-}24h)}$ on day –10, 0 and 1 were 40.73 ± 1.42 ng-h/dL, 46.30 ± 12.46 ng-h/dL and 50.46 ± 10.54 ng-h/dL, respectively. Mean $AUC_{(0\text{-}24h)}$ values on days 0 and 1 were statistically significantly higher than those on day –10 with p-values of p=0.017 on day 0 and p< 0.001 on day 1. Serum estradiol concentrations in male partner subjects, as measured by geometric mean fold ratios in $AUC_{(0\text{-}24h)}$, increased approximately 14% after 1 day of intentional transfer exposure and 25% after 2 days of exposure. Similar increases in serum concentrations were seen for estrone and estrone sulfate. After two days of Estrasorb™ exposure the serum estrone level had increased by 34% and the estrone sulfate level by 17%.

The mean C_{max} values for estradiol on days –10, 0 and 1 were 2.17 ± 0.60 ng/dL, 2.49 ± 0.90 ng/dL and 2.83 ± 0.81 ng/dL, respectively. Mean C_{max} values on day 0 were not statistically significantly higher than on day –10 (p=0.099), but were statistically significantly higher on day 1 (p=0.0005). After serial intentional transfer of ESTRASORB™, estradiol in male subjects, as measured by geometric mean fold ratios in C_{max}, increased about 13% after day 1 and 30% after day 2. The mean T_{max} values were 10.00 hours ± 8.33 hours on day 0 and 13.14 hours ± 6.97 hours on day 1.

All 14 female subject applied a total of 3.48 grams of Estrasorb™ containing 2.5 mg of estradiol/gram (equivalent of 8.7 mg of estradiol or 8700 micrograms) per day. No deaths or serious adverse events occurred in Study E2002-1. Nine adverse events were reported (6 reports of adverse events in 3 female subjects and 3 reports of adverse events in 3 male subjects). Two female subjects reported mild headaches, possibly related to study medication, and two female subjects reported four occurrences of mild erythema at the application site (1 report in 1 subjects and 3 reports in 1 subject). Two male subjects reported mild headaches, and one male subject reported mild rhinitis.

Reviewer's Comments

Per the results reported for Study E2002-1, after two days of intentional exposure to Estrasorb™, the mean estradiol serum concentrations for the 14 male subjects are within the normal range of 0.8-3.5 ng/dL (day 0 results ranged from 1.76 to 2.41 ng/dL and day 1 results ranges from 1.74 to 2.80 ng/dL). For the individual male subject assessment, only 1 male subject (Subject 07M) with a baseline estradiol serum concentration within normal limits exceeded the normal range after exposure at 3 of the 14 sample time points as stated above (2 and 18 hours on day 0 and 18 hours on day 1). The second male subject that exceeded the normal range at the 18 hour sample time point on the second day (Subject 015M) had an elevated screening serum estradiol level (4.3 ng/dL).

Overall, the majority of individual male subjects in Study E2002-1 had serum estradiol concentrations on the two post-exposure days that ranged within the normal limits of 0.8-3.5 ng/dL. However, the mean $AUC_{(0\text{-}24h)}$ values on days 0 and 1 were statistically significantly higher than reported at screening with p-values of p=0.017 on day 0 and p< 0.001 on day 1.

The implication of these findings to children is of concern. Although limited, published literature reports indirect exposure to excessive amounts of topical estrogen with resulting gynecomastia, rapid changes in growth, and advanced bone age in prepubertal children.[3] Custom-compounded topical estrogen creams applied by mothers (9 mg of estradiol per 1 gram cream applied twice daily to thighs for 8 months and 24 mg of estradiol per 1 gram of cream applied twice daily to abdomen for 4 months) resulted in gynecomastia in 3 male children (33 months of age, 28 months of age, and 8 years). Serum estradiol concentrations were reported at 3.5 ng/dL, 4.8 ng/dL, and 10 ng/dL, respectively (normal values for age is < 1.5 ng/dL). Upon discontinuation of topical applications of cream, all 3 male children had regression of gynecomastia without recurrence and estradiol levels < 1.5 ng/dL. Although the exact route

[3] Felner, EI, White, PC. Prepubertal gynecomastia: indirect exposure to estrogen cream. J Pediatr. 2000;105(4):E55.

