Supportive Studies, Continued

Results of Supportive Studies

In all reviewed studies, all drug products except a research formulation of 17α-dihydroequilin (which was weakly effective) were shown to reduce vasomotor symptoms to substantial and satisfactory degree. However, in no case did the treatment eliminate all severe hot flashes for all patients, though higher doses tended to reduce the number of symptomatic patients. All studies that compared two drug products showed similar reductions for both products.

In those studies using a placebo control, a marked decrease in hot flashes was noted in the placebo arm. Often, the decrease in the placebo arm paralleled and nearly equaled the decrease seen in the active treatment arm(s) for the first few weeks, after which the number of hot flashes in the placebo arm leveled off or began to return to baseline values for most patients. This observed placebo effect in vasomotor studies has been attributed to the subjective nature of the assessment – most studies use self-assessment diaries. However, the placebo effect has been objectively observed using thermography [11]. It is thought that patients who are motivated to seek treatment and are given placebo initially can regulate their bodies thermal response but that this capacity lessens over time.

Conclusions

The following conclusions can be drawn from the literature regarding the effectiveness of estrogens as a class for the treatment of vasomotor symptoms in postmenopausal women:

- The dose required to completely resolve all vasomotor symptoms differs by individual
  - There is a wide range of dosage strengths that are effective for a population. Doses equivalent to 0.3 – 2.5 mg conjugated estrogens may be required, depending on the individual.
  - Dosing should begin at the lowest effective dose and increased based on efficacy and tolerance
- All sources of estrogens that are capable of delivering blood levels of estradiol–estrone, estradiol, conjugated estrogens, esterified estrogens – are equally effective at treating vasomotor symptoms.
- The source of therapeutic estrogens can be oral, transdermal or vaginal. [12,13]

In 1972, as part of the Drug Efficacy and Safety Initiative (DESI), the FDA determined[14] that many of the products then available on the market were safe and effective for the treatment of several postmenopausal symptoms, including vasomotor symptoms and atrophic vaginitis. The drug substances contained in these DESI-reviewed products included estrone sulfate (stabilized as the piperazine salt), estradiol, esterified estrogens, synthetic conjugated estrogens and conjugated estrogens. The drug products on the approved list included both innovator and generic versions.

Supportive Studies, Continued

Table 1

Single-Active Drug Product Efficacy Studies for Vasomotor Symptoms

Drug	Daily Dose	Study Design	Treatment Duration	No. of Patients	Reference
Estrone					
Harmogen (PES)	3.0 mg	Double-blind, placebo-controlled, crossover	6 months	66	Poller
See Wilcox under Equilin					Wilcox
Estradiol, Oral					
E2; Oestrogel	2-4 mg; 3 mg	Randomized, comparative	6 months	38	Fahraeus
E2 (Syntex)	2 mg	Open-label	3-month intervals	1951 patient-months	Martin
E2	1-4 mg	Open-label	6 months	369	Callantine
Estradiol, Transdermal					
Estraderm TTS	50 mcg	Double-blind, placebo-controlled	6 weeks	19	Haas
FemPatch	20 and 40 mcg	Double-blind, placebo-controlled	12 weeks	324	Speroff
Estraderm TTS	*	Double-blind, placebo-controlled	3 weeks	20	Laufer
Estraderm TTS	25, 50, and 100 mcg	Randomized, dose-response	3 weeks	26	Selby
Estraderm TTS	25, 50, 100, and 200 mcg	Double-blind, randomized, prospective, placebo-controlled	20 days	50	Steingold
Alora TD	50, 100 mcg	Double-blind, placebo controlled, double-dummy, randomized, parallel-group	12 week	273	Good
E2 TD	50 mcg	Double-blind, placebo-controlled, randomized, multicenter	12 weeks	242	Wiklund
Equilin					
17α- DHQ sulfate; Ogen (PES)		Prospective, randomized	3 months	21	Wilcox
See Beck under Comparative Studies					Beck
Multiple Ingredient Products					
Premarin	1.25 mg	Double-blind, placebo-controlled	3 months	30	Coope
Estratab (Esterified estrogens)	0.3, 0.625, and 1.25 mg	Double-blind, placebo-controlled, prospective, multicenter	2 years	406	Mortola
Premarin	1.25 mg	Double-blind, placebo-controlled, crossover	2-6 months	68	Campbell

Abbreviations: PES: piperazine estrone sulfate; EE: ethinyl estradiol; E2: estradiol; CEE: conjugated equine estrogens; TD: transdermal; HF: hot flashes; E2: estradiol; E1: estrone; PM: Postmenopausal

*Dose not specified.

