CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-992

MEDICAL REVIEW(S)

NDA 20-992

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Medical Officer's Review
(Original Review)

Sponsor: Duramed Pharmaceuticals, Inc.

Drug:

Generic: Synthetic Conjugated Estrogens A

Trade: Cenestin™

Chemical: Estrogens:

Estrone: 3-Hydroxyestra-1,3,5(10)-tien-17-one
Equilin: 3-Hydroxyestra-1,3,5(10),7-tetraen-17-one
17 α-Dihydroequilin: (17α)-estra-1,3,5(10),7-tetraene-3,17-diol
17α-estradiol: (17α)-estra-1.3.5(10)-triene-3,17-diol
17β-Dihydroequilin: (17β)-estra-1,3,5(10),7-tetraene-3,170diol
17α-Dihydroequilenin: (17α)-estra-1,3,5,7,9-pentaen-3,17-diol
17β-Dihydroequilenin: (17β)-estra-1,3,5,7,9-pentaen-3,17-diol
Equilenin: 3-hydroxyestra-1.3.5.7.9-pentaen-17-one
17β-estradiol: (17β)-estra-1,3,5(10)-triene-3,17-diol

Route: Oral

Dosage Form: Tablet

Strength: 0.3 mg, 0.625 mg, and 0.9 mg

Proposed Indications: 1) Treatment of moderate to severe vasomotor symptoms associated with the menopause.

Related Submission: IND
NDA 20-992, Amendments dated: 5/27/1998, 12/9/98, 12/15/98

Related Documents: *Minutes of meetings* dated: 6/19/97, 7/22/97, 7/23/97, 5/1/98, 5/28/98, 5/29/98, 6/15/98, 7/20/98, 7/22/98, 9/1/98
Minutes of teleconferences dated: 7/25/97, 9/4/97, 6/16/98, 8/6/98, 9/21/98

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1. Resume

This 27 volume NDA, originally submitted by Duramed Pharmaceuticals, Inc. on March 27, 1998 and amended on May 27, 1998 contains a report of a pivotal double-blind, four-center, placebo-controlled study in 120 menopausal women to determine the efficacy of Cenestin™ (synthetic conjugated estrogens A) after 12-weeks of treatment of moderate to severe vasomotor symptoms (MSVS). This pivotal clinical study was conducted under Protocol Number 366.

Two pre-NDA conferences were held with the Division concerning the proposed NDA filing of Cenestin™. The first pre-NDA conference, held June 19, 1997, outlined the logistics for filing the NDA and included:

- Submission of one adequate, well-controlled, clinical study performed using the to-be-marketed product. The clinical study design should be a randomized, double-blind, placebo-controlled study of 12 weeks treatment in postmenopausal women with treatment of moderate to severe vasomotor symptoms as the primary endpoint;
- Submission of an IND to the Division;
- Submission of Chemistry, Manufacturing and Control data, including tablet formulation data, four months in advance of the NDA submission.

The established name of the drug product under consideration was "synthetic conjugated estrogens". The sponsor met these conditions with one minor exception. The sponsor elected to submit their clinical vasomotor study including peri-menopausal as well as post-menopausal women.

The second pre-NDA conference, held January 27, 1998, reached the following decisions:

- The NDA could reference the previously submitted ANDA Chemistry, Manufacturing and Control section with the NDA containing only updated data;
- The request for three-year market exclusivity was acceptable;
- The NDA should contain the following information for each study center:
  1) baseline values and descriptions of the primary (not secondary) efficacy variable results;
  2) descriptions of the adverse events data;
  3) complete case report forms on dropouts.
- Data should be stratified and summarized by dosage strength; any waiver for intermediate doses should be justified by appropriate data;
- The sponsor's proposal to submit summaries of their four Clinical Pharmacology and Biopharmaceutics studies with reference to the ANDA for complete results was acceptable;
- The primary variable in the study would be the absolute number of reduction of vasomotor symptoms at 4, 8, and 12 weeks; percent change would also be examined for consistency with absolute change.

The sponsor met the conditions outlined at the January 27, 1998 meeting. After submission of the NDA, upon initial review of the application, the Division requested resubmission of the data using the actual (arithmetic) difference rather than the absolute difference in reduction of vasomotor symptoms. This re-analysis was submitted in Amendment 1 on May 27, 1998.

