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APPROVAL PACKAGE

APPLICATION NUMBER(S)

21-371

MEDICAL REVIEW(S)

NDA 21-371/S-000

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Review Finalized:	**10/9/03**

Medical Officer's Review

Sponsor:	**Novavax, Inc.** **12111 Parklawn Drive** **Rockville, MD 20852**
Drug Name:	
Generic:	**Estradiol, USP as estradiol hemihydrate**
Trade:	**Estrasorb™**
Pharmacologic category:	**Estrogen**
Route of Administration:	**Transdermal**
Dosage Form:	**Topical emulsion**
Strength:	**3.48 grams of Estrasorb™ containing 8.7 mg of estradiol (2.5 mg of estradiol/gram), USP as estradiol hemihydrate applied daily**
Proposed Indications:	**Treatment of moderate to severe vasomotor symptoms associated with the menopause.**
Related Submission:	**IND 49, 761 (submitted on January 16, 1996)** **NDA 21-371/S-000 (submitted on June 29, 2001,** [redacted]
Related Documents:	**NDA 21-371/S-000 Amendments dated 11/27/02, 12/5/02, 12/17/02, 1/13/03, 1/16/03, 1/28/03, 2/15/03, 4/30/03, 5/5/03, 5/19/03, 5/22/03, 6/5/03, 6/16/03, 7/11/03, 7/29/03, 7/31/03, 8/4/03, 9/5/03, 10/3/03, 10/9/03**

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The Executive Summary of the Primary Clinical Review

1. RECOMMENDATION

1.1. Recommendations on Approvability

From a clinical perspective, the reviewer recommends approval of 3.48 grams of Estrasorb™ (estradiol topical emulsion) containing 8.7 mg of estradiol (2.5 mg of estradiol/gram). 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™, delivered in two 1.74 gram foil-laminated pouches, applied topically each day, for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

1.2 Recommendations on Postmarketing Studies and/or Risk Management Steps Where Appropriate

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™ and the 3.48 gram dose recommended for approval in this submission. This recommendation is based on the data submitted for NDA 21-371. In a 4-week dose-ranging study (Study E98-2), 125 postmenopausal women were randomized to placebo or 1.15 grams (1 foil-laminated pouch), 2.30 grams (two 1.15 gram pouches), or 3.45 grams of Estrasorb™ (three 1.15 gram pouches) containing 2.5 mg of estradiol per gram per day. A linear reduction in vasomotor symptom relief was not demonstrated (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 moderate to severe hot flushes at week 4. The 2.30 gram Estrasorb™ treatment group did not although this dose produced a trough serum estradiol concentration of 34 pg/ml. In the Division's experience from reviews of other clinical trial data for a vasomotor symptoms 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 vasomotor symptoms 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). The results for Study E98-2 leave concerns that the lowest effective dose of Estrasorb™ for this indication has not been determined.

Amendment 24 to NDA 21-372, submitted on October 9, 2003, provides a commitment by Novavax, Inc. to conduct a Phase 4 clinical trial to determine the lowest effective dose of Estrasorb™ per the following timeline: protocol submission within 6 months of the date of receipt of the Estrasorb™ approval letter from the Division of Reproductive and Urologic Drug Products (DRUDP), study start within 6 months of the protocol agreement with DRUDP, and a final study report submitted within 6 months of the study completion.

No risk management steps are recommended.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of the Clinical Program

Estrasorb™ is a topical water-in-oil emulsion containing estradiol USP as estradiol in the hemihydrate form (estradiol hemihydrate). Estrasorb™ utilizes micellar nanoparticles for the topical delivery of estradiol. A micellar nanoparticle is a sub-micron-sized nanoemulsion. The average particle size of the emulsion is

approximately 1 micron. Injecting water into a mixture of soybean oil, polysorbate 80 (a surfactant), and estradiol dissolved in ethanol produces the nanoemulsion.

Estrasorb™ contains estradiol as estradiol hemihydrate at a concentration of approximately 2.5 mg/gram. The recommended dose of Estrasorb™ is 3.48 grams per day containing 2.5 mg of estradiol/gram (total 8.7 mg of estradiol). In the primary clinical trial, a total of 3.45 grams of Estrasorb™ (total 8.625 mg of estradiol) was applied topically each day as follows: 1.15 grams to the right anterior thigh, 1.15 grams to the left anterior thigh, 1.15 grams split between the right and left calf areas. Upon application of the recommended dose, an estimated 50 micrograms of estradiol is delivered to the systemic circulation per day.

Estradiol is an estrogen class hormone. Estrasorb™ is the first estradiol formulated with a topical nanoemulsion delivery system. The treatment of moderate to severe vasomotor symptoms associated with the menopause is the indication being sought by Novavax, Inc. in this submission.

Three early human pharmacokinetic studies were conducted in the clinical development program with micellar nanoparticles containing estradiol hemihydrate. All of these early Phase 1 studies utilized a cream formulation containing — water (Studies N95-3, N96-1, and N97-3) that was packaged in a syringe and only stable at 4° C. Four clinical trials were later conducted utilizing a cosmetic lotion formulation with — water that is — packaged in 1.15 gram foil-laminated pouches (used in phase 1 Studies E98-1 and E2000-1, phase 2/3 Study E98-2, and phase 3 Study E99-1). Two recent studies also utilized the formulation with — water packaged in 1.74 gram foil-laminated pouches (Phase 1 Studies E2002-1 and E2002-2). A total of 375 subjects participated in these six studies with the to-be-marketed formulation.

All nine studies included in the submission were reviewed individually. Phase 3 Study E99-1, conducted to evaluate the safety and efficacy of 3.45 grams of Estrasorb™ containing 8.625 mg of estradiol (2.5 mg of estradiol/gram) versus placebo, was the only study submitted that met the Agency's hormone therapy clinical evaluation guidance treatment duration for a symptomatic indication. A 12-week study duration is required for a symptomatic indication. Phase 2/3 Study E98-2, which also evaluated the safety and efficacy of Estrasorb™, was only 4 weeks in duration. Therefore, Study E98-2 was considered for safety outcomes and not included in efficacy analyses. Phase 1 Study E98-1 evaluated the pharmacokinetics and pharmacodynamics of single-site versus split-site application of 1.15 grams of Estrasorb™ daily for 8 days. Study E2000-1 was initiated at the recommendation of the Agency to evaluate the amount of residual estradiol on the skin after application of 1.15 grams of Estrasorb™ to each thigh. Studies E2002-1 and E2002-2, both initiated at the recommendation of the Agency, evaluated the transfer potential of estradiol to male partners and the effects of the application of sunscreen on the systemic absorption of estradiol, respectively.

Safety data submitted in the 4-Month Safety Update (dated January 13, 2003), in the Second Safety Update (dated May 5, 2003), and in the Twelve-Month Safety Update (dated September 5, 2003) were reviewed upon receipt.

2.2. Efficacy

Overall, the data presented shows that the daily application of 3.45 grams of Estrasorb™ containing 8.625 mg of estradiol (2.5 mg of estradiol/gram) is effective in relieving the frequency and severity of moderate to severe hot flushes associated with the menopause in generally healthy postmenopausal women.

Two hundred (200) healthy postmenopausal women were randomized in the primary 12-week clinical trial (Phase 3 Study E99-1) conducted at 20 US investigational sites. One hundred subjects were randomized to the placebo treatment group and 100 subjects were randomized to the 3.45 gram Estrasorb™ treatment group. Seventy-six percent (76%) of the study population was white, 19% of the study population was black.

The daily application of 3.45 grams of Estrasorb™ containing 8.625 mg of estradiol (2.5 mg of estradiol/gram) was effective in reducing both the frequency and severity of moderate to severe hot flushes at weeks 4 and 12, the primary efficacy time points for a vasomotor symptoms indication ($p<0.001$ versus placebo at both time points).

2.3. Safety

Estradiol has been used clinically for postmenopausal hormone therapy, either given alone or in combination with a progestin, since the mid-1970s. Formulations of estradiol for oral, transdermal and vaginal administration are approved for the indications of treatment of moderate to severe vasomotor symptoms, moderate to severe symptoms of vulvar and vaginal atrophy, hypoestrogenism due to hypogonadism, castration or primary ovarian failure, the palliative treatment of metastatic breast cancer and androgen-dependent carcinoma of the prostate, and for the prevention of postmenopausal osteoporosis.

In total, 425 postmenopausal women were included in the nine studies conducted during the development of Estrasorb™. Three hundred thirty-five subjects (335) appear in the three studies included in the Integrated Summary of Safety (ISS, integrated Studies E98-1, E98-2, and E99-1), and 90 subjects appear in the six non-integrated studies (Studies N95-3, N96-1, N97-3, E2000-1, E2002-1, and E2002-2). There were no deaths reported during any of the clinical trials with Estrasorb™.

Safety evaluations and monitoring were adequate and complete for the 335 subjects in the safety population in the ISS with the exception of the following inconsistencies in the completeness of endometrial monitoring at the end-of-study. Fifty percent of subjects in Study E99-1 had a uterus (101 of 200 subjects). Twelve of these 101 subjects with uteri (12%) were found to have a double-wall endometrial thickness > 4 mm on transvaginal ultrasound examination at end-of-study, but refused to have an endometrial biopsy performed per protocol. These 12 subjects were not provided a second course of medroxyprogesterone acetate, per protocol, and no information was provided regarding referral to private healthcare providers. However, a double-wall endometrial thickness > 4 mm is not unexpected during 12 weeks of unopposed Estrasorb™ in subjects with uteri.