Supportive Studies, Continued

Table 2

Multiple-Active Drug Product Efficacy Studies for Vasomotor Symptoms

Drug	Daily Dose	Study Design	Treatment Duration	No. of Patients	Reference
Ogen (PES); Premarin	1.5 mg; 0.625 mg	Double-blind, crossover, multicenter	28 days	168	Lozman
Climara; Premarin	50, 100 mcg; 0.625 mg	Double-blind, placebo-controlled, parallel-group	11 weeks	603	Gordon
Sodium equilin sulfate; Premarin	0.1, 0.25, 0.5 mg; 0.625 mg	Double-blind, sequential, crossover	4-12 weeks	18	Beck
Estraderm TTS (Ciba-Geigy); EE	50 mcg; 20 mcg	Double-blind, crossover, placebo-controlled	6 months	25	Pattison
Estraderm; Premarin	0.1 mg; 0.625 and 1.25 mg	Double-blind, randomized, parallel-group	3 weeks	166	Place
PES; EE	1.5 mg; 0.01 mg	Double-blind, crossover, multicenter	6 weeks	79	Flury
Study A: Menorest; Premarin Study B: Menorest; Estraderm TTS	A: 50 mcg; 0.625 mg B: 50 mcg; 50 mcg	A: Double-blind, randomized, comparative, parallel-group, multicenter, international B: Open-label, randomized, comparative, parallel-group, multicenter, international	A: 4 months B: 4 months	A: 214 B: 205	Pornel

Abbreviations: PES: piperazine estrone sulfate; EE: ethinyl estradiol; E2: estradiol; CEE: conjugated equine estrogens; TD: transdermal; HF: hot flashes; E2: estradiol; E1: estrone; PM: Postmenopausal

Continued on next page

Supportive Studies, Continued

Poller L, 1975: This was a randomized, double blind, placebo-controlled study designed to evaluate the effects of piperazine estrone sulfate (PES) on depression, hot flushes, blood clotting, and fibrinolysis. Fifty-five (55) menopausal women completed this 14-month trial. The women were randomized to one of two treatment groups: Group A (N=29) received piperazine estrone sulfate 3 mg daily for 21 days out of 28 days for 6 months with an interval of 2 months non-matching (single-blind) placebo tablets followed by 6 months of cyclical matching placebo. Group B (N=26) received the same treatment in the reverse order. A coagulation profile was performed on 28 serial entrants to the study. Daily flush counts were recorded on diary cards, and the Beck Depression Inventory was completed at baseline, 6, 8, and 14 months. Serum estrone, FSH, and a biochemical profile were performed on fasting blood at baseline, 6, 8, and 14 months. Women were asked to assess their state of health (global assessment) at the beginning and end of each course of treatment. **Efficacy in Hot Flushes:** Both groups showed similar and significant improvement from baseline for two months; after two months, the two groups differed. After 5 months of therapy, the PES group showed a significantly greater reduction ($P<.05$) in mean hot flushes than the placebo group. At 6 months, the significant difference remained the same, but at 7 months, the group withdrawn from estrogen and given placebo showed a rapid deterioration and reached the baseline level of flushes at 8 months. From 8 to 14 months, this group was treated with matching placebo but showed no placebo response. The group who received placebo for the first 6 months showed a 50% placebo response until 8 months. During months 9 and 10 and months 11 through 14, they showed a significant improvement ($P<.05$ and $P<.01$, respectively).