of transmission to each male child was not certain (application sites were normally clothed), the authors speculated that estrogen was spread from traces remaining on the mothers' hands after application, possibly via food preparation. Prepubertal gynecomastia has also been reported associated with estrogen-containing hair cream[4] and food ingested by children.[5]

In Study E2002-1, 2 of 14 male subjects had isolated sample time elevations of serum estradiol concentrations above the reported normal range of 0.8-3.5 ng/dL after 2 days of intentional exposure. From this information and the literature information on prepubertal gynecomastia attributable to exposure of topical estrogens, albeit larger doses applied that utilized in Study E2002-1, it appears prudent to recommend in labeling that topical applications sites be covered to prevent exposure, — and that hands be thoroughly washed after application. This information should be conveyed in labeling.

Prior to and after the application of Estrasorb™ on days 0 and 1 the two 1.74 gram pouches (combined) were weighed. The difference in weight on each day is the amounts expressed. The nominal weight of two Estrasorb™ foil-laminated pouches is 3.48 grams. The pouches mean weight ± standard deviation (SD) on day 0 was 3.204 ± 0.116 grams and 3.170 ± 0.120 grams on day 1, which are, respectively, 7.93% and 8.91% below the nominal weight. The range of pouch expression weights were 2.95 to 3.33 grams on day 0 and 2.96 to 3.36 grams on day 1. The mean difference of pouch weight expression on the two days combined was –0.033 ± 0.133 grams.

Reviewer's Comments

There is no evidence of a significant change in pouch expression between the two days suggesting that subjects are in compliance with the instructions given for application.

Study E2002-2

Study E2002-2 was an open-label Phase 1 study, conducted in 1 US center, in which 14 postmenopausal women (mean age of 52.4 ± 3.4 years) applied 3.48 grams of Estrasorb™ to both thighs and calves daily for 24 days, one 1.74 gram pouch to the left thigh and calf and one 1.74 gram pouch to the right thigh and calf under the supervision of the study nurse. Subjects had serum estradiol, estrone, estrone sulfate, FSH, total testosterone, free testosterone, and dihydrotestosterone concentrations determines at screening day –24. Subjects also had serum estradiol, estrone, estrone sulfate and FSH concentrations drawn prior to dosing on days 0, 7, 15 and 23 and 1, 2, 4, 8, 12, 18, and 24 hours post-dosing. On days 8 through 14, SPF 15 sunscreen was applied to thighs and calves 10 minutes prior to dosing. On days 16 through 22, SPF 15 sunscreen was applied to thighs and calves 25 minutes after dosing. Subjects were exposed to sunlight for 10 minutes on day 24 and observed for 2 hours for any photosensitivity reactions. Pouches were weighed prior to and after administration to determine the amount of product expressed by each subject. Other acceptable laboratory evaluations were obtained pre-dosing and at the end-of-study. Adverse events were recorded and reported in an acceptable manner. See the reported findings below:

	Estradiol (ng/dL) (Mean ± SD)	Estrone (ng/dL) (Mean ± SD)	Estrone Sulfate (ng/dL) (Mean ± SD)	FSH (mIU/mL) (Mean ± SD)
Day –24	0.46 ± 0.34	1.68 ± 1.40	45.00 ± 27.31	73.93 ± 25.63
Day 0:				
0 hour	0.65 ± 0.72	2.08 ± 1.07	47.36 ± 28.20	69.71 ± 18.78
1 hr. post-dose	0.81 ± 0.64	1.74 ± 0.90	45.93 ± 26.62	66.36 ± 14.46
2 hrs. post-dose	0.79 ± 0.61	1.92 ± 1.24	50.36 ± 32.48	66.79 ± 20.18
4 hrs. post-dose	1.29 ± 1.56	1.82 ± 1.24	47.29 ± 27.68	67.36 ± 20.16
8 hrs. post-dose	1.56 ± 1.56	1.94 ± 1.18	63.07 ± 41.01	62.64 ± 15.65

[4] Edidin DV, Levitsky LL. Prepubertal gynecomastia associated with estrogen-containing hair cream. Am J Dos Child. 1982;136(7):587-8.