Seven serious adverse events requiring hospitalization occurred in 6 subjects (3 subjects in the placebo treatment group and 3 subjects in the Estrasorb™ treatment group). All of these serious adverse events resolved, and none required discontinuation from the studies.

Headaches (9%, 32 of 335 subjects), endometrial disorder (9%, 32 of 335 subjects), infection (7%, 29 of 335 subjects), breast pain (6%, 20 of 335 subjects), and sinusitis (5%, 16 of 335 subjects) were some of the more common treatment-emergent adverse events reported in the three integrated safety studies. Only 12 subjects in the ISS reported application site reactions (3%, 12 of 335 subjects). These reported treatment-emergent adverse events may be considered expected, and are generally similar to adverse events known to occur during treatment with estrogens.

Seven percent of subjects in the ISS (25 of 335 subjects) discontinued study medication due to an adverse event. This rate of discontinuation due to adverse events is not unusual and poses no safety concerns.

2.4. Dosing, Regimen, and Administration

Estradiol, given alone, is approved for use in a variety of delivery systems that include oral tablets (Estrace®), vaginal tablets (Vagifem®), vaginal cream (Estrace® Cream 0.01%), vaginal ring (Estring® IVR and Femring®), and transdermal patch systems (Estraderm®, Vivelle®, Vivelle-Dot®, Climara®, Alora®, and Esclim®). There is one approved combination transdermal system, Combipatch™, containing estradiol and norethindrone acetate. No estradiol transdermal lotions or creams are currently marketed for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

In the primary safety and efficacy clinical trial (Study E99-1), subjects applied the content of three 1.15 gram foil-laminated pouches according to the application sequence described below:

- The content of the first pouch was applied to the top of the right thigh over a two minute period.
- The content of the second pouch was applied to the top of the left thigh over a two minute period,

- The content of ½ of the third pouch was applied to the left calf for over a one minute period; the remaining ½ of the third pouch was applied to the right calf over a one minute period,
- Any excess on either hand was applied to the buttock area.

Shaving of the thighs and calves was permitted during the clinical trial. Subjects participating in Study E99-1 were advised to apply Estrasorb™ to a clean, dry surface (after a shower or bath) free of erythema or lesions. Study subjects were cautioned not to apply any other lotions or creams (e.g., sunscreen) to the application site areas during the study treatment duration. These limitations will be reflected in labeling.

In the proposed labeling submitted, two 1.74 gram foil-laminated pouches are proposed for drug delivery. An *in vitro* bridging study was performed to confirm that the contents expressed from two 1.74 gram pouches (packaged in boxes of 14 pouches for 7 days of use) provide the same amount of Estrasorb™ as the contents expressed from three 1.15 gram foil-laminated pouches (used in primary Study E99-1). The results of the pouch expression study showed a statistically significant difference ($p<0.0001$) in the amount of content expressed from three 1.15 gram pouches and two 1.74 gram pouches. Although these differences are statistically significant, the adjusted lot effects are less than 0.07 grams and not felt to have clinical significance. Overall, the calculated daily estradiol delivery rate of Estrasorb™ expressed from two 1.74 gram pouches of 0.057 mg/day is similar to the calculated daily estradiol delivery rate of Estrasorb™ expressed from three 1.15 gram pouches (0.05 mg/day) and raises no safety concerns.

2.5. Drug-Drug Interactions

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. This information will be provided in labeling.

2.6. Special Populations

Estrasorb™ is only indicated for use in postmenopausal women. There were insufficient numbers of geriatric subjects in Studies E98-1, E98-2, and E99-1 to determine if those over 65 years of age differ from younger subjects in their response to Estrasorb™.

Estrasorb™ was not studies in women with liver disease or renal impairment. Estrasorb™ should not be used in pregnant women.

Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indications, Dose, Regimen, Age Groups

Estrasorb™ is a topical drug delivery system containing estradiol, USP as estradiol hemihydrate that utilizes micellar nanoparticle proprietary technology. A micellar nanoparticle is a sub-micron-sized nanoemulsion. Injecting water into a mixture of soybean oil, polysorbate 80 (a surfactant), and estradiol dissolved in ethanol produces the nanoemulsion ([ ] The components are then mixed using high speed mixing equipment, and have the consistency of an emulsion. Estrasorb™ contains estradiol at a concentration of 2.5 mg of estradiol/gram.

Estradiol is an estrogen class hormone. Estrasorb™ is the first estradiol formulated with a topical nanoemulsion delivery system.

The Sponsor's proposed indication is the treatment of moderate to severe vasomotor symptoms associated with the menopause. A total of 3.48 grams of Estrasorb™ containing 8.7 mg of estradiol (2.5 mg of estradiol/gram) is applied topically each day as follows: 1.74 grams split between the right anterior thigh and right calf areas, and 1.74 grams split between the left anterior thigh and left calf areas.

1.2. State of Armamentarium for Indication(s)

The 2003 Agency draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation", recommends that products intended to treat moderate to severe vasomotor symptoms should show both a clinically and a statistically significant reduction in the frequency and severity of hot flushes in the treated groups compared to the control groups. This reduction in the frequency and severity of hot flushes should occur within 4 weeks of initiation of treatment and should be maintained throughout 12 weeks of treatment. Subjective measures (i.e., patient daily diary entries) are used as primary efficacy endpoints.

1.3. Important Milestones in Product Development

IND 49,761/S-000 was submitted on January 16, 1996. The original study, Study N95-3, was a Phase 1 study in which subjects applied 1 ml of micellar nanoparticles containing 2.5 mg of estradiol as estradiol hemihydrate to the abdomen daily. No adverse skin reactions or other significant adverse events were recorded. At an end-of-Phase 1 meeting with the Agency on December 16, 1996, the Sponsor revealed that the bioavailability of estradiol from this 2.5 mg dose formulation was limited. Serum estradiol levels > 40 pg/ml were not achieved as expected. This original formulation of Estrasorb™, containing [ ] water, was packaged in a syringe and required refrigerated storage.

In 1997, one open-label, dose-ranging pharmacokinetic study was conducted (Study N96-1) utilizing the original formulation, wherein subjects applied either 2 or 3 ml of Estrasorb™ daily for 14 days to the right anterior thigh. In addition, one double-blind, placebo-controlled trial (Study N97-3) was conducted in which twenty symptomatic postmenopausal women applied either placebo or 3 ml Estrasorb™ containing 7.5 mg of estradiol to the right and left calf areas (1.6 ml was applied to the right calf area with any residual cream on the hand rubbed into the right thigh; 1.4 ml was applied to the left calf area with any residual cream on the hand rubbed into the left thigh). In both studies, vasomotor symptom relief was limited for the 3 ml dose (7.5 mg of estradiol). Relief of vasomotor symptoms was poor for the 2 ml dose (5.0 mg of estradiol) in Study N96-1.

In 1998, the Estrasorb™ formulation was modified. A Phase 1 pharmacokinetic study (Study E98-1) was completed that compared two formulations of estradiol hemihydrate, 3 ml of 7.125 mg estradiol — water formulation (original formulation), and 1ml of the modified — water formulation versus placebo. Per the submission, the modified — water formulation prolonged the room-temperature stability, increased the

concentration of estradiol per unit weight of Estrasorb™, improved the product "feel", and enhanced skin absorption.

At a meeting with the Division on April 15, 1998 to discuss the Sponsor's biopharmaceutics protocols for Estrasorb™, the following decisions were reached:

- A clinically relevant and well-absorbed formulation for Estrasorb™ should be developed before addressing the issue of residual absorption;
- Estrasorb™ should show 90% efficacy for the relief of vasomotor symptoms;
- The run-in period for baseline data should be 14-days; data from the run-in period can be averaged before randomization to verify the number of hot flushes a subject is experiencing;
- A study performed without a placebo treatment arm would not qualify as a primary efficacy trial; and
- Study subjects should be recruited from a large variety of races to assess whether differences exist in safety and efficacy of the drug product across racial groups.

On October 6, 1998, the Division conducted a teleconference with the Sponsor to discuss Phase 2/3 Study E98-2. Study E98-2 was designed to assess the efficacy and safety of a range of daily doses of Estrasorb™ (7.5, 5.0, and 2.5 mg of estradiol) versus placebo, applied daily for 28 days, for relief of vasomotor symptoms in a postmenopausal population. Per the protocol, color-coded, pre-filled foil pouches of study medication were dispensed for application according to the following sequence:

1) the entire content of the green pouch was rubbed into the anterior surface of one thigh until absorbed;
2) the entire content of the yellow pouch was rubbed into the anterior surface of the opposite thigh; and
3) one-half of the content of the white pouch was rubbed into the calf areas of each leg.

Any residual material on the subject's hand(s) could be rubbed into the buttock areas. Per protocol convention, the first pouch in sequence (green pouch) would contain active drug (1.15 grams of Estrasorb™ containing 2.5 mg of estradiol/gram) when active drug was given.

The Sponsor was advised that:

- The variability between the sites of application and the proposed doses may confound the study analyses;
- A more appropriate design might be to study fewer doses;
- Other studies might be needed later; and
- The study using the "old" formulation (2.5 mg of estradiol/ml) involving multiple sites may not be able to distinguish the effect of the different application sites.