Fahraeus, 1982: This uncontrolled study was designed to compare the effects during 6 months of treatment with oral and cutaneous estradiol on the plasma levels of estrone, estradiol, LH, FSH, and sex hormone binding globulin (SHBG). Thirty-eight symptomatic postmenopausal women who had not received ERT for at least 3 months before study initiation were randomized to treatment. Study personnel interviewed patients about their symptoms at baseline, 2, 4, and 6 months using the Kupperman mean menopausal index. **Efficacy in Hot Flashes:** Before treatment, the mean menopausal index was 23 in the oral and 22 in the cutaneous group. After 2, 4, and 6 months of therapy, the indexes were 12, 9, and 6 in the oral and 9, 5, and 4 in the cutaneous group, respectively. The indexes were significantly reduced ($P<.001$) in both groups at all treatment intervals. No significant differences between the groups were observed.

Continued on next page

Supportive Studies, Continued

Martin, 1972

This uncontrolled study was initiated to evaluate the tolerance and clinical effectiveness of oral estradiol (E2). The 112 patients in this study, who had expressed a preference for oral estradiol in a pre-study preference trial, were evaluated at 3-month intervals for a total of 1951 patient-months. Some were on a 3-week cyclic schedule of 1 tablet daily for 3 weeks on and 1 week off; and others were on a continuous schedule of 1 tablet daily with interval shedding each 90 days, using one of several progestin preparations. **Efficacy in Hot Flashes:** Of the 112 patients, 85 reported no hot flushes, 19 reported mild, 7 reported moderate, and 1 patient reported severe hot flushes after treatment with E2.

Callantine, 1975:

This uncontrolled study was a follow-on to the Martin, et al, study. A total of 369 patients with estrogen deficiency and related menopausal symptoms received cyclic (21/28 days) micronized estradiol (E2) therapy. The initial daily dose of E2 was determined by the number of hot flushes the patient experienced each day: those who had < 5 flushes/day received 1 mg E2; patients who reported > 6 flushes/day were given 2 mg E2. Response to therapy was evaluated at intervals of 2 months or less during the first 6 months and every 3 months thereafter. If symptoms were not relieved within 7 days after beginning therapy, the dose was increased stepwise to a maximum of 4 mg/day. The incidence of menopausal symptoms, including genital atrophy, were evaluated. **Efficacy in Hot Flashes**: Over 95% of the 319 patients evaluable for efficacy obtained satisfactory relief of their symptoms. Hot flushes, sweating, tingling, and genital atrophy disappeared in 76% (227/298), 80% (131/164), 94% (62/66), and 88% (44/50) of patients, respectively.

Continued on next page

Supportive Studies, Continued

Haas, 1988: Nineteen women, who had undergone bilateral oophorectomy at least 1 month earlier or natural menopause at least six months earlier and who had recorded 8 or more subjective hot flashes/day, were enrolled in this double-blind, placebo-controlled study. Seventeen patients completed the 12-week study. Patients had not received HRT for at least 30 days before study initiation. Patients were randomized to receive either transdermal estradiol or placebo. The study was divided into a 4-week pretreatment phase, a 6-week treatment phase, and a 2-week placebo phase, during which subjects continued to monitor symptoms while using a placebo patch. Each day subjects noted the number of mild, moderate, and severe hot flashes. Thermography was also performed. **Efficacy in Hot Flashes:** Hot flashes among placebo patients were never statistically significant from baseline for any subcategory (mild, moderate, or severe) or for the total number of hot flashes. In contrast, patients on transdermal estradiol reported a 35% decline in hot flashes at week 6 and a 74% decline at week 8, with a stable rate thereafter. ANOVA showed this decrease to be statistically significant for total, severe, and moderate hot flashes ($P<.002$), but not for mild flashes. Vasomotor flushes objectively quantified by skin temperature recordings were significantly decreased ($P<.01$). No significant differences in reported hot flashes between the transdermal estradiol and placebo groups were found until the fourth week.