In the clinical trial submitted, MSVS were recorded by patients' self-assessment of daily hot flashes. The primary efficacy analysis was the difference between drug and placebo treatment in the actual change of MSVS from baseline to 4, 8 and 12 weeks of treatment. Secondary efficacy criteria included changes from baseline throughout the 12 weeks of treatment in the mean number of MSVS, in the mean severity score, and in the Kupperman Index of vasomotor symptoms (the Kupperman Index includes 11 elements: paresthesia, insomnia, nervousness, melancholia, vertigo, weakness [fatigue], arthralgia and myalgia, headache, palpitations, and formication).

Principal study investigators were medical directors at the clinical sites of MDS Harris (Lincoln and Omaha, Nebraska and Phoenix, Arizona) and Phoenix International Life Sciences in Cincinnati, Ohio. The current established name of this product is "synthetic conjugated estrogens A".

2. Background

2.1 Regulatory history

In 1972, as part of the Drug Efficacy and Safety Initiative (DESI), the FDA determined that certain of the estrogens then available on the market were safe and "effective" for the treatment of several postmenopausal symptoms, including vasomotor symptoms and atrophic vaginitis and "probably effective" in selected cases of osteoporosis. The drug substances (both innovator and generic) contained in these products included estrone sulfate (stabilized as the piperazine salt), estradiol, esterified estrogens and conjugated estrogens. Premarin® (a mixture of conjugated estrogens derived from the urine of pregnant mares) was the most prescribed product approved under DESI but various generic versions of this product were marketed from 1972 to 1990. Most of these were composed of a combination of natural source and synthetic, or purely synthetic sources of estrogens. Duramed, for example, produced over 1.2 billion tablets of conjugated estrogens. In 1986, on the basis of studies submitted by the manufacturer of Premarin®, the FDA concluded that a 0.625 mg dose of Premarin® daily was effective for the prevention of osteoporosis.

Between 1989 and 1991, three FDA advisory committee meetings were held, and in 1991 the FDA published a bioequivalence guidance that specified the following composition of a generic conjugated estrogens drug product:

- 5 mandatory estrogens: estrone and equilin as the active ingredients; 17α- and 17β-dihydroequilin and 17α-estradiol as concomitant components,
- equilenin and 17β- and 17α-dihydroequilenin as signal impurities, and
- 17β-estradiol and $\Delta^{8,9}$-dehydroestrone as ordinary impurities subject to a limit test.

In 1990, the manufacturer of Premarin® argued that generics were not bioequivalent to Premarin®, which was a modified release dosage form while the generic versions were immediate release products. On the basis of this argument, the FDA ordered the generics products withdrawn from the market stating that the difference in release rates may have a negative impact on the safety and effectiveness of the generics in preventing osteoporosis.

2.2 Clinical implications of preclinical sections

2.2.1 Chemistry, manufacturing and controls

Please refer to Chemistry, Manufacturing and Controls Review.

Synthetic Conjugated Estrogens A Solution drug substance contains the following estrogenic substances: sodium estrone sulfate, sodium equilin sulfate and sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, 17β-dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17β-estradiol sulfate. Synthetic conjugated estrogens A are water soluble. Duramed Pharmaceuticals, Inc. is the manufacturer for all strengths of synthetic conjugated estrogens A tablets.

2.2.2 Pharmacology and toxicology

Please refer to Pharmacology Review.

Duramed has not conducted any clinical pharmacology or toxicology studies. The Pharmacology Team Leader, Division of Reproductive and Urologic Drug Products, concluded in a memorandum prepared October 26, 1998: "Any difference in toxicity between Premarin® and Cenestin™ would be expected to be small and subtle. No current animal toxicology studies have the power to detect such differences, if they exist, and the applicability of any small measured differences from such preclinical testing would be questionable. It is concluded that additional toxicology studies are not needed nor appropriate to support the safety of Cenestin™."

2.3 Human pharmacokinetics/bioavailability

Please refer to the Clinical Pharmacology and Biopharmaceutics Review.