The final study report of Study E98-2, submitted on April 21, 1999, indicated that the relief of vasomotor symptoms at week four was statistically significant for the 3.45 gram dose and the 1.15 gram dose but not the 2.30 gram dose (each dose containing 2.5 mg of estradiol/gram), and that the 3.45 gram dose reached stable estradiol levels after day 15. Based on the results of Studies N95-3 and N96-1 (original — water formulation) and Study E98-2 (modified — water formulation), the Sponsor reached a decision that the 3.45 gram dose (containing 8.625 mg of estradiol [2.5 mg of estradiol/gram]) was the most consistent clinically and statistically effective dose, and therefore, the appropriate dose for use in the phase 3 clinical trial.

On July 19, 1999, the Division met with the Sponsor to discuss the proposed Phase 3 clinical trial (Study E99-1) to assess the efficacy of 3.45 grams of Estrasorb™ versus placebo for the treatment of moderate to severe vasomotor symptoms associated with the menopause. Comments and recommendations regarding the content and study design of Study E99-1 were provided which included modifying the eligibility criteria, baseline and end-of-study procedures and evaluations, and the proposed analysis plan. In addition, the Agency recommended the following:

1) The issue of sunscreen use should be addressed;
2) The DMFs for the drug substance and the foil pouch and laminate are required;

3) 1-year of stability data would be required;
4) The degradation product should be monitored. The method for monitoring degradation products must be validated;
5) The changes in water content and emulsifiers (i.e., polysorbate 80) should be tabulated with batch numbers;
6) Upper and lower limits for particle size and viscosity specifications should be provided methods could be used to determine particle size);
7) The Sponsor must demonstrate that the product does not have phase separation before packaging for content uniformity;
8) A bridging study may be needed if the drug product used in the clinical trial is not the same as the to-be-marketed drug formulation;
9) Photosensitization and delayed hypersensitivity should be monitored, as soybean oil can be hyperallergenic (D-rays scoring should be considered).

Following recommendations of the Division, a Phase 1 study was conducted to evaluate the amount of Estrasorb™ on the skin surface after application of one 1.15 gram foil-laminated pouch containing 2.5 mg of estradiol per gram on each thigh at either 2 or 8 hours post application (Study E2000-1).

On May 24, 2001, the Division responded in writing to questions submitted in a pre-NDA package as follows:

- It is acceptable to submit the case report tabulations and case report forms in electronic format according to the electronic submission guidelines.
- The proposed ISE is acceptable for filing. Only Study E99-1 can be used to support efficacy. Study E98-2 can be mentioned in support of the primary Study E99-1.
- The proposed ISS is acceptable. A request for a pediatric waiver should be submitted with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 at the time of the NDA submission.
- Investigator certification and/or disclosure should be submitted at the time of the NDA submission.

On June 22, 2001, a teleconference with the Sponsor was held to discuss the change in manufacturing site from) because had received a Warning letter from the Agency. In order to compare the products manufactured at the two different sites, the Sponsor was advised to follow the guidances entitled,

1. "Guidance for Industry, Nonsterile Semi Solid Dosage Forms, Scale-up and Post Approval Changes: Chemistry, Manufacturing, and Controls; In vitro Release Testing and in vivo Bioequivalence Documentation."
2. "Nonsterile Semisolid Dosage From Scale Up and Post Approval Changes; Chemistry, Manufacturing and quality Control In Vitro Testing and In Vivo Bioequivalence."
3. "Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Documentation."

In addition, the Division indicated that the submission of six months of stability data for the 1.74 gram unit dose pouch with updated data during the review cycle was acceptable.

NDA 21-371/S-000 for Estrasorb™ was originally filed on June 29, 2001. At the end of the original NDA review cycle, several outstanding Chemistry, Manufacturing and Controls (CMC) approvability issues remained as well as several requested facilities inspections. In addition, the facility that prepared the Estrasorb™ formulation utilized in the Phase 3 clinical trial) received a Form-483 for GMP violation. The Office of Compliance requested a "For Cause" inspection of this facility, and on April 23, 2002 issued a recommendation of "Withhold" approval.

On April 29, 2002, the Sponsor submitted a request for withdrawal of the NDA application.

In an advice letter to the Sponsor dated August 1, 2002, Clinical and Chemistry, Manufacturing and Controls deficiencies were identified. The Clinical deficiencies included:

1) Conducting a residual and transfer potential study.
2) Conducting a PK study designed to demonstrate the effect of sunscreen on the absorption of Estrasorb™.

The Chemistry, Manufacturing and Controls deficiencies included:

1) Address deficiencies provided in the Form-483 by the inspector.
2) Conducting content uniformity test according to USP<905> for suspensions in single unit. Test method and method validation should be provided.
3) Homogeneity of estradiol in the multiple dose package should be established. Test method and method validation should be provided.
4) Stability indicating HPLC assay method should be established. Test method and method validation should be provided.
5) Specific reason and remedy for assay failures during stability in the 1.15 gram pouch configuration should be provided.
6) An assay specification for the surfactant polysorbate 80 should be adopted.
7) The in-process control for estradiol homogeneity in various portions of bulk estradiol emulsion should be established.
8) The drug product batches should be examined with a suitable test method for the presence of [redacted] form as a function of time during storage, an acceptance criterion for the number of [redacted], allowed per unit dose should be adopted.
9) A specification for in vitro release rate should be adopted.
10) The extractable and leachable information for the foil laminate should be provided according to the "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics, May 1999".

The sponsor was requested to respond to these deficiencies when the NDA was resubmitted.

On September 12, 2002, the second submission of NDA 21-371/S-000 was received and includes the original clinical trial data and additional CMC data. Please see the Chemistry, Manufacturing and Controls (CMC) Review for a full description of CMC issues. The final report for an Estrasorb™ Pouch Expression Study, dated April 23, 2002 but not reviewed in the original review cycle, was again submitted for review.

On November 27, 2002, the Sponsor submitted Protocol E2002-1 entitled, "Estradiol Partner Transfer Study" (revised December 17, 2002 and January 16, 2003) to NDA 21-371. Study E2002-1 was initiated on February 21, 2003 and completed April 29, 2003. The final report for Study E2002-1 was submitted to the NDA on May 19, 2003. Study E2002-1 is included in this review.

On December 5, 2002, the Sponsor submitted Protocol E2002-2 entitled, "Estrasorb Sunscreen and Photosensitivity Study" (revised January 28, 2003) to NDA 21-371. Study E2002-2 was initiated on March 17, 2003 and completed on June 11, 2003. The final report for Study 2002-2 was submitted to the NDA on July 11, 2003. Study E2002-2 is included in this review.

1.4. Other Relevant Information

Estrasorb™ is not currently approved for marketing in any country.

1.5. Important Issues with Pharmacologically Related Agents

Estradiol has been used clinically for estrogen-alone therapy since the mid-1970s with the approval of generic oral 1 mg and 2 mg Estrace® Tablets (Estradiol tablets, USP) for the treatment of moderate to severe vasomotor symptoms (VMS), vulvar and vaginal atrophy (VVA), hypoestrogenism due to hypogonadism, castration or primary ovarian failure, and the palliative treatment of metastatic breast cancer and androgen-dependent carcinoma of the prostate. Estrace® 0.5 mg Tablets are approved for the prevention of postmenopausal osteoporosis. More recent efforts have centered on the approval of alternate delivery systems with estradiol, namely, estradiol vaginal tablets (Vagifem®), estradiol vaginal cream (Estrace® Cream 0.01%) estradiol

vaginal ring (Estring® IVR approved for the treatment of VVA, Femring® approved for the treatment of VMS and VVA), and estradiol transdermal systems approved for the treatment of VMS, VVA, and/or hypoestrogenism due to hypogonadism, castration or primary ovarian failure and the prevention of postmenopausal osteoporosis. Currently, six approved transdermal systems deliver daily estradiol: Estraderm®, Vivelle®, Vivelle-Dot®, Climara®, Alora®, and Esclim®.

There is one approved combination transdermal system, Combipatch™, containing 0.05 mg estradiol and 0.14 or 0.25 mg norethindrone acetate. No estradiol transdermal lotions/creams or emulsions are currently marketed in the US for the treatment of moderate to severe vasomotor symptoms associated with the menopause.

2. SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY

2.1 Chemistry, Manufacturing and Controls

This topical, cosmetic-like delivery system consists of surfactant stabilized micelles containing estradiol. The micelles are produced by injecting water into a mixture of an oil, a stabilizer (surfactant polysorbate 80) and an initiator (ethanol in which the estradiol is dissolved). The components are then mixed with either a reciprocating syringe or continuous flow instruments or high speed mixing equipment. Since the particles are less than one micron in diameter, the preparation is therefore called micellar nanoparticles. The preferred ratio of the pre-mixed mixture of oil, surfactant and estradiol dissolved in ethanol to water is [redacted]

Chemically, the active ingredient in Estrasorb™ is estradiol hemihydrate. The chemical name is (17β)-estra-1, 3, 5 (10)-triene-3, 17β-diol, hemihydrate. The molecular formula of estradiol hemihydrate is $C_{18}H_{24}O_2$, ½ H_2O and the molecular weight is 281.4.