Speroff, 1996: A total of 324 surgically or naturally menopausal women, all with prior hysterectomy and moderate to severe vasomotor symptoms (56 to 140 hot flushes per week), participated in two independent, 12-week, randomized, double-blind, placebo-controlled studies. Each patient received either one estradiol transdermal system, two estradiol transdermal systems, or placebo applied every week for 12 weeks. Efficacy was measured as a reduction in hot flush frequency, determined from subject diaries. **Efficacy in Hot Flashes:** The mean hot flush frequency was reduced by 84% after 12 weeks of the transdermal estradiol treatment. This reduction was statistically significant from weeks 3 through 6 ($P<.001$). Compared with placebo, the decrease in hot flush frequency for transdermal estradiol was significant as early as weeks 2 and 3 and was maintained through week 12 ($P<.001$). More subjects withdrew from the placebo group because of lack of efficacy (9 [6%]) than from the estradiol group (2 [1%]).

Continued on next page

Supportive Studies, Continued

Laufer, 1983: Twenty postmenopausal women with a frequency of >10 hot flashes per day were randomized to receive either transdermal estradiol or placebo in a double-blind fashion for 3 weeks. Twenty premenopausal women were studied during the early and late portions of the follicular phase of their menstrual cycle for comparison. Hot flashes were recorded both objectively (by thermography) and subjectively. **Efficacy in Hot Flashes:** Patients receiving transdermal estradiol experienced a significant (P<.002) reduction in the frequency of hot flashes compared to placebo, and hot flashes were completely eliminated in 3 of the 10 patients. The placebo group did not experience a change between baseline and end-of-treatment values.

Selby, 1986: Twenty-six symptomatic postmenopausal women, who had not received HRT within the month before study initiation, were randomized to one of three doses of transdermal estradiol, 0.025, 0.05, or 0.1 mg, for 3 weeks. A symptom score was derived after a clinical assessment,. **Efficacy in Hot Flashes:** All doses of estrogen reduced symptom scores, with the 0.05 mg and 0.1 mg doses exhibiting a statistically significant decrease (P<.01 and P<.001, respectively).

Steingold, 1985: Fifty postmenopausal women with > 10 hot flashes per day were prospectively assigned to receive one of three doses of transdermal estradiol (0.025, 0.05, 0.1, and 0.2 mg/day) or placebo for 20 days. Patients had discontinued ERT at least 30 days before start of study. Hot flashes were measured subjectively and objectively by thermography. **Efficacy in Hot Flashes:** A linear reduction in hot flashes with increasing doses was observed. A 91% reduction in hot flashes was seen with the 0.2 mg group. During the placebo, 0.025, 0.05, 0.1, and 0.2 mg dosage treatments, 0, 0, 3, 3, and 6 women, respectively, had no hot flashes. All women using the 0.05 mg or higher dosage noted substantial relief of symptoms.

Continued on next page

Supportive Studies, Continued

Good, 1996: In this 12-week, double-blind, double-dummy, randomized, parallel-group study, the efficacy and safety of an estradiol matrix transdermal delivery system (Alora) was compared with placebo in 273 healthy postmenopausal women who were experiencing at least 60 moderate-to-severe hot flushes per week. After a 2-week therapy-free screening period, patients were randomized into one of the following parallel treatment groups: 50 μg of estradiol/day (88 patients); 100 μg of estradiol/day (94 patients); or placebo (91 patients). For 12 weeks, patients recorded the frequency (weekly number) and severity (mild, moderate, or severe) of hot flushes on diary cards. **Efficacy in Hot Flashes:** In the intent-to-treat population, a statistically significant decrease in moderate-to-severe hot flushes occurred by week 3 for the 50-μg/day group and by week 2 for the 100 μg/day group ($P<.02$ and $P<0.001$, respectively, compared with placebo). At week 12, the mean percent reduction in moderate-to-severe hot flushes was 86.6% (from 90 per week to 12 per week) for the 50 μg /day group and 92.5% (from 90 per week to 7 per week) for the 100 μg/day group. Hot flushes disappeared in 48% of patients in the 50 μg/day group and in 68% of patients in the 100 μg/day by week 12.