No pharmacokinetic and bioavailability data is presented from Protocol # 366. However, one pilot and four definitive bioavailability studies were conducted between July 1993 and December 1995. Two bioavailability studies, under fasted conditions, were conducted comparing 2 x 0.625 mg Cenestin™ versus 2 x 0.625 mg Premarin® (number BN038) and 1 x 1.25 mg Cenestin™ versus 1 x 1.25 mg Premarin® (number BN037). The mean plasma concentration versus time after dosing for total estrone and equilin and free estrone and equilin (baseline corrected for total and free estrone) show that a dose of 2 x 0.625 mg Cenestin™ gives a C_{max} and AUC similar to a single tablet dose of 1 x 1.25 mg. Since these studies were not done on the same subjects at the same time, the comparison is not strictly valid especially considering the high inter-and intra-subject variability (see NDA 20-992, Amendment 1, Figure 5, Comparison of mean Plasma Concentrations of Total and Free Estrone and Equilin After Either a 2 x 0.625 mg or 1 x 1.25 mg Dose of Cenestin™ Under Fasting Conditions, page 01-080). Therefore, the across study comparison of 2 x 0.625 mg and 1 x 1.25 mg doses of Cenestin™ do not clearly establish bioequivalence.

Two bioavailability studies (numbers 930125 and 941817) were conducted to evaluate the effect of food on the rate and extent of absorption of Cenestin™ and showed no effect of food based on a comparison of AUC and C_{max} parameters between the fasted and fed studies.

3. Description of clinical data source

Duramed Pharmaceuticals, Inc. was the sponsor of this pivotal Study Number 366: a 12 week, randomized, double-blind, placebo-controlled, dose-titration study of 120 menopausal women conducted in four centers. This study differs from past studies in both the target population and dosing regimen.

First, minimal inclusion/exclusion criteria were required "to be more representative than past studies of the patient population seen clinically for the treatment of vasomotor symptoms." Per the sponsor, including only patients with last menses 12 months prior to dosing, or with last menses 6 months prior to dosing with required FSH and/or estradiol levels, would lead to the exclusion of many women who seek medical relief for moderate to severe hot flashes even while experiencing an occasional (some even regular) menstrual period. Thus, the sponsor broadened their entry criteria to include these women, many of whom could be considered peri-menopausal. In addition, the Duramed study had no weight restriction (studies usually include women within ± 15% of normal weight for a given height), and the only restricted concomitant medication was medication that could produce an estrogen-related response.

Second, the sponsor selected a dosing regimen "that reflected current clinical practice." Per the sponsor, the current clinical practice of titrating a patient to achieve adequate control of vasomotor symptom is reflected in the labeling for estrogen and estrogen/progestin products. This pivotal study therefore utilized dose titration. The initial dose assigned at randomization was a daily dose of 1 x 0.625 mg Cenestin™ or placebo. After 7 days, if adequate clinical response was not achieved, the daily dose was increased to 2 x 0.625 mg Cenestin™ or placebo. No additional increase in dose was allowed for the remaining 11 weeks of the study. After day 7 the dose could be lowered, at any time, to a minimum daily dose of 1 x 0.3 mg Cenestin™ or placebo.

4. Clinical trial 366

4.1 Objectives/rationale

In the human female, estrogens are present in varying amounts from before menarche through the menopause and postmenopause period. The three naturally occurring estrogens are estrone, estradiol, and estriol. The primary source of estrogen in normally cycling women is the ovarian follicle which secretes 70 to 500 micrograms of 17β-estradiol daily (the principle estrogen produced by the functioning premenopausal ovary) depending on the phase of the menstrual cycle. The second major naturally occurring human estrogen is estrone. At menopause, no further ovulatory cycles are produced and the

production of 17β-estradiol decreases dramatically. After menopause, most endogenous estrogen is produced by the conversion of androstenedione, secreted by the adrenal cortex, to estrone by adipose tissues. In postmenopausal women, estrone sulfate is the most abundant circulating estrogen.

Administered estrogens and their sulfate ester forms are handled within the body essentially the same as endogenous hormones. Estrogens are metabolized and conjugated by the liver in order to increase their solubility in water in preparation for excretion. Naturally occurring estrogens circulate in the blood largely bound to sex hormone-binding globulin and albumin. Only unbound estrogens enter target tissue cells. Estrogen receptors have been identified in tissues of the reproductive tract, breast, pituitary, hypothalmus, liver, and bone of women.