[5] Saenz de Rodriguez CA, Bongiovanni AM, Conde de Borrego L. An epidemic of precocious development in Puerto Rican children. J Pediatr. 1985;107(3):393-6.

12 hrs. post-dose	1.56 ± 1.61	2.39 ± 1.32	62.50 ± 28.62	62.14 ± 14.63
18 hrs. post-dose	2.15 ± 1.92	2.50 ± 1.57	64.29 ± 27.81	63.00 ± 18.58
24 hrs. post-dose	1.99 ± 1.43	3.58 ± 1.78	88.57 ± 44.41	63.79 ± 17.65

Reviewer's Comments

As shown above, the mean serum estradiol concentration doubled within four hours of dose application (from 0.65 ± 0.72 to 1.29 ± 1.56 ng/dL) and tripled by 18 hours (from 0.65 ± 0.72 to 2.15 ± 1.92 ng/dL). These results are attributable to 7 of the 14 subjects with end-of-day serum estradiol concentrations above 3.0 ng/dL (Subjects 4, 11, 23, 26, 27, 31, and 35). The mean estradiol $AUC_{(0\text{-}24h)}$ and C_{max} were 38.91 ± 32.27 ng-h/dL and 2.50 ± 2.11 ng/dL, respectively. On day 0, the accumulation of serum estrone was slower than serum estradiol with only a moderate increase after 18 hours, and the mean FSH concentration changed only slightly.

	Estradiol (ng/dL) (Mean ± SD)	Estrone (ng/dL) (Mean ± SD)	Estrone Sulfate (ng/dL) (Mean ± SD)	FSH (mIU/mL) (Mean ± SD)
Day 7:				
0 hour	3.42 ± 1.97	6.74 ± 4.61	230.21 ±160.62	52.36 ± 15.44
1 hr. post-dose	3.01 ± 1.96	6.79 ± 3.78	217.79 ± 165.67	49.79 ± 15.01
2 hrs. post-dose	3.24 ± 2.12	6.25 ± 3.55	207.43 ± 125.19	49.00 ± 13.64
4 hrs. post-dose	3.81 ± 2.39	6.44 ± 3.31	220.21 ± 152.29	49.71 ± 12.08
8 hrs. post-dose	4.39 ± 3.47	6.64 ± 3.58	187.21 ± 113.54	50.14 ± 15.79
12 hrs. post-dose	3.34 ± 2.42	6.68 ± 3.94	193.57 ± 126.92	47.86 ± 13.51
18 hrs. post-dose	4.30 ± 2.84	5.81 ± 2.96	147.43 ± 86.92	48.15 ± 13.78
24 hrs. post-dose	3.91 ± 2.38	6.83 ± 3.33	214.14 ± 135.72	53.29 ± 16.81

Reviewer's Comments

Days 0 through 6 are Estrasorb™ dosing without sunscreen in Study E2002-2. The serum estradiol concentrations reported for day 7 were above 2 ng/dL at all time points with higher means at 8 and 18 hours (4.39 ± 3.47 and 4.30 ± 2.84 ng/dL, respectively). The mean estradiol $AUC_{(0\text{-}24h)}$ on day 7 was 92.35 ± 57.63 ng-h/dL and the mean C_{max} was 5.54 ± 3.56 ng/dL. By day 7, the mean estrone concentration was almost double the highest day 0 estrone concentration, and the mean FSH concentration decreased about 20% from day 0 levels.

	Estradiol (ng/dL) (Mean ± SD)	Estrone (ng/dL) (Mean ± SD)	Estrone Sulfate (ng/dL) (Mean ± SD)	FSH (mIU/mL) (Mean ± SD)
Day 15:				
0 hour	3.43 ± 2.38	8.16 ± 4.93	256.00 ±176.07	48.43 ± 15.55
1 hr. post-dose	3.47 ± 2.01	8.00 ± 4.28	249.71 ± 175.98	44.14 ± 12.27
2 hrs. post-dose	3.63 ± 1.99	7.65 ± 4.47	242.64 ± 171.57	45.50 ± 13.98
4 hrs. post-dose	3.80 ± 2.13	7.35 ± 4.29	243.86 ± 175.69	44.71 ± 14.04
8 hrs. post-dose	7.16 ± 9.55	6.89 ± 4.25	236.07 ± 147.33	44.36 ± 12.60
12 hrs. post-dose	5.04 ± 3.90	7.98 ± 4.39	251.07 ± 171.16	42.43 ± 13.30
18 hrs. post-dose	8.01 ± 7.67	7.92 ± 4.41	209.71 ± 128.95	44.21 ± 14.14
24 hrs. post-dose	4.36 ± 3.16	7.69 ± 3.9 3	256.00 ± 181.92	44.79 ± 13.79