Wiklund, 1993: A total of 242 symptomatic postmenopausal women were enrolled in this double-blind, placebo-controlled study, which was designed to compare the effects of transdermal estradiol (E2) and placebo on menopausal symptoms and quality of life. Clinical and tolerability and efficacy data were evaluated at baseline and after 6 and 12 weeks of treatment. Menopausal symptoms were assessed using a menopausal index, slightly modified from that of Kupperman. One hundred seventeen were randomized to receive transdermal estradiol replacement therapy and 122 to placebo treatment. **Efficacy in Hot Flashes:** For the Women Health Questionnaire, which rated psychological and somatic symptoms experienced by perimenopausal women, the mean vasomotor symptom score at 3 months decreased from 7.1 to 3.0 for patients receiving transdermal E2 and from 7.1 to 5.8 for patients receiving placebo. The mean difference between the two treatments was statistically significant ($P=.0001$). In addition, the women rated menopausal symptoms using visual analog scales. For vasomotor symptoms, the mean score fell from 107.5 to 23.5 for the E2 group and from 103.9 to 85.0 for the placebo group ($P=.0001$ compared to placebo).

Continued on next page

Supportive Studies, Continued

Wilcox, 1996: Twenty-one postmenopausal women were enrolled in this 3-month, prospective, randomized uncontrolled clinical trial designed to evaluate the biological effects of 17α-dihydroequilin sulfate. The women were randomized into one of three treatment groups (7 women per group): estrone sulfate 1.2 mg; 17α-dihydroequilin sulfate 0.2 mg; or the combination of both. During each visit, subjects were asked to report the number of severe vasomotor episodes (hot flashes or night sweats). **Efficacy in Hot Flashes:** All subjects in the estrone sulfate and combination groups noted subjective relief of vasomotor symptoms, but not in the 17α-dihydroequilin sulfate group at the dose administered (previous studies indicate that 17α-dihydroequilin possesses biological potency[15])

Coope, 1975: In this double blind, placebo-controlled study, 30 women presenting with menopausal symptoms for over 6 months were randomized to one of two groups (15 patients each). Group 1 patients received Premarin during three 21-day courses with a 7-day interval between each course followed by 3 months of placebo. Group 2 patients received placebo first followed by Premarin. Efficacy was measured using the Kupperman menopausal index. **Efficacy in Hot Flashes:** The menopausal index scores improved significantly in both groups during the first 3 months, though the difference between the two groups was not statistically significant (P=.07). However, after the exclusion of 3 patients who had no hot flushes at the onset of the study, the proportional reduction in hot flushes on Premarin compared to placebo was statistically significant (P=.04). In Group 2 patients, a further improvement in scores after changing to Premarin was seen. Ten women on Premarin compared to 4 on placebo reported total disappearance of hot flushes during the first 3 months.

Mortola, 1996: This 2-year, double blind, placebo-controlled, multicenter, prospective study in 406 early postmenopausal women evaluated the effects of 3 doses of esterified estrogen. Severity of symptoms was measured with the Kupperman index at baseline and at 6-month intervals. The analysis population consisted of 365 patients who returned for at least one menopausal symptom evaluation after baseline. **Efficacy in Hot Flashes:** At 6, 12, 18, and 24 months, the mean changes from baseline for the Kupperman index total menopausal score were statistically significant (P<.05) for all three esterified estrogen treatment groups but not for placebo.

Continued on next page

Supportive Studies, Continued

Campbell, 1977: Depending on the severity of their symptoms, patients were allocated to one of two double-blind, placebo-controlled, randomized, crossover studies: 68 patients with severe symptoms were allocated to a 4-month study in which Premarin and placebo were each taken for 2 months; 68 patients with less severe symptoms were allocated to a 12-month study in which Premarin and placebo were each taken for 6 months. Patients were evaluated every 2 months. Sixty-four patients on the short study and 61 patients on the long study were available for analysis. **Efficacy in Hot Flashes:** In the 4-month study, patients receiving Premarin showed a statistically significant improvement in hot flushes compared with patients receiving placebo ($P<0.001$).