The initial estradiol hemihydrate formulation used in early nonclinical and clinical studies (Studies N95-3, N96-1 and N97-3) contained [redacted] water. This [redacted] water formulation was manufactured at Novavax, Inc., packaged in syringes and was stable at 4° C. This initial formulation required refrigeration. The Estrasorb™ formulation utilized in the primary clinical trial was prepared by [redacted] and contained [redacted] water and was [redacted]. Estrasorb™, now manufactured by [redacted] is proposed for [redacted]

The packaging utilized in the clinical trial was three 1.15 gram pouches (total of 3.45 grams) each containing 2.5 mg of estradiol/gram as estradiol hemihydrate (total dose of 8.625 mg of estradiol). In the submission, the packaging proposed are two 1.74 gram foil-laminated pouches each containing 4.35 mg of estradiol (2.5 mg of estradiol/gram) as estradiol hemihydrate (total dose of 8.7 mg of estradiol). Daily topical application of the contents of two 1.74 gram foil-laminated pouches provides an estimated systemic delivery of 0.057 mg estradiol per day that is comparable to the estimated daily systemic delivery rate of 0.05 mg/day using three 1.15 gram pouches.

[redacted] manufactured the three 1.15 gram pouches utilized in Study E99-1. However, as previously noted, [redacted] received a Form-483 for cGMP violation. The Office of Compliance conducted a "For Cause" inspection of the [redacted] facility on April 23, 2002 and issued a recommendation of "Withhold" approval. Among several cGMP violations cited, the potential cross contamination of the clinical supplies from previous manufacturing activities was the most significant quality issue. Based on the sequence of clinical supply manufacturing activities, a cosmetic preparation [redacted] had been manufactured prior to the placebo lot for Study E99-1. The drug product lot for Study E99-1 was manufactured after the placebo lot for Study E99-1. It was documented that the cleaning procedure after manufacturing of each lot was not validated.

Reviewer's Comments

The change in the mean daily number and severity of hot flushes in the placebo treatment group reported in Study E99-1 is comparable to results reported in other VMS clinical trials. It appears that the quality of the placebo clinical supplies was not compromised during manufacture.

Study E99-1 was conducted using a drug formulation with the identical composition to that of the to-be-marketed formulation manufactured by [redacted]. A bridging study was conducted between the two different sources of drug product supplies [redacted] for the Phase 3 clinical supplies and [redacted] for the to-be-marketed drug product) using an *in vitro* methodology recommended by SUPPAC-SS. Per the Clinical Pharmacology review dated April 24, 2002, adequate bridging between the clinical trial and the to-be-marked drug product was demonstrated.

However, the to-be-marketed drug product batches manufactured by [redacted] show the presence of [redacted] Since the examination of the placebo samples under the polarized microscope do not show the presence of [redacted] presence in the drug product batches are determined to be estradiol. The total amount of [redacted] form is unknown. This is important because the [redacted] found in the to-be-marketed drug product batches could result in less available estradiol for absorption. However, the Sponsor is investigating various stability lots of the to-be-marketed drug product to quantitate the number of [redacted] per unit dose (six samples of to-be-marketed Lot # 091200NS2 have been analyzed for the number of [redacted] per microliter of sample). The results show large number of [redacted] per microliter (mean of 223, SD ± 40 for the first analyst, mean of 196, SD ± 53 for the second analyst). These results are the only data available to date on the variability of the analytical method.

Reviewer's Comments

Please see the Chemistry, Manufacturing and Controls Review.

The drug product utilized in primary Phase 3 Study E99-1 was not tested for the presence of [redacted] These clinical supplies are now 5 years old and unsuitable for testing. Therefore, it is not certain whether the clinical trial drug product also contained [redacted] either formed at manufacture or as a function of time. The Sponsor is developing a method development validation for determination of [redacted] veight with a projected timetable for completion of January 26, 2004. This timetable is acceptable to the CMC reviewer.

Per the CMC review, the number of [redacted] per microliter of drug product should be set at [redacted] accounts for arbitrary analytical variability) or at a maximum of [redacted] per microliter. The Sponsor has agreed with this acceptance criterion.

2.2. Animal Pharmacology and Toxicology

Three nonclinical studies were conducted to determine the ability of various formulations of estradiol hemihydrate to systemically deliver estradiol via micellar nanoparticles. A single dose dermal application pharmacokinetic study in female and castrated male rabbits was conducted. Six treatment groups received different formulations of estradiol hemihydrate and two control groups received estradiol in ethanol. In the [redacted] water formulation groups (the formulation that is the subject of this review), more rapid serum estradiol concentration increases and higher peak serum concentrations were observed than were observed in the [redacted] water formulation groups or the estradiol/ethanol control groups.

A second pharmacokinetic study in female rhesus monkeys was conducted to observe estrogenic activity following a single dermal application of two different formulations, either 1 mg estradiol in 0.42 ml absolute alcohol or 1 mg estradiol in 0.42 ml micellar nanoparticles. In this animal model, estradiol serum concentrations increased dramatically (> 14-fold the lower limit of quantitation) with both formulations. The dermal administration of estradiol via micellar nanoparticles (absolute bioavailability of approximately 9%) and ethanol (absolute bioavailability of approximately 15%) suggested the dermal application of estradiol via micellar nanoparticles was satisfactory.

The cumulative irritation potential of estradiol hemihydrate was observed in a repeat dose study in rabbits. Sterile water, micellar nanoparticles, and micellar nanoparticles containing estradiol were administered once a week over a 91-day period (application of 13 doses). A localized mild to moderate inflammatory response was observed with the micellar nanoparticles that was more intense for the micellar nanoparticles containing estradiol than the micellar nanoparticles without estradiol. In addition, the micellar nanoparticles containing estradiol produced an estrogenic-related decrease in food consumption and increased spleen size without evidence of apparent histopathologic changes in the spleen. These effects are not considered toxicologically relevant.

Reviewer's Comments

No safety concerns result from the findings of the limited number of nonclinical studies submitted.

2.3. Microbiology

Estrasorb™ is a non-sterile, topical emulsion. The proposed labeling that accompanied the first submission of NDA 21-371 included [redacted] package configurations for the daily delivery of Estrasorb™: [redacted], two 1.74 gram foil-laminated pouches, and [redacted] Per the Microbiology Review, the unit dose formulation "conforms to microbial limit specifications". However, "microbial replication in the finished product following formulation and filling of the unit-dose packaging may diminish the concentration of the active drug substance prior to patient use and/or result in hazardous levels of microorganisms in the product". Therefore, the "unit-dose formulation should be demonstrated to be bacteriostatic". In addition, the [redacted] formulation should meet the USP criteria for antimicrobial preservative effectiveness".

Reviewer's Comments

Please see the Microbiology Reviews dated November 7, 2001 and January 17, 2002 that were completed during the first submission of NDA 21-371.

Following a meeting with the Agency on January 25, 2002, the Sponsor completed preservative challenge testing on the drug product. Per the Microbiology Review dated April 4, 2002, the data submitted indicates that the product formulation exceeded USP Category 2 (topically used products made with aqueous bases or vehicles, nonsterile nasal products, and emulsions, including those applied to mucous membranes) criteria for preservative effectiveness. "The submission is recommended for approval on the basis of antimicrobial effectiveness and microbial quality of the product."

In this submission only the two 1.74 gram foil-laminated pouch unit-dose packaging is proposed.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

Please see the Clinical Pharmacology and Biopharmaceutics Review for a full review of the pharmacokinetic and pharmacodynamic studies conducted during the Estrasorb™ development program.

Three early human pharmacokinetic studies were conducted with micellar nanoparticles containing estradiol hemihydrate as cream formulations containing [redacted] water (Protocols N95-3, N96-1, and N97-3). Study N95-3 was a Phase 1, single dose study of 2.42 mg of estradiol per 1 ml of micellar nanoparticles applied to the abdomen. Study N96-1 was a Phase 1 multiple dose study evaluating 2 ml of micellar nanoparticles (5 mg of estradiol) or 3 ml micellar nanoparticles (7.5 mg of estradiol) applied to the right calf for 14 days. The estradiol C_{avg} was 4.4 ng/dL for the 3 ml treatment group and 2.9 ng/dL for the 2 ml treatment group. Study N97-3 was a double-blind Phase 1 study evaluating split-site application of 3.2 ml of micellar nanoparticles containing 7.5 mg of estradiol or placebo to the left and right calves for 14 days. These studies, both single and multiple dose studies, suggested steady-state trough serum estradiol concentrations were reached in 3-5 days.

However, the formulations used in these early studies were stable at 4°C and required packaging in a syringe and refrigeration.

In 1997, a new [redacted] formulation was developed, which contained additional surfactant and water [redacted] water on a volume per volume basis). Estrasorb™ [redacted] water formulation), with the consistency of a cosmetic lotion was packaged in foil-laminated pouches, and was utilized in a 8-day Phase 1 study (Study E98-1), a 4-week Phase 2 study (Study E98-2), a single dose residual estradiol study (Study E2000-1), a 2-day partner transfer study (Study E2002-1), a 24-day sunscreen and photosensitivity study (Study E2002-2), and the primary 12-week Phase 3 study (Study E99-1).