Reviewer's Comments

Days 8 through 14 are the study days in which SPF 15 sunscreen was applied to thighs and calves 10 minutes prior to dosing. With continued daily application there was a moderate amount of additional accumulation of serum estradiol concentration, again showing higher means at 8 and 18 hours (7.16 ± 9.55 and 8.01 ± 7.67 ng/dL, respectively). The mean estradiol $AUC_{(0\text{-}24h)}$ on day 15 was 134.75 ± 107.06 ng-h/dL and the mean C_{max} was 9.72 ± 10.60 ng/dL. By day 15, the mean FSH concentration decreased about 30% from day 0 levels.

	Estradiol (ng/dL) (Mean ± SD)	Estrone (ng/dL) (Mean ± SD)	Estrone Sulfate (ng/dL) (Mean ± SD)	FSH (mIU/mL) (Mean ± SD)
Day 23:				
0 hour	3.83 ± 2.49	8.50 ± 6.31	278.07 ±270.10	44.57 ± 15.82
1 hr. post-dose	3.54 ± 2.00	8.00 ± 7.17	288.07 ± 245.40	43.14 ± 14.84
2 hrs. post-dose	3.56 ± 2.00	7.71 ± 5.93	235.29 ± 175.58	41.57 ± 13.56
4 hrs. post-dose	3.90 ± 1.92	7.52 ± 6.39	194.79 ± 162.94	41.79 ± 14.11
8 hrs. post-dose	5.74 ± 3.02	7.18 ± 4.88	246.21 ± 151.27	42.29 ± 14.53
12 hrs. post-dose	4.06 ± 2.28	7.29 ± 4.81	197.07 ± 124.58	43.36 ± 14.74
18 hrs. post-dose	5.54 ± 3.66	7.19 ± 5.30	181.00 ± 132.60	43.71 ± 14.48
24 hrs. post-dose	5.70 ± 6.78	8.06 ± 6.27	233.86 ± 153.62	44.86 ± 16.70

Reviewer's Comments

Days 16 through 23 are the study days in which SPF 15 sunscreen was applied to thighs and calves 25 minutes after dosing. The mean $AUC_{(0\text{-}24h)}$ on day 23 was 115.22 ± 68.70 ng-h/dL and the mean C_{max} was 8.44 ± 6.07 ng/dL. No further change was observed in the mean FSH concentration over day 15 values.

The pharmacokinetic parameters for mean estradiol $AUC_{(0\text{-}24h)}$, C_{max}, and T_{max} for day 7 (without sunscreen), day 15 (sunscreen applied 10 minutes before Estrasorb™), and day 23 (sunscreen applied 25 minutes after Estrasorb™) are as follows:

	Estradiol $AUC_{(0\text{-}24h)}$ (Mean ± SD)	Estradiol C_{max} (Mean ± SD)	Estradiol T_{max} (Mean ± SD)
Day 0	38.91 ± 32.27 ng-h/dL	2.50 ± 2.11 ng/dL	11.1 ± 9.2 hours
Day 7	92.35 ± 57.63 ng-h/dL	5.54 ± 3.56 ng/dL	9.3 ± 8.5 hours
Day 15	134.75 ± 107.06 ng-h/dL	9.72 ± 10.60 ng/dL	10.1 ± 7.2 hours
Day 23	115.22 ± 68.70 ng-h/dL	8.44 ± 6.07 ng/dL	11.7 ± 8.1 hours

Serum trough estradiol concentrations were observed daily between days 0 and 24. The mean serum estradiol trough level prior to the first dose on day 0 was 0.65 ± 0.72 ng/dL which increased to 1.99 ± 1.43 ng/dL by day 1 and to 3.52 ± 3.81 ng/dL by day 4. The daily mean trough levels were between 3.11 and 4.36 ng/dL from days 5 to 23 with two exceptions (elevated mean of 5.70 ± 6.78 on day 24 for Subjects 23 and 31). PK parameters for serum trough estradiol concentrations are as follows:

	Estradiol $AUC_{(0\text{-}24h)}$ (Mean ± SD)	Estradiol C_{max} (Mean ± SD)	Estradiol T_{max} (Mean ± SD)
Days 0-7	18.43 ± 12.24 ng-h/dL	4.93 ± 3.54 ng/dL	5.6 ± 1.6 hours
Day 8-15	25.52 ± 15.88 ng-h/dL	5.61 ± 3.15 ng/dL	3.2 ± 2.5 hours
Day 16-23	26.92 ± 16.33 ng-h/dL	6.18 ± 3.89 ng/dL	3.0 ± 2.4 hours

Reviewer's Comments

In primary Study E99-1 trough steady state estradiol levels were not achieved until week 8 of daily application of three 1.15 gram foil-laminated pouches of Estrasorb™. Although not verifiable in 24-day Study E2002-1, observed differences between period 2 (application of sunscreen 10 minutes before the application of Estrasorb™) and period 3 (application of sunscreen 25 minutes after the application of Estrasorb™) in estradiol profile and trough AUC and C_{max} would be attributable to the impact of sunscreen application.

As shown above, comparison of estradiol AUC and C_{max} show significantly elevated AUC and C_{max} in the two latter periods compared to days 0-7 (34% and 29% increases in estradiol profile AUC and 44% and 54% increases in estradiol trough AUC, respectively). The trough data suggest that use of sunscreen either before or after application of Estrasorb™ enhance the absorption of Estrasorb™ with little difference according to the order of application. This information should be conveyed in labeling.

In Study E2002-2 there were 3 reports of adverse events in 3 subjects (2 subjects with headache and dizziness and 1 subjects with constipation). No subjects dropped out because of an adverse event. There were no serious adverse events or deaths in Study E2002-2. Ten-item dermal assessments (erythema, edema, eschar, blanching, ulceration, desquamation, fissuring, eschar exfoliation, staining test site, and ancillary irritation) were conducted at hours 0, 2 and 24 each on days 0, 7, 15, and 23. The same dermal assessment was completed on day 24 at 2-hours post-exposure to direct exposure to sunlight. All of the reaction categories were negative at all collection time points.

Reviewer's Comments

There were no positive dermal responses and no indication of photosensitivity in any subject at any data collection time.

Prior to and after the application of Estrasorb™ on days 0 through 24 the two 1.74 gram pouches (combined) were weighed. The difference in weight on each day is the amounts expressed. The nominal weight of two Estrasorb™ foil-laminated pouches is 3.48 grams. The daily pouch weight mean ± standard deviation (SD) over the 14 subjects were between 3.25 and 3.31 grams with SD between 0.05 and 0.11 grams, which are, respectively, 4.89% and 6.61% below the nominal weight, respectively. With only 1 exceptionally high pouch expression of 4.29 grams on day 8 by Subject 26, the range of all daily pouch expression weights were between 2.97 and 3.44 grams.

Reviewer's Comments

With the exception of a few outliers, there is no evidence of a significant change in pouch expression suggesting that subjects are in compliance with the instructions given for application.

As previously noted in the Chemistry, Manufacturing and Controls subsection of this review on page 12, the appearance [redacted] in the to-be-marketed formulation is of concern. Due to the current unavailability of the drug formulation used in primary Study E99-1, no direct comparison with the to-be-marketed formulation can be made. However, pharmacokinetic parameters collected in Phase 1 Study E98-1 (which used the same drug formulation as Study E99-1) can be compared with the pharmacokinetic parameters obtained during the Estrasorb™ -only period in Study E2002-2 (first 7 days). The PK results of Study E98-1 (split dose application of 3 grams containing 7.5 mg of estradiol to both left and right thighs daily for 8 consecutive days, and Study E2002-2 (split dose application of 3.48 grams containing 8.7 mg of estradiol to left and right thighs and calves) over days 0 to 7 are shown in Table 12.

Table 12: Comparison of Serum Profile Estradiol Concentrations between Studies E98-1 and E2002-2.