Lozman, 1971 A total of 168 patients were enrolled in and 131 completed this multicenter, double-blind, crossover study, which was designed to compare cyclic doses of piperazine estrone sulfate (Ogen) and conjugated estrogens equine (Premarin). Patients were asked to evaluate the presence or absence of target symptoms and their severity (mild, moderate, or severe). **Efficacy in Hot Flashes:** Two-thirds of the patients were either asymptomatic or reported fewer target symptoms after 21 days of treatment. Between 40% and 60% of patients were asymptomatic for any given symptom during both cycles. No flushes were reported by 45% of the patients during either cycle, and 56% of patients did not experience sweats. In patients who had symptoms, a larger percentage of patients reported that flushes (25% to 19%) and sweats (22% to 13%) were less severe during the conjugated estrogens equine cycle than during the piperazine estrone sulfate cycle.

Gordon, 1995 This article presents data from the combined analysis of studies comparing the efficacy and safety of a 7-day estradiol transdermal system, 0.625 mg conjugated equine estrogens, and placebo. In one study, two doses of the patch were compared with conjugated estrogens in 342 women. **Efficacy in Hot Flashes:** Compared with baseline, all three treatments significantly reduced hot flushes over the 11-week trial ($P<.01$). Both 7-day patches were comparable in efficacy to the conjugated estrogens. In the study in 191 women comparing the two 7-day patches with placebo, both estradiol groups were significantly more effective across all treatment cycles ($P<.05$) compared with placebo.

Continued on next page

Supportive Studies, Continued

Beck, 1975	This uncontrolled study was designed to compare the effects of 0.1, 0.25, and 0.5 mg sodium equilin sulfate and 0.625 mg Premarin in 12 postmenopausal women and 6 ovariectomized women. Patients were dosed with 0.25 mg equilin for 12 weeks. After a 1-week washout , patients were dosed with 0.625 mg Premarin for 5 weeks. After a 1-week washout, patients were dosed with 0.5 mg equilin followed by 8 weeks of 0.1 mg equilin. **Efficacy in Hot Flashes:** Equilin sulfate in a range of 0.2 to 0.3 mg was considered optimal in alleviating vasomotor symptoms
Pattision, 1989	Twenty-five postmenopausal women were enrolled in this 6-month, double blind, placebo-controlled crossover study. Patients were assigned to one of the following two treatments: transdermal estradiol and oral placebo or placebo patch and oral ethinyl estradiol. Each treatment phase lasted 3 months. Patients completed a Postmenopausal Symptom Diary. **Efficacy in Hot Flashes:** The patients' symptom scores were improved after both transdermal estradiol and oral ethinyl estradiol treatment. A statistically significant difference from baseline in vasomotor symptom scores was seen in patients taking transdermal estradiol and oral ethinyl estradiol. No significant difference was seen between treatments.
Place, 1985	A total of 166 patients who had been maintained on conjugated equine estrogens (CEEs) were entered into this double blind, placebo-controlled, randomized, parallel group, multicenter study. After study entry, patients remained on their CEE dosage for 3 weeks while wearing placebo transdermal systems. They then entered a 1-week phase in which they received placebo doses of both oral and transdermal (Estraderm) administrations. At week 5, patients were randomized to one of 4 treatment groups: 0.625 mg Premarin; 0.625 mg Premarin, then Estraderm 0.1 mg; 1.25 mg Premarin; 1.25 mg Premarin, then Estraderm 0.1 mg. Patients received diaries with instructions to record daily the number and intensity of hot flushes (on a scale of 0 to 9) and the frequency and intensity of other menopausal symptoms. **Efficacy in Hot Flashes:** 124 patients completed at least 6 weeks of the study and were included in the efficacy analysis. The percentage of women within each treatment group that showed no flushes was consistently between 25% and 50%. Neither within- nor between-patient comparisons revealed any statistically significant differences in frequency of hot flushes between the Estraderm and Premarin groups. Results of a within-patient comparison of the frequency of hot flushes in weeks 1 to 3 versus weeks and 5 to 7 showed no statistically significant differences (P>.10) in the mean number of hot flushes per week for the four groups. About 85% of the women experienced eight or fewer hot flushes per week during the study. Mean values for symptom severity ranged between 0.83 and 1.69 (where 0 was the mildest and 9 the most severe).