Study E98-1 compared the uptake of Estrasorb™ applied as either a 3.2 ml dose (estimated total dose of 7.5 mg of estradiol) to a single anterior thigh daily to the split-dose application of 1.6 ml to an equivalent area on both thighs daily for 8 consecutive days (two groups of 5 subjects each, 4 = active drug and 1 = placebo in each group of 5). Serial serum estradiol, estrone and estrone sulfate samples were drawn daily on days 1 and 8 at 0, 0.5, 1, 2, 4, 6, 8, 12, 18, and 24 hours post-dose. On days 0, 2, 3, 4, 5, 6 and 7, samples were obtained immediately before dosing for additional trough serum concentration determinations. Results indicated that the steady state serum estradiol concentrations achieved after once daily application of 3.2 ml dose of Estrasorb™ (7.5 mg of estradiol), either single-site or split-site, were similar to those observed in the early follicular phase of pre-menopausal women (range of 1-9 ng/dL). No differences in pharmacokinetic parameters were noted between the single-site or split-site applications. In most subjects, steady state was reached during the 8-day study period (4 subjects reached steady state by day 4 and 4 subjects by day 8), and estradiol levels increased approximately four-fold by day 8. The day 8 estradiol uncorrected for baseline mean $AUC_{(0\text{-}24hr)}$ values were 148 and 92.7 ng• h/dL for the single versus the split-site applications, respectively (day 8 estradiol uncorrected for baseline median $AUC_{(0\text{-}24hr)}$ values were 128 and 104 ng• h/dL for the single versus the split-site applications, respectively).

For Study E98-1, unadjusted PK parameters (estradiol, estrone, and estrone sulfate) were summarized to document overall systemic exposure to estrogens. To obtain the best estimate of apparent clearance (CL, dose/AUC), the Sponsor used an AUC value based on estrogen concentrations only from the administered dose (7.5 mg of estradiol) and not from endogenous estrogen. Therefore, to calculate AUC and apparent clearance, estrogen concentrations were corrected by first subtracting baseline hormone concentrations. The day 8 estradiol corrected for baseline mean $AUC_{(0\text{-}24hr)}$ values were 117 and 77.7 ng• h/dL for the single versus the split-site applications, respectively (day 8 estradiol corrected for baseline median $AUC_{(0\text{-}24hr)}$ values were 109 and 85.0 ng• h/dL for the single versus the split-site applications, respectively). Results suggested very little overall difference between the two methods of application. These estradiol clearance values were subsequently used to calculate bioavailability (F) and daily systemic dose.

In Study E98-1, the median, corrected estradiol topical clearance (CL/F) following both application treatments (single and split-dose) was approximately 1980 mL/min/kg. In postmenopausal women > 60 years of age, estradiol clearance is approximately 13.1 mL/min/kg.[1] Taking the ratio of these values (13.1/1980 = 0.0066), the estimate of absolute bioavailability of estradiol is approximately 0.66%, corresponding to an estimated estradiol systemic delivery rate of 0.05 mg/day (0.0066 x 7.5 mg of estradiol/day = 0.05 mg of estradiol/day).

The estimated terminal half-life of drug absorption in Study E98-1was 2.4 days. When given orally, estradiol is extensively metabolized with a half-life of approximately 1 hour. Thus, Study E98-1 indicates that estradiol accumulation from Estrasorb™ occurs due to a very slow and protracted absorption process, i.e., "flip-flop" model.[2]

In Study E98-2, the split-site application (thighs and calves) of either placebo or 1.15 grams of Estrasorb™ (2.5 mg of estradiol/gram), 2.30 grams, or 3.45 grams of Estrasorb™ for four weeks was observed. Trough serum estradiol, estrone, estrone sulfate, and FSH levels were measured on days 1(end of screening), 8 (end of placebo run-in period), 15, 22, 29 and 36. In addition, a pharmacokinetic (PK)/pharmacodynamic (PD) analysis was

[1] Longcope C. Hormone dynamics at the menopause. Ann NY Acad Sci. 1990;592:21-30.
[2] Boxenbaum H. Pharmacokinetic tricks and traps: flip-flop models. J Pharm Pharmaceut Sci. 1995;1(3):90-91.

done to establish a correlation between the pharmacokinetic (measures of estradiol, estrone and FSH) and pharmacodynamic (hot flush count) measures in Study E98-2. However, the range of PK and PD measures was smaller in the placebo group and more difficult to detect. Therefore, the within subjects analyses were presented for the pooled Estrasorb™ groups.

Results of Study E98-2 show that a PK/PD relationship was detected in the within subject analysis for the pooled Estrasorb™ treated subjects (p-values for treatment by PK interaction terms were all statistically significant (p=0.0411 for treatment by estradiol, p=0.0001 for treatment by estrone, and p=0.0006 for treatment by FSH). As the Estrasorb™ dose increased, the estradiol and estrone means and $AUC_{1\text{-}24hr}$ increased in a dose dependent manner and the hot flush count decreased. As the average FSH levels decreased in the Estrasorb™ treatment groups, the hot flush count decreased. In the placebo treatment group, estradiol, estrone, estrone sulfate, and FSH levels remained relatively unchanged.

Reviewer's Comments

In Study E98-2, there is a relatively good correlation between trough estradiol and estrone serum concentrations and hot flushes. As trough hormone concentrations increased the frequency and severity of hot flushes decreased. More complete results of Study E98-2 are presented under subsection 6.3. Detailed Review of Trials by Indication, Supportive Study E98-2, on page 27 of this review.

Study E2000-1 was an open-label, non-randomized single-dose study in which 12 postmenopausal women applied one 1.15 gram pouch of Estrasorb™ to each thigh (containing 2.5 mg estradiol/gram). Study E2000-1 evaluated the amount of residual estradiol on the skin utilizing the alcohol swipe method at 2 hours or 8 hours post application. At two hours, 100% of subjects (12 of 12 subjects) had detectable residual estradiol present. The amounts detected at two hours post-application ranged from 220 micrograms to 803 micrograms. At eight hours 100% of subjects (12 of 12 subjects) had detectable residual estradiol present. The amounts detected at 8 hours post-application ranged from 70 micrograms to 582 micrograms. After washing the left and right thighs with soap and water, 25% of subjects (4 of 12 subjects) still had detectable residual estradiol ranging from 17.8 micrograms to 38.3 micrograms.

Reviewer's Comments

Please see subsection 7.4. Safety Findings from Clinical Studies, Study E2000-1, on page 37 of this review for additional comments on the results of Study E2000-1.

Study E2002-1 entitled, "Estradiol Partner Transfer Study" was an open-label, two treatment days study in which 14 women applied the contents of two 1.74 gram foil-laminated pouches to their right and left thigh and calf areas on each of two days (one pouch to the left thigh and calf and one pouch to the right thigh and calf). At 2 and 8 hours after each female subject applied Estrasorb™, each male partners (14) vigorously rubbed his forearms against his female partner's thighs (left forearm against left thigh at 2 hours, right forearm against right thigh at 8 hours). All dosing was performed at the study site under the supervision of the study nurse.

One objective of Study E2002-1 was to determine if systemic absorption of estradiol occurs in the male subject after intentional contact exposure to the application areas. Serum hormone levels, including estradiol, estrone, estrone sulfate, and FSH were measured in the female subjects prior to the initial dosing and at 1, 2, and 8 hours after dosing on both treatment days (day 0 and day 1). In male subjects, serum estradiol, estrone and estrone sulfate levels were measured prior to initial intentional contact and at 1, 2, 4, 8, 12 and 24 hours after contact on days 0 and 1. In addition, a dermal assessment of the application site of the female subjects and the forearms of the male subjects was performed prior to dosing/exposure and 2 hours post dosing/exposure. Female and male subjects were questioned regarding the presence or absence of adverse events. The second objective of Study E2002-1 was to determine the actual amount of Estrasorb™ expressed from the 1.74 gram foil-laminated pouches. Between-subject and within-subject variability in pouch expression was reported.

Reviewer's Comments

The results of Study E2002-1 are discussed under subsection 7.4. Safety Findings from Clinical Studies, Study E2002-1, on page 38 of this review.

Study E2002-2 entitled, "Estrasorb Sunscreen and Photosensitivity Study" was an open-label, non-randomized multiple-dose study in which 14 postmenopausal women applied two 1.74 gram foil-laminated pouches of Estrasorb™ to the thighs and calves daily for 24 days. The objectives of Study E2002-2 were as follows:

a. To determine if systemic absorption of estradiol is significantly altered by application of sunscreen before or after Estrasorb™ application.
b. To determine if Estrasorb™ exposure causes photosensitivity reactions.
c. To determine the actual amount expressed from the packaging solution.

Twenty-four hour PK blood draws occurred on days 0, 7, 15, and 23 (pre-dose and 1, 2, 4, 8, 12, 18 and 24 hours post-dose). On days 8 through 15, SPF-15 sunscreen was applied to both thighs and calves 10 minutes prior to the daily application of Estrasorb™. On days 16 through 23, SPF-15 sunscreen was applied to both thighs and calves 25 minutes after the daily application of Estrasorb™. On day 24 (weather conditions permitting), each subject was exposed to sunlight for 10 minutes.

Reviewer's Comments

The results of Study E2002-2 are discussed under subsection 7.4. Safety Findings from Clinical Studies, Study E2002-2, on page 41 of this review.

The Sponsor also conducted an *in vitro* pouch expression study to demonstrate that the content of the drug product expressed in the proposed 2-package market configuration (two 1.74 gram foil-laminated pouches) is similar to the content of the drug product expressed in the 3-package clinical trial dose configuration (three 1.15 gram foil-laminated pouches) utilized in the primary Phase 3 Study E99-1. Twelve subjects and 1 analyst participated in the pouch expression study. Three lots of drug products were utilized, Lots 038 and NS1 for the 1.15 gram foil-laminated pouches and Lot NS2 for the 1.74 gram foil-laminated pouches. Two types of analyses were carried out: 1) using the scaled weight expressed, and 2) using the weights standardized by their nominal contents.