Common symptoms of the menopause and postmenopausal years include hot flushes, paresthesias, palpitations, cold hands and feet, headaches, vertigo, irritability, anxiety, nervousness, depression, fatigue, weight gain, insomnia, night sweats, forgetfulness, and inability to concentrate. Hot flushes, perhaps the most common complaint, are experienced by more than 75% of women with decreasing estrogen levels, and may persist for one or more years. Many women will have only mild (or no) menopausal symptoms and will not need to use estrogen drugs for these symptoms. Others may need to take estrogens temporarily while their bodies adjust to lower estrogen levels. The majority of women who need estrogen replacement therapy will not need it for longer than six months for the relief of vasomotor symptoms.

The primary objective of Study 366 was to compare the effects of oral administration of synthetic conjugated estrogens A tablets to that of matching placebo tablets on the reduction in the mean number of moderate to severe vasomotor symptoms (MSVS) per 24 hours during the two week baseline period to the mean reduction in the number of MSVS during weeks 4, 8, and 12 of treatment. Secondary study objectives included: 1) the evaluation of the safety and acceptability of synthetic conjugated estrogens A tablets, and 2) evaluating the efficacy of synthetic conjugated estrogens A and placebo throughout the 12 weeks of treatment by assessing the overall changes in mean number of MSVS, the mean change in the severity of vasomotor symptoms, and the mean change in vasomotor symptoms related to estrogen deficiency using the Kupperman Index.

4.2 Design

This study was a randomized (ratio of 3:2, active drug:placebo), placebo-controlled, double-blind, four site clinical trial in which 120 healthy adult menopausal women, meeting the inclusion and exclusion criteria, were enrolled. The study consisted of three distinct periods: a screening period during which patients were screened to determine eligibility, a two week baseline period during which pre-dose hot flashes and nocturnal sweating were measured to qualify the patient for the study, and a twelve week treatment period. This was a titration study designed to examine a subset of possibilities. The initial dose assigned at randomization was a daily dose of 1 x 0.625 mg of synthetic conjugated estrogens A or placebo. After 7 days, if adequate clinical response was not achieved (defined as a 50% reduction in the baseline number of moderate and severe vasomotor symptoms), the daily dose could be increased to 2 x 0.625 mg of synthetic conjugated estrogens A or placebo. No additional increase in dose was allowed during the 12 week study. However, at any time during the 12 weeks of treatment, the dose could be lowered to a minimum daily dose of 1 x 0.3 mg of synthetic conjugated estrogens A or placebo if patients exhibited signs of study drug intolerance such as breast tenderness, bloating/water retention or persistent headache and/or nausea.

4.3 Study Population

A total of 120 women were randomly assigned to the two treatment regimens. Seventy-two of these patients received active drug and 48 received placebo.

The sponsor selected to include minimal inclusion and exclusion criteria for this study in an effort to reflect more accurately the patient population seen clinically for the treatment of vasomotor symptoms (see NDA 20-992, Volume 1.7, page 7). Early postmenopausal women and women who were receiving concomitant medication (except those that could produce an estrogen-related response) were enrolled as long as the

concomitant medication use was stable throughout the treatment period. The study also did not require specific FSH and/or estrogen levels or strict weight restrictions.

The demographics of the patient population by treatment are summarized in Table 1. The average patient age was 48 years. Fifty percent (N=60) of the patient had been menopausal for > 36 months, 16 % (N=19) had been menopausal for 13 – 36 months, 6% (N=7) had been menopausal 6 – 12 months, and 28% (N=34) of patients had been menopausal for < 6 months. Sixty-eight percent of the patients were Caucasian, and 28% of patients were Black. There were no statistically significant differences between these characteristics and other characteristics (weight, height, systolic and diastolic blood pressure, pulse rate) between groups (see Table 1).

Table 1: Demographics of Patient Population by Treatment

	Synthetic Conjugated Estrogens A			Placebo			Overall		
Characteristics	N	Mean	SD	N	Mean	SD	N	Mean	SD
Age (yrs)	72	49	6	48	48	4	120	48	5
Duration since last menstrual period (months)	72	87	109	48	85	92	120	86	102
Patients whose last menstrual period was:									
< 6 months ago	19			15			34		
6 – 12 months ago	6			1			7		
13 – 36 months ago	13			6			19		
> 36 months ago	34			26			60		
Weight (lb)	68	163	34	47	168	32	115	165	33
Height (in)	69	64	2	48	65	3	117	64	3
Systolic Blood Pressure (mmHg)	71	123	13	48	127	14	119	125	13
Diastolic Blood Pressure (mmHg)	71	79	11	48	83	9	119	80	10
Pulse Rate (bpm)	71	73	11	48	77	9	119	74	10
Race (%)									
Caucasian		67			71			68	
Black		29			25			28	
Asian/Not Oriental		0			2			1	
Other		4			2			3	
Smoker (%)		29			31			30	

Source Data: NDA 20-992, Amendment 1, Volume 2, Page 02-063.