	C_{max} (ng/dL)		$AUC_{(0\text{-}24h)}$ (ng-h/dL)	
	E98-1 3.2 ml Estrasorb™ (N = 4)	E2002-2 1.74 g Estrasorb™ (N = 14)	E98-1 3.2 ml Estrasorb™ (N = 4)	E2002-2 1.74 g Estrasorb™ (N = 14)
1st Dose	3.45 ± 2.66	2.5 ± 2.11	37.3 ± 25.1	38.91 ± 32.27
8th Dose	5.48 ± 1.40	5.54 ± 3.56	92.7 ± 28.9	92.35 ± 57.63

Source: NDA 21-371, Amendment-018 dated July 11, 2003, Table 11.4.1.1-1, page 55.

Reviewer's Comments

From the descriptive PK parameters shown in Table 12, the serum estradiol concentrations reported for Study E98-1 and Study E2002-2 are comparable and are within the expected ranges. Considering the variability between the two studies, it appears that the [ ] in the to-be-marketed formulation in Study E2002-2 do not influence the absorption of estradiol.

As previously noted, the CMC Reviewer has established a specification criterion of [ ] accounts for arbitrary analytical variability) or at a maximum of [ ]' per microliter for the bulk

and stability lots of the to-be-marketed drug product. The Sponsor has agreed with this acceptance criterion.

7.5. Miscellaneous Studies

Nine studies constitute the database for the information provided in this application. No additional studies were conducted that contribute to either the historical information regarding product development or actual safety and efficacy data.

7.6. Literature Review for Safety

No independent literature review was conducted. Estradiol use in hormone replacement therapy is well accepted, and the safety profile of estradiol is well defined.

7.7. Postmarketing Surveillance

Estrasorb™ is not marketed, either in the US or internationally.

7.8. Safety Update

4-Month Safety Update

On January 13, 2003, the Sponsor submitted the 4-Month Safety Update as Amendment-005. No additional studies with Estrasorb™ had been initiated, and no additional safety data had been collected since the NDA second submission.

Second Safety Update

On May 5, 2003, the Sponsor submitted the Second Safety Update (Eight Month Safety Update) as Amendment –012. Study E2002-1 entitled, " Estradiol Partner Transfer Study" was completed. Two of the 14 postmenopausal women enrolled in Study E2002-1 experienced mild headaches related to medication use that quickly resolved. Study E2002-2 entitled, " Estrasorb Sunscreen and Photosensitivity Study" was ongoing. No serious adverse events were reported for Study E2002-2.

Twelve-Month Safety Update

On September 5, 2003, the Sponsor submitted a Twelve-Month Safety Update as Amendment-021. Study E2002-2, which was ongoing at the time of the Second Safety Update, was completed. Three of 14 subjects reported adverse events. These included headache, mild dizziness, and constipation. No clinically significant dermal findings and no photosensitivity skin reactions occurred during the conduct of Study E2002-2.

7.9. Drug Withdrawal, Abuse, and Overdose Experience

No serious adverse events were reported as a result of Estrasorb™ abuse or overdose during the clinical trials. Overdosage of estradiol may cause nausea and vomiting and withdrawal bleeding in postmenopausal women with uteri.

7.10. Adequacy of Safety Assessment

Safety assessments were similar in the integrated studies in the ISS (Studies E98-1, E98-2 and E99-1). These included routine collection of vital signs, physical examination, FSH and estradiol serum concentrations, clinical laboratory tests (hematology, chemistry, urinalysis, HIV/RPR/hepatitis screens, urine drug screen, TSH-ICLA), EKGs, mammogram, Pap smear, and pelvic exams, and dermal assessment. In Study E99-1, in addition, a transvaginal ultrasound and an endometrial biopsy were performed. Treatment emergent adverse events and serious adverse events were recorded and reported in all studies.

A total of 335 subjects were randomized across the three studies included in the integrated safety database (78% were white, 18% were black, 4% were other races). One hundred thirty four (134) subjects received placebo. A total of 201 subjects received Estrasorb™ with 139 of these Estrasorb™ subjects receiving the 3.45 gram Estrasorb™ dose containing 2.5 mg estradiol/gram, the subject of this NDA (32 received 1.15 grams of Estrasorb™ and 30 received 2.30 grams of Estrasorb™).