Analysis 1 using the scaled weight expressed is the analysis performed by the Sponsor to demonstrate similarity in expressed content between the two packaging configurations. The observed weights for 2-pack NS2 lot were multiplied by a factor of 2/3 so the weight is on the same scale as those from 3-pack 038 and NS1 lots samples. Analysis 2 using the weights standardized by their nominal contents was performed by the Sponsor to demonstrate differences between the trained analyst and the subjects. Analysis 1 is the analysis of most interest. A two-way Analysis of Variance (ANOVA) was used to study sources of variation.

On average, the mean amounts expressed from the foil-laminated pouches were 0.110 ± 0.030 grams (9%) below the nominal weights of the 1.15 gram pouches or the 1.74 gram pouches. Using pouch weight as the dependent variable for Lot NS1 (1.15 gram pouches) versus Lot NS2 (1.74 gram pouches) and Lot 038 (1.15 gram pouches) versus Lot NS2 (1.74 gram pouches) with no interaction of subject (or analyst) and lot, the results show a difference in the amount expressed of 0.060 grams $\pm$ 0.0048 (three 1.15 gram pouches) and 0.068 $\pm$ 0.0048 (two 1.74 gram pouches), respectively, that is statistically significant (p-value < 0.0001).

Reviewer's Comments

The results of the pouch expression study confirmed that there is a statistically significant difference ($p<0.0001$) in the amount of content expressed from three 1.15 gram foil-laminated pouches and two 1.74 gram foil-laminated pouches. Although these differences are statistically significant, adjusted lot effects are less than 0.07 grams.

Of concern is whether or not this mean 0.07 gram increase in pouch content expressed from the two 1.74 gram pouches is clinically meaningful. However, this pouch expression study is unable to provide any

clinical response information. Nonetheless, the information obtained from this pouch expression study allows the calculation of the approximate daily estradiol delivery rate from two 1.74 gram foil-laminated pouches based on the estimate of absolute bioavailability of estradiol as discussed previously for Study E98-1. The two 1.74 gram foil-laminated pouches deliver approximately 0.057 mg of estradiol/day (2 x 1.74 grams = 3.48 grams x 2.5 mg/gram = 8.7 mg x 0.0066 = 0.057 mg/day). This daily estradiol delivery rate is similar to the delivery rate of 0.05 mg/day calculated in Study E98-1 and raises no safety concerns.

Reviewer's Comments

Please see the Clinical Pharmacology and Biopharmaceutics Review for a full review of the Phase 1 studies conducted during the Estrasorb™ development program.

3.2. Pharmacodynamics

As noted above, as the dose increased in Phase 1 Study E98-2 from 1.15 grams to 2.30 grams to 3.45 grams of Estrasorb™, the estradiol and estrone means and $AUC_{0\text{-}24hr}$ increased in a dose dependent manner. The most statistically significant decrease in moderate to severe hot flushes occurred in the 3.45 gram treatment group. The Sponsor, therefore, determined that the 3.45 gram Estrasorb™ dose containing 8.6 mg of estradiol (2.5 mg of estradiol/gram) should be utilized in the Phase 3 clinical trial.

Reviewer's Comments

See Supportive Study E98-2 on page 27 of this review for a full description of the safety and efficacy results reported in 28-day supportive Study E98-2.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

The clinical development program for Estrasorb™ consisted of one Phase 1 study (Study E98-1) in which 3.2 ml of Estrasorb™ containing 7.5 mg of estradiol was administered daily for 8 days as either single-site or split-site applications to assess the safety, tolerance and pharmacokinetics of the heat stable micellar nanoparticles containing estradiol hemihydrate formulation. A 28-day dose ranging, Phase 2/3 study was conducted (Study E98-2) to assess the safety and efficacy of three dosage strengths of Estrasorb™ versus placebo. Study subjects received either placebo, 1.15 grams, 2.30 grams, or 3.45 grams of micellar nanoparticles containing 2.5 mg of estradiol/gram. Study E99-1, the primary Phase 3 study, evaluated the efficacy and safety of a 3.45 grams split-site topical application of Estrasorb™.

4.2. Overview of Clinical Trials

See Table 1 for a summary of studies utilizing the heat stable formulation of Estrasorb™ in the clinical development program.

Table 1: NDA 21-371 Clinical Development Program

Protocol No.	Study Design	Total Daily Dose (mg), Application Site and Duration	No. of Treated Subjects
E98-1 Phase 1	Randomized, parallel-group, PK study after single-dose topical application. One placebo subject was entered for each application group.	3.2 ml estradiol hemihydrate daily single-dose application to one thigh or split across both thighs for 8 days.	10
E98-2 Phase 2/3	Multi-center, double-blind, randomized, parallel-group, placebo-controlled.	1.15 g, 2.30 g, 3.45 g estradiol hemihydrate or placebo; daily application over both thighs and calves for 28 days.	125

E99-1 Phase 3	Multi-center, double-blind, randomized, parallel-group, placebo-controlled.	3.45 g of estradiol hemihydrate or placebo; daily application over both thighs and calves for 12 weeks.	197
E2000-1 Phase 1	Open-label, single dose	1.15 g estradiol hemihydrate applied to both thighs for 1 day	12
E2002-1 Phase 1	Open-label, two treatment days	3.48 g estradiol hemihydrate applied to both thighs and calves for 2 days	14
E2002-2 Phase 1	Open-label, 24 treatment days	3.48 g estradiol hemihydrate applied to both thighs and calves for 24 days	14

Source: Adapted from NDA 21-371data submitted June 29, 2001, Panel 8.8.1.2, Volume 26, page 42 and modified by the Medical Officer.

4.3. Postmarketing Experience

Estrasorb™ is not approved for marketing in any country.

4.4. Literature Review

References are provided in the submission that pertains, primarily, to approved estradiol transdermal systems. No additional FDA literature review was conducted.

5. CLINICAL REVIEW METHODS

5.1. Describe How Review was Conducted

All studies submitted were reviewed individually. Study E99-1, a Phase 3 study conducted to evaluate the safety and efficacy of Estrasorb™, was the only study submitted that met the Agency's hormone therapy guidance for consideration for symptomatic indications. Study E98-2, a Phase 2/3 study that also evaluated the safety and efficacy of Estrasorb™, was only 4 weeks in duration (12 weeks study duration is required for a symptomatic indication). Therefore, Study E98-2 was considered for safety outcomes and not included in efficacy calculations. In addition, data from four Phase 1 studies (Studies E98-1, E2000-1, E2002-1 and E2002-2) was also reviewed. Phase 1 Study E98-1 evaluated the pharmacokinetics and pharmacodynamics of single-site versus split-site application of 3.2 ml of Estrasorb™ containing 7.5 mg of estradiol daily for 8 days. Study E2000-1 was initiated at the suggestion of the Agency to evaluate the amount of residual estradiol on the skin after application of 1.15 grams of Estrasorb™ containing 2.5 mg of estradiol hemihydrate/gram to both thighs. Studies E2002-1 and E2002-2, both also initiated at the suggestion of the Agency, were conducted to evaluate partner transfer of estradiol hemihydrate and the effects of sunscreen on Estrasorb™ absorption, respectively. Safety data submitted in the 4-Month Safety Update (dated January 13, 2003), the Second Safety Update (dated May 5, 2003), and in the Twelve-Month Safety Update (dated September 5, 2003) were reviewed upon receipt.

5.2. Overview of Materials Consulted in Review

The final study report of IND 49,761/SN-000 (dated January 16, 1996), the initial submission of Protocol E99-1, was reviewed in detail.

Three early non-clinical studies were conducted using a [ ] water formulation (studies N95-3, N96-1, and N97-3). These studies were reviewed for historical content regarding the development of a [ ] water formulation.

Study E98-2 was a Phase 2/3, double-blind, placebo-controlled study conducted in 6 US centers that randomized 125 postmenopausal women to placebo or 1.15 grams, 2.30 grams, or 3.45 grams of Estrasorb™ containing 2.5 mg of estradiol/gram for 28 treatment days. Three color-coded pouches, each containing 1.15 grams of Estrasorb™ or placebo were applied. The content of the green pouch was applied to one thigh, the content of the yellow pouch was applied to the opposite thigh, and the content of the white pouch was split between both calves. A daily diary card was used to record the number and severity of hot flushes during a one-week placebo run-in period prior to treatment and during the 28 treatment days. Trough serum estradiol,

estrone, estrone sulfate, and FSH levels were measured on days 1, 8, 15, 22, 29, and 36. Safety assessments were conducted per schedule and procedure.

Study E99-1 was the primary Phase 3 study. Study E99-1 was a double-blind, placebo-controlled clinical trial conducted in 21 US centers that randomized 200 postmenopausal women to either placebo or 3.45 grams of Estrasorb™ containing 8.625 mg of estradiol (2.5 mg of estradiol/gram) for 12 treatment weeks. A daily diary card was used to record the number and severity of hot flushes during a one-week placebo run-in period prior to treatment and the 12-week treatment duration. Trough serum estradiol, estrone and FSH levels were measured at screening and before dosing on day 1 and at the end of weeks 2, 4, 8, and 12. Safety assessments were conducted per schedule and procedure. All subjects with an intact uterus were required to take medroxyprogesterone acetate, 10 mg/day for 14 days at the end of study medication. A transvaginal ultrasound was then performed and if the double-wall endometrial thickness was > 4 mm, an endometrial biopsy was performed.