4.4 Inclusion and Exclusion Criteria

Inclusion criteria (NDA 20-992, Volume 1.7, Pages 43 - 44)
To be included in this clinical trial the women:

1) Either exhibited natural menopausal symptoms or had bilateral oophorectomy for a benign illness;
2) Exhibited at least 60 moderate to severe vasomotor symptoms per week (hot flashes and nocturnal sweating);
3) Presented, a priori, adequate time availability and motivation to participate in the trial, as well as the ability to communicate, understand, and comply with the requirements of the study;
4) Read the patient informed consent form and give their written consent;

5) Had a medical history and screening criteria reviewed and accepted by the principal investigator.

Exclusion criteria (NDA 20-992, Volume 1.7, Pages 44 – 45)

1) Any estrogen therapy within the two weeks prior to the first dose;
2) Unexplained or otherwise abnormal vaginal bleeding in the 6-months preceding receipt of the first dose;
3) A history or presence of known contraindications to estrogen therapy, such as thrombophlebitis, thromboembolic disease, estrogen-dependent neoplasia, or carcinoma of the breast;
4) A history of any uncontrolled endocrine disorders;
5) A history of diabetes mellitus requiring pharmacologic therapy;
6) Clinical evidence of any significant chronic illness, including cardiovascular, renal, neurologic, hepatic, endocrine, gastric, or central nervous system disease, which could affect efficacy or safety of study medication;
7) Use of other investigational drugs or participated in another clinical trial within 30 days of the first dose;
8) A history of clinically significant depression or severe psychiatric disturbances within the last two years;
9) Concurrent administration of liver enzyme-inducing drugs, such as rifampicin; barbiturates, carbamazepine, dichlorlphenazine, phenylbutazone, phenytoin, or primidone; clonidine, anticholinergics, type B MAO inhibitors, levodopa, dopamine agonists and antiagonists; estrogens, other than the study drug; and progestogens;
10) Clinically relevant abnormal serum biochemistry or hematology;
11) Presence of any manifest premalignant or malignant disease;
12) A history or presence of any drug abuse or alcohol abuse within the last two years;
13) Clinically abnormal mammogram within 6 months of first dose;
14) Clinically abnormal PAP and pelvic exam on screening;
15) Pregnancy.

Reviewer's Comments

Per the 1995 "Guidance for Clinical Evaluation of Estrogen- and Estrogen/Progestin-Containing Drug Products Used For Hormone Replacement Therapy in Postmenopausal Women," menopausal status is recognized as 12 months of spontaneous amenorrhea or 6 months of amenorrhea with serum levels of FSH > 50 mIU/ml (currently revised to >40 mIU/ml) and estradiol < 20 pg/ml. In addition, the guidance states: "For subjects on previous estrogen and/or progestin hormone replacement therapy, the following washout periods are required before baseline assessments are made: --- for studies of menopausal symptoms and/or endometrial protection, at least 8 weeks for prior oral estrogen and/or progestin therapy, at least 4 weeks for prior transdermal hormone therapy or systemically available vaginal hormone therapy, and at least one week for prior vaginal hormonal product therapy (rings, creams, gels)."

In this study, the sponsor elected to accept women who had not used any estrogen therapy within only two weeks prior to the first treatment dose and to accept women who exhibited at least 60 moderate to severe hot flashes and nocturnal sweating per week irrespective of the length of their menopausal status and without any determination of baseline FSH and estradiol levels. By not recognizing menopausal status as requiring 12 months spontaneous amenorrhea or 6 months amenorrhea with serum levels of FSH >40 mIU/ml and estradiol < 20 pg/ml, and not requiring an 8 week washout period for prior estrogen therapy, the sponsor accepted the risk of selecting a perimenopausal population instead of a postmenopausal population for their study (see June 19, 1997 Meeting