Reviewer's Comments

The pre-study and on-treatment safety assessments were appropriate for an HRT clinical trial in postmenopausal women. The number of subjects exposure to treatment in Studies E98-1, E98-2, and E99-1 is similar to, and exceeds in some cases, the subject population in other clinical trials for a vasomotor symptoms indication.

As previously noted under Section 7.4. Safety Findings from Clinical Studies, Reviewer's Comments, page 35, the finding demonstrated inconsistencies in implementation of the study design for Study E99-1 regarding safety monitoring of the endometrium following exposure to estradiol in women with uteri. Nine subjects in the Estrasorb™ treatment group with an end-of-study transvaginal ultrasound double-wall endometrial thickness > 4 mm refused to have an end-of-study endometrial biopsy after 12 weeks of unopposed estradiol and were not provided a second course of medroxyprogesterone acetate per protocol. It is uncertain from the submission if these subjects were referred to private healthcare providers for further evaluations.

As previously stated, every effort should be undertaken to encourage study participants in estrogen alone and estrogen/progestin treatment groups in clinical trials to comply with the recommendation for a baseline and end-of-study endometrial biopsy with appropriate referral for definitive management, when necessary.

7.11. Labeling Safety Issues and Postmarketing Commitments

The proposed labeling for Estrasorb™ complies with the Agency's 2003 draft labeling guidance for estrogen drug products.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

Based on the preliminary information obtained in the supportive 4-week, dose-finding Study E98-2, the 3.48 gram Estrasorb™ daily dose containing 8.7 mg of estradiol (2.5 mg of estradiol/gram) demonstrates effectiveness for the relief of moderate to severe vasomotor symptoms in postmenopausal women. See the discussion of the findings of Supportive Study E98-2 on page 27 of this review.

In the primary safety and efficacy clinical trial (Study E99-1), Estrasorb™ topical emulsion was administered daily utilizing three 1.15 gram foil-laminated pouches each containing 2.5 mg estradiol/gram as estradiol hemihydrate. Study E2000-1, to evaluate estradiol residual on the skin surface, also utilized the 1.15 gram foil-laminated pouch. No direct clinical data was presented for any other packaging configuration. However, in the submission, the Sponsor submitted the results of an *in vitro* pouch expression study comparing the three 1.15 gram pouches packaging configuration to the two 1.74 gram pouches packaging configuration. In addition, the Sponsor reported the results of two phase 1 studies using the two 1.74 gram pouches packaging configuration (Study E2002-1 and Study E2002-2).

Reviewer's Comments

Based on the information provided in the NDA, the two 1.74 gram pouches packaging configuration (3.48 grams of Estrasorb™) is acceptable.

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicants Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity. Comments on Adequacy of the Applicant's Analyses

Estrasorb™ should only be used in postmenopausal women for the relief of moderate to severe vasomotor symptoms. The majority of subjects in the integrated studies in the ISS were between 50 to 59 years of age (59%, 199 of 335 subjects). Thirty-one percent (31%) of subjects were < 50 years of age (104 of 335 subjects), and 10% of subjects were > 59 years of age (32 of 335 subjects). The majority of subjects were white (78%, 260 of 335 subjects).

For the 12-week primary Study E99-1, 60% of subjects were between 50 to 59 years of age (119 of 200 subjects), 30% were < 50 years of age (61 of 200 subjects), and 10% were > 59 years of age (20 of 200 subjects). Upon request, the Sponsor provided data on the change from baseline for the frequency and severity of moderate to severe hot flushes by age category (< 50 years of age, 50 to 59 years of age, > 59 years of age) for Study E99-1. The changes in the frequency and severity of moderate to severe hot flushes were similar for the < 50 and 50 to 59 years of age subgroups at weeks 4, 8, and 12. This was not so for the > 59 years of age subgroup. However, the > 59 years of age subgroup has too few subjects (10%, 20 of 200 subjects) to permit conclusions.

For both the frequency and severity of hot flushes, 3.45 grams Estrasorb™ containing 2.5 mg of estradiol/gram, applied daily, demonstrated a consistent statistically significant reduction at weeks 4 and 12 in the < 50 and 50 to 59 years of age subgroups.