Study E2000-1 was an open-label, non-randomized, Phase 1 study conducted in 2 US centers in which 12 postmenopausal women received a single administration of the contents of one 1.15 gram pouch of Estrasorb™ to the left thigh and one 1.15 gram pouch to the right thigh. A 6 x 8-inch application area was delineated, using waterproof adhesive tape, on the anterior aspect of both thighs. The subject vigorously massaged Estrasorb™ into the delineated area for 2 minutes. Subjects were advised not to use any creams or cosmetics on their thighs prior to dosing and were questioned regarding whether or not the application areas had been shaved in the previous 24 hours. Residual estradiol determinations were performed using a [ ] test developed by Novavax, Inc. The left anterior thigh was swiped at 2 hours post-dose. The right anterior thigh was swiped at 8 hours post-dose. At 8 hours the left and right thighs were then washed with soap and rinsed with water and swiped again post-washing. Safety and tolerability were assessed by evaluating adverse events and dermal assessments.

Study E2002-1 was an open-label Phase 1 study, conducted in 1 US center, in which 14 postmenopausal women applied 3.48 grams of Estrasorb™ containing 8.7 mg of estradiol (2.5 mg of estradiol/gram) to both thighs and calves for two days, one 1.74 gram pouch to the left thigh and calf and 1.74 gram pouch to the right thigh and calf. Fourteen male partners attempted to transfer estradiol to his forearm by vigorously rubbing them against his female partner's thighs for 2 minutes. Trough serum estradiol, estrone, estrone sulfate and FSH were measured prior to initial dosing and at 1, 2 and 8 hours after dosing in female subjects. Estradiol, estrone and estrone sulfate serum hormone levels were measured in male subjects prior to initial attempted transfer and at 1, 2, 4, 8, 12, 18 and 24 hours post dosing on both days. Safety and tolerability were assessed by evaluating adverse events and dermal assessments.

Study E2002-2 was an open-label Phase 1 study, conducted in 1 US center, in which 14 postmenopausal women applied 3.48 grams of Estrasorb™ containing 8.7 mg of estradiol (2.5 mg estradiol/gram) to both thighs and calves daily for 24 days, one 1.74 gram pouch to the left thigh and calf and 1.74 gram pouch to the right thigh and calf. Subjects had estradiol estrone, estrone sulfate and FSH levels drawn prior to dosing on days 0, 7, 15 and 23 and at 1, 2, 4, 8, 12, 18, and 24 hours post dosing. On days 2 through 6, 9 through 14, and 17 through 23, subjects had estradiol, estrone, estrone sulfate and FSH levels drawn prior to dosing. On days 8 through 14, SPF 15 sunscreen was applied to thighs and calves prior to dosing. On days 16 through 22, SPF 15 sunscreen was applied to thighs and calves after dosing. Subjects were exposed to sunlight on day 24. Safety and tolerability were assessed by evaluating adverse events and dermal assessments.

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity

Two study sites were recommended for Division of Scientific Investigation (DSI) audits during the first submission of NDA 21-371. Estradiol is an approved drug for use in vaginal, oral, and transdermal systems routes of administration and extensive clinical safety data is available. However, safety data on the use of estradiol hemihydrate emulsion for topical application is limited.

Site # 1, [redacted] (Charles H. Miller, M.D.), and Site # 3, [redacted] were recommended for DSI audits.

Reviewer's Comments

Per the Division of Scientific Investigations (DSI) letter, dated January 31, 2002, Dr. Charles H. Miller (Site # 1, [redacted]) "did adhere to all pertinent federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects".

The [redacted] was also audited. Per the Division of Scientific Investigation, a Form 483 was issued to The [redacted] for minor infractions. As described, these minor infractions would not affect the validity of study data contributed by this site.

5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards

The informed consent document proposed for use in the clinical trials was appropriate. Appropriate standards of patient care were administered during the conduct of clinical trials.

5.5. Evaluation of Financial Disclosure

Only two of 102 investigators did not respond to the request for financial disclosure. Both investigators were at Site #4, the [redacted] which was closed due to non-performance. No subjects were enrolled at this site.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

The data presented in NDA 21-371 provides evidence from one placebo-controlled clinical trial to support the safety and efficacy of 3.48 grams of topical Estrasorb™ containing 2.5 mg of estradiol/gram, applied daily, for the treatment of moderate to severe hot flushes associated with the menopause.

6.2. General Approach to Review of the Efficacy of the Drug

The Integrated Summary of Efficacy (ISE) in the submission includes two studies, Study E99-1 and Study E98-2. However, only Phase 3 Study E99-1 met the study design requirements for a VMS symptomatic indication as outlined in the Agency's draft 2003Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Clinical Evaluation" (12-weeks duration, double-blind, placebo-controlled). Therefore, Study E99-1 is the subject of this review.

Phase 2/3 Study E98-2, included in the ISE as a supportive efficacy study, does not meet the requirements for a VMS symptomatic indication, as the treatment duration was limited to 4 weeks. Therefore, the results of Study E98-2 are not integrated in the efficacy analyses but are included in the Integrated Summary of Safety (ISS). An integrated database was not used across the two studies for the ISE.

No other studies were included in the ISE. Although Study N97-3 was placebo-controlled, this Phase 1 pharmacokinetic study was conducted using the "original" formulation Estrasorb™, and therefore, is not included in the ISE.

6.3. Detailed Review of Trials by Indication

Study E99-1, the primary Phase 3 study, was a double blind, randomized, placebo-controlled clinical trial in symptomatic postmenopausal women. Eighteen (18) of the initial 20 investigational sites in the US randomized subjects for this study. The number of randomized subjects at a site ranged from zero (0) at site # 4 [redacted] and site # 8 [redacted] to 46 at site # 3 [redacted]. All sites with less than 8 enrolled subjects were combined into one pooled site. Sites with 8 or more subjects were considered as individual sites. Eight (8) investigational sites enrolled less than 8 subjects, 10 investigational sites enrolled more than 8 subjects.

Following screening, all potential subjects were enrolled in a 7-day placebo run-in period in which all subjects applied daily split-site topical applications of placebo. Following this one-week placebo run-in period, randomized subjects applied either placebo or 3.45 grams of Estrasorb™ (three 1.15 gram foil-laminated pouches) containing 8.625 mg of estradiol (2.5 mg of estradiol/gram) daily for 12 weeks. The split-site application sequence was conducted as follows:

- The content of the first pouch was applied to the top of tne right thigh over a two minute period.
- The content of the second pouch was applied to the top of the left thigh over a two minute period,
- The content of ½ of the third pouch was applied to the left calf for over a one minute period; the remaining ½ of the third pouch was applied to the right calf over a one minute period,
- Any excess on either hand was applied to the buttock area.

Two hundred postmenopausal women were enrolled in 18 centers for this clinical trial. The primary efficacy parameter was the change from baseline of the average daily count of moderate to severe hot flushes at weeks 4 and 12. The primary efficacy conclusion was drawn at both week 4 (days 22 to 28) and week 12 (days 78 to 84).

The subject completed a daily diary card to record the number of hot flushes according to severity, defined clinically as:

- Grade 1 = Mild: sensation of heat without perspiration
- Grade 2 = Moderate: sensation of heat with perspiration, able to continue activity; and
- Grade 3 = Severe: sensation of heat with sweating, causing the woman to stop activity.

At each visit following randomization (weeks 2, 4, 8, and 12), the diary cards were reviewed and study personnel transcribed data from the diary card entries onto the case report form. The completed diary cards were retained as part of the subject's study source documentation.

Trough serum estradiol, estrone, and FSH serum concentrations were measured at baseline, days 1, and at the end of weeks 2, 4, 8, and 12. All blood draws occurred in the morning before dosing. The samples were frozen at –20° C and shipped to [redacted] for assay.

Effects on Vasomotor Symptoms

Vasomotor symptoms were assessed by evaluation of the subject's daily diary for reports on the number and severity of hot flushes. Hot flush severity was graded on a scale of 1 to 3 as described above.

For Study E99-1, the primary efficacy parameter was the change from baseline (days –7 to –1) to week 4 (days 22-28) and week 12 (days 78-84) in the number of hot flushes. The secondary parameters included the severity of hot flushes calculated as a severity score index, the clinical response defined as the absence of moderate and severe hot flushes in any seven-day dosing period, and trough serum concentrations of estradiol, estrone, ratio of estradiol to estrone, and FSH.

Statistical tests for treatment group comparisons were two-sided and performed at the 0.05 level of significance. Treatment-by-site interactions and treatment-by-stratum (intact uterus versus hysterectomy) interactions were assessed tested at the 0.10 alpha level. No adjustment was required for controlling Type 1 error for analysis of multiple comparisons.

Missing values for hot flush data were "imputed" by using the "most recent value carried forward" method. The imputation for missing data was performed prior to calculating the primary and secondary efficacy parameters for the analyses. All efficacy variables related to moderate to severe hot flushes were performed using analysis of covariance (ANCOVA) with effects for treatment, baseline daily average count of moderate to severe hot flushes, and stratum (intact uterus versus hysterectomy). The primary outcome was drawn from the analysis of change from baseline to week 4 and week 12 using the intent-to-treat (ITT) population. All

randomized subjects in Study E99-1 who applied at least one dose of study medication including the placebo period, and who had any hot flush data in the screening period were considered part of the ITT population. If there were more than 2 days in a seven-day interval that had data that was imputed, the average daily count of moderate and severe hot flushes was not calculated for that week. A secondary analysis of the primary efficacy parameter was performed and based on the efficacy evaluable population (EFF) defined as all subjects in the ITT population who has at least 5 days of hot flush data in both week 4 and week 12.