Continued on next page

Supportive Studies, Continued

Flury, 1977

This study was a 6-week, double blind, multicenter, crossover trial in 79 women with postmenopausal symptoms. After a 2-week control period in which no medication was given, patients were treated with piperazine estrone sulfate (PES) and ethinyl estradiol (EE) in a 3-week crossover fashion. Assessments of the severity (severe, moderate, mild, and absent) and response of 10 named symptoms were made initially, at the end of the 2-week control period, and at the end of each 3-week treatment period. **Efficacy in Hot Flashes:** During the control period, little change in the mean severity of symptoms was seen, but during the first 3-week treatment period, a similar reduction in mean severity in both groups was seen. During the second 3-week period, the results were similar for both groups; only a slight reduction in the mean scores was observed. A 44% improvement in mean scores was seen with PES and 40% with EE; this difference was not statistically significant. For both groups, a 53% improvement in mean severity of vasomotor symptoms was seen.

Pornel, 1996

In these two randomized, parallel-group, international, multicenter studies of 4 months' duration, the women had moderate to severe vasomotor symptoms (21 hot flushes/week) for the last 2 weeks of the 4-week run-in period. Study A enrolled 214 women and Study B, 205. Patients enrolled in Study A were randomized in double-blind fashion to receive either continuous Menorest 50 (applied twice weekly) or continuous Premarin 0.625 mg/day. All the women received dydrogesterone 10 mg/day on the last 12 days of each 28-day cycle. Patients enrolled in Study B, an open-label study, received either Menorest 50 or Estraderm TTS 50, both applied twice weekly for 25 days of each 28-day cycle. The mean change in the number of hot flushes per day at week 12 compared with baseline was the primary efficacy criterion. **Efficacy in Hot Flashes:** A significant decrease in the number of hot flushes per day at week 12 compared with baseline was observed in both studies. Most of the improvement had occurred by week 6 of treatment. No significant difference between treatments was observed in either of the studies. In study A, the mean number of hot flushes decreased from 7.14 per day at baseline to 0.92 per day at cycle 3 in the Menorest group and from 6.66 to 0.54 in the Premarin group. In study B, the mean number of hot flushes decreased from 6.5 per day at baseline to 0.3 per day at cycle 3 in the Menorest group and from 6.4 per day to 0.4 per day in the Estraderm group.