9.2. Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

A request for a pediatric waiver was submitted on June 29, 2001. Estrasorb™ is recommended for use in postmenopausal women for the treatment of moderate to severe hot flushes associated with the menopause.

Reviewer's Comments

A pediatric waiver should be granted.

9.3. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy

No data is available or needed for other special populations. Estrasorb™ should not be used during pregnancy.

10. CONCLUSIONS, RECOMMENDATIONS, AND LABELING

10.1. Conclusions Regarding Safety and Efficacy

Estradiol has been used clinically for hormone replacement therapy for many years and estradiol drug products have been shown to be safe and effective for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Both oral tablets or transdermal systems are currently approved for this indication. However, orally administered estrogens are subject to metabolite formation due to the first pass effects of the liver which could result in increased systemic effects. On the other hand, transdermal system estrogens are not subject to metabolite formation due to the first pass effects of the liver that could result in reduced systemic effects, but transdermal systems could produce mild erythematous local skin reactions. Poor adhesion to skin surfaces may also complicate patch use.

In this submission, an alternate delivery system is proposed utilizing a topical water-in-oil emulsion containing estradiol. Estrasorb™ is rubbed daily into the upper thighs and calf areas of both legs. This delivery system could prove beneficial for postmenopausal women who cannot or will not take tablets and who prefer not to apply a transdermal patch every four days or once weekly.

Results from one placebo-controlled clinical trial have demonstrated a clinically and statistically significant relief of moderate to severe hot flushes associated with the menopause in healthy postmenopausal women.

Only a limited number of mild and moderate adverse events were reported with Estrasorb™ use in the nine clinical trials included in this submission.

10.2. Recommendations on Approvability

The data presented in this new drug application (NDA) provides evidence from one controlled clinical trial (Study E99-1) to support the safety and efficacy of 3.48 grams of Estrasorb™ (two 1.74 gram foil-laminated pouches) containing 8.7 mg of estradiol (2.5 mg of estradiol/gram), applied topically each day, for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

10.3. Labeling

The trademark Estrasorb™ was submitted to the Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS) for assessment of the proposed propriety drug name. DMETS has no objection to the use of the propriety name, Estrasorb™.

The established name '[redacted]." was consulted with The Labeling and Nomenclature Committee (LNC). The LNC recommended the established name be revised to read, "estradiol topical emulsion". This revision has been incorporated into labeling.

The proposed labeling submitted has been modified in accordance with the Agency's 2003 draft labeling guidance entitled, "Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Prescribing Information for Healthcare Providers and Patient Labeling" (see **Federal Register**/ Volume 68/ Monday, February 3, 2003/Notices). Several major and minor changes are recommended. See the attached labeling in Appendix 1 of this review.

The **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** and **Special Populations**, subsections have been revised to include information found in other approved estrogen labels. The **Drug Interactions** subsection has been revised to include information on P450 3A4 inducers and inhibitors. In the **Clinical Studies** subsection, the Sponsor is requested to delete the proposed table and figure and insert two tables showing: (1) the change in the mean numbers of moderate to severe vasomotor symptoms, ITT population, and (2) the change in the mean severity of vasomotor symptoms, ITT population.

The **INDICATIONS AND USAGE** and **CONTRAINDICATIONS** sections have been revised in accordance with the Agency's 2003 draft labeling guidance. Under the **WARNINGS** section, revised language has been recommended for the following subsections, **Cardiovascular disorders** and **Malignant neoplasms. A Visual abnormalities** subsection has been added. In the **PRECAUTIONS, A. General** subsection, revised language is recommended for the following subsections, **Elevated blood pressure, Hypothyroidism, Exacerbation of endometriosis**, and **Hypocalcemia** subsections. The following subsections have been added under **PRECAUTIONS, A. General, Ovarian cancer** and **Exacerbation of other conditions.**

Pregnancy, Nursing Mothers, Pediatric Use subsections have been modified. A **Geriatric Use** subsection has been added.

The **PATIENT INFORMATION** insert has been modified in compliance with the plain language initiative, recommendations from the Division of Drug Marketing, Advertising and Communications (DDMAC), and the Division of Surveillance, Research & Communication Support (DSRCS), and the Agency's 2003 draft labeling guidance.

Number of Pages Redacted 23

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/s/

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