For the presentation of estradiol, estrone, and FSH data, treatment group comparisons were performed on the changes in trough serum concentrations using an ANCOVA with effects for treatment, baseline hormone level, BMI and stratum as covariates.

Of the 200 subjects randomized, 197 subjects received treatment. Three subjects discontinued prior to the start of study medication (2 were randomized to the Estrasorb™ treatment group and 1 was randomized to the placebo treatment group). Of the 197 treated subjects, 183 completed the study (90 completers in the Estrasorb™ treatment group and 93 completers in the placebo treatment group). The mean duration of exposure in the ITT population was similar in both treatment groups, 81.1 days for subjects treated with placebo and 80.5 days for subjects treated with Estrasorb™. Per the submission, subjects were very compliant with the treatment regimen as documented on the dosing log. The reasons for discontinuation are presented in Table 2.

Table 2: Subject Disposition for Study E99-1

Parameter	Treatment Group		Total
	Placebo	Estrasorb™	
Total Number of Subjects	N = 100	N = 100	N = 200
In the ITT population (%)	100 (100%)	100 (100%)	200 (100%)
Who Completed the Study	93 (93%)	90 (90%)	180 (90%)
Who Discontinued the Study	7 (7%)	10 (10%)	17 (9%)
Reasons for Discontinuation			
Developed an Adverse Event	3 (3%)	2 (2%)	5 (3%)
Subject Lost to Follow-up	1 (1%)	0	1 (<1%)
Withdrawal of Consent	1 (1%)	4 (4%)	5 (3%)
Non-compliant	2 (2%)	2 (2%)	4 (2%)
Other	0	2 (2%)	2 (1%)

Source: Modification of Panel 8.7.3.1, NDA 21-371 data submitted June 29, 2001, Volume 25, page 42.

Three of the 17 subjects who discontinued Study E99-1 did so during the placebo run-in period. One of the three subjects discontinued because of an application site reaction (Subject 15017, rash on arms, calves and right buttock). The other two subjects discontinued due to withdrawal of consent (Subject 07711) and high baseline eosinophil count (Subject 02205). The two most common reasons for discontinuation were adverse event and withdrawal of consent (3% each, 5 of 200 subjects each). Greater then 90% (180 of 200 subjects) of subjects in Study E99-1 completed the study without early discontinuation.

One hundred twenty-two (122) subjects with protocol violations are listed for Study E99-1 (59 subjects in the placebo treatment group and 63 subjects in the Estrasorb™ treatment group). Sixty-three subjects had a positive urine drug screen at baseline (30 in the placebo treatment group and 33 in the Estrasorb™ treatment group). Per the submission, no drugs of abuse were detected in the positive urine drug screens, only prescription or non-prescription drugs. Forty-three subjects had unacceptable baseline clinical laboratory results (21 in the placebo treatment group and 22 in the Estrasorb™ treatment group). Other reasons for protocol violations include:

- failure to obtain an endometrial biopsy at end-of-study for a transvaginal ultrasound double-wall endometrial thickness > 4 mm and/or failure to repeat the 14-day course of medroxyprogesterone acetate at end-of-study for a transvaginal ultrasound double-wall endometrial thickness > 4 mm (7 placebo subjects and 16 Estrasorb™ subjects),
- failure to obtain a baseline mammogram in subjects when one was not done within the past 9 months (5 subjects),

- abnormal Pap smears (3 subjects) or EKGs at baseline (7 subjects),
- two subjects were randomized without documentation of 120 hot flushes over a two weeks period prior to randomization,
- one subject did not undergo the prescribed washout period.

Reviewers Comments

For the most part, protocol violators were evenly distributed across both treatment groups in Study E99-1. Although a number of protocol violations were attributed to positive drug screens, these were determined to be due to the use of acceptable prescription and non-prescription drugs by the principle investigators. From the data presented, it is unlikely that efficacy results were affected by non-adherence to inclusion/exclusion criteria, particularly in relation to < 120 hot flushes over two weeks at baseline (2 subjects) or inappropriate washout periods (1 subject).

However, 23 of the 122 subjects with protocol violations had incomplete safety follow-up at end-of-study. These protocol violations involved either not obtaining an end-of-study endometrial biopsy for a transvaginal ultrasound double-wall endometrial thickness > 4 mm (1 subject) or not repeating the end-of-study medroxyprogesterone acetate treatment (11 subjects), or both (11 subjects). These finding will be further discussed in the Integrated Review of Safety (ISS). See Section 7.4 Safety Findings from Clinical Studies, Reviewer's Comments on page 35 of this review.

In the data submitted, the severity score index was calculated as 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. It is standard practice in the Division of Reproductive and Urologic Drug Products (DRUDP), however, to utilize a severity score (not a severity score index) to demonstrate the mean change in severity of hot flushes. 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. 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 are presented on page 27 of this review.

Overall, for Study E99-1 there were no statistically significant differences between the placebo and Estrasorb™ treatment groups in demographic and baseline characteristics of age, race, height, weight, and intact uterus versus hysterectomy. However, categorizing body mass index (BMI) into groups: < 24 kg/m^2, 24 – 27 kg/m^2, and > 27 kg/m^2, shows that a larger number of women in the Estrasorb™ treatment group had BMI values > 27 kg/m^2 compared to women in the placebo treatment group (50%, 50 of 100 subjects versus 36%, 30 of 100 subjects, respectively). See Table 3.

Table 3: Demographic Information for Study E99-1, Intent to Treat Population

	Treatment Groups	
Parameter	Placebo N (%)	Estrasorb™ N (%)
Subjects in the ITT Population	100 (100)	100 (100)
Mean Age (years) (SD)	51.8 (6.0)	52.0 (6.0)
< 50 years	29 (29)	32 (32)
50 - 59 years	62 (62)	57 (57)
> 59 years	9 (9)	11(11)
Race		
White	72 (72)	79 (79)
Black	22 (22)	17 (17)
Asian	1 (1)	0
Hispanic	4 (4)	3 (3)
Other	1 (1)	1 (1)

BMI (kg/m^2)		
Mean (SD)	26.80 (5.57)	27.83 (5.48)
< 24 kg/m^2	37 (37)	26 (26)
24 – 27 kg/m^2	27 (27)	22 (22)
> 27 kg/m^2	36 (36)	50 (50)
Spontaneous Amenorrhea		
Yes	51 (51)	50 (50)
No	49 (49)	50 (50)
Hysterectomy		
Yes	49 (49)	50 (50)
No	51 (51)	50 (50)

Source: Modification of Panel 8.7.4.1, NDA 21-371 data submitted June 29, 2001, Volume 25, page 49.

Reviewer's Comments

As shown in Table 3, baseline demographics were similar between placebo and the Estrasorb™ treatment groups in Study E99-1. However, differences are evident in the comparison of the categorized BMI (calculated as weight in kilograms divided by height in meters squared categorized as < 24 kg/m^2, 24 – 27 kg/m^2, and > 27 kg/m^2) between the placebo treatment group and the Estrasorb™ treatment group. While subjects in the placebo treatment group were similarly distributed across the three categorized BMI groups (37%, 27%, and 36%, respectively), this was not so for the Estrasorb™ treatment group. Fifty percent of the subjects in the Estrasorb™ treatment group (50 of 100 subjects) had a BMI > 27 kg/m^2 (26% had a BMI of < 24 kg/m^2, and 22% had a BMI of 24 – 27 kg/m^2).

To fully explore the possible imbalance in BMI across the two treatment groups, the Statistician completed an exploratory analysis of hot flush data (frequency and severity of hot flushes at week 4 and week 12) using an ANCOVA model with terms for baseline, treatment, BMI category (≤ 27 kg/m^2, > 27 kg/m^2), and treatment-by-BMI interaction for each of the four co-primary endpoints. Per the Statistician, none of the analyses indicated any relationship between BMI and treatment effect.

The primary efficacy parameter for Study E99-1 was the mean change from baseline of the average daily number of moderate to severe hot flushes at both week 4 and week 12. As shown in Table 4, the mean average daily moderate to severe hot flush count was similar at baseline for the two treatment groups, 13.63 for the placebo treatment group and 13.05 for the Estrasorb™ treatment group. By week 4 and continuing through week 12, the Estrasorb™ treatment group demonstrated a clinically and statistically significant reduction in the number and severity of moderate to severe hot flushes as compared to the placebo treatment group ($p<0.001$ for weeks 4 and 12). The Estrasorb™ treatment group experienced a greater average reduction of three or more hot flushes per day relative to the placebo treatment group.

Table 4: Change in the Mean Daily Number of Moderate to Severe Hot Flushes During Treatment, Intent-to-Treat Population, Most Recent Value Carried Forward.

Time Point	Placebo	Estrasorb™
Baseline	(N = 100)	(N = 100)
Mean Number per Day (SD)	13.63 (5.48)	13.05 (5.78)
Week 4	(N = 97)	(N = 96)
Mean Number per Day (SD)	7.46	4.42
Mean Change from Baseline (SD)	-5.97 (4.76)	-8.56 (6.19)
p-value versus Placebo[a]	NA	<0.001
Week 12	(N = 90)	(N = 90)
Mean Number per Day (SD)	5.88	2.00
Mean Change from Baseline (SD)	-7.20 (5.39)	-11.11 (6.84)
p-value versus Placebo[a]	NA	<0.001

Source: Adapted from NDA 21-371 data submitted June 29, 2001, Volume 25, Table 6, pages 118-122.
SD = Standard deviation; NA = Not applicable