Continued on next page

Supportive Studies, Continued

References of Studies

1. Beck VA, Friedrich F. Equilinsulfat zur substitution beim menopause-syndrom. Wiener Klinische Wochenschrift. 1975;87(2):59-62. (English transcription supplied)
2. Callantine MR., Martin PL, Bolding OT, Warner PO, Greaney MO. Micronized 17β-estradiol for oral estrogen therapy in menopausal women. *Obstet Gyn.* 1975;46(1): 37-41.
3. Campbell S, Whitehead M, Oestrogen therapy and the menopausal syndrome. *Clin Obst Gynaec.* 1977;4(1):31-47.
4. Coope J, Thomson JM, Poller L. Effects of "natural oestrogen" replacement therapy on menopausal symptoms and blood clotting. *Br Med J.* 1975; 4:139-143.
5. Fahraeus L, Larsson-Cohn U. Oestrogens, gonadotrophins and SHBG during oral and cutaneous administration of oestradiol-17β to menopausal women. *Acta Endocrinol. 1982; 101:592-596.*
6. Good WR, John VA, Ramirez M, Higgins JE. Double-masked, multicenter study of an estradiol matrix transdermal delivery system (Alora™) versus placebo in postmenopausal women experiencing menopausal symptoms. *Clin Ther.* 1996; 18(6): 1093-1105.
7. Gordon SF. Clinical experience with a seven-day estradiol transdermal system for estrogen replacement therapy. *Am J Obstet Gynecol.* 1995; 173(3 Part 2):998-1006.
8. Haas S, Walsh B, Evans S, Krache M, Ravnikar V, Schiff I. The effect of transdermal estradiol on hormone and metabolic dynamics over a six-week period. Obstet Gynecol, 1988; 71(5):671-676
9. Jones MM, Pearlman B, Marshall DH, Crilly RG, Nordin BEC. Dose-dependent response of FSH, flushes and urinary calcium to oestrogen. *Maturitas.* 1982; 4:285-290.
10. Laufer LR, DeFazio JL, Lu JKH, et al. Estrogen replacement therapy by transdermal estradiol administration. *Am J Obstet Gynecol.* 1983; 146(5): 533-540.
11. Lozman H, Barlow AL, Levitt DG. Piperazine estrone sulfate and conjugated estrogens equine in the treatment of the menopausal syndrome. *South Med J.* 1971; 64(9):1143-1149
12. Martin PL, Burnier AM, Greaney MO. Oral menopausal therapy using 17β- micronized estradiol. A preliminary study of effectiveness, tolerance and patient preference. *Obstet Gyn.* 1977; 39(5): 771-774.
13. Mashchak CA, Kletzky, OA, Artal R, Mishell DR. The relation of physiological changes to subjective symptoms in postmenopausal women with and without hot flushes. *Maturitas.* 1984; 6:301-308.
14. Mortola J, Akin M, Lucas JD, McNaney-Flint HM, Nolan J, Yang HM, Silfen SL. Reduction in menopausal symptoms following 0.3 mg Estratab administration compared to higher doses and placebo. Poster Presentations. North American Menopausal Society. Chicago. September 26, 1996 to September 28, 1996. Abstract #96.027
15. Natural and synthetic oestrogens in the female climacteric. *The Practitioner.* 1977; 218:573-579.
16. Pattison NS, Uptin T, Knox B, France J, Transdermal oestrogen for postmenopausal women: a double blind crossover comparative study with ethinyl oestradiol. *Aust NZ J Obstet Gynaecol.* 1989; 29:62-65.
17. Place VA, Powers M, Darley PE, Schenkel L, Good WR. A double-blind comparative study of Estraderm and Premarin in the amelioration of postmenopausal symptoms. *Am J Obstet Gynecol.* 1985;152(8):1092-9.
18. Poller L, Thomson JM, Coope J. A double-blind cross-over study of piperazine oestrone sulphate and placebo with coagulation studies. *Br J Obst Gynaec.* 1980; 87:718-725.
19. Pornel B. Efficacy and safety of Menorest® in two positive-controlled studies. *Eur J Obstet Gynecol Reprod Biol.* 1996; 64 Suppl 1:S35-S37.
20. Selby PL, Peacock M. 1986. Dose-dependent response of symptoms, pituitary, and bone to transdermal oestrogen in postmenopausal women. *Br Med J.* 1986; 293(6558) 1337-9.
21. Speroff L, Whitcomb RW, Kempfert NJ, Boyd RA, Paulissen JB, Rowan JP. Efficacy and local tolerance of a low-dose, 7-day matrix estradiol transdermal system in the treatment of menopausal vasomotor symptoms. *Obstet Gynecol.* 1996; 88(4 part 1):587-92.
22. Steingold KA, Laufer L, Chetkowski J, et al. Treatment of hot flashes with transdermal estradiol administration. *J Clin Endoc Met.* 1985; 61(4): 627-632.

References of Studies

23. Stone SC, Mickal A, Rye PH. Postmenopausal Symptomatology, Maturation Index, and Plasma Estrogen Levels. *Obst Gyn.* 1975;45(6):625-627.
24. Thomson J, Oswald I. Effect of oestrogen on the sleep, mood, and anxiety of menopausal women. *Br Med J.* 1977; 2:1317-1319.
25. Wiklund I, Karlberg J, Mattsson L-A. Quality of life of postmenopausal women on a regimen of transdermal estradiol therapy: A double-blind placebo-controlled study. *Am J Obstet Gynecol.* 1993; 168(3):824-30.
26. Wilcox JG, Stancyk FZ, Morris RS, Gentzschein E, Lobo RA. Biologic effects of 17α- dihydroequilin sulfate. *Fertil Steril.* 1996; 66(5): 748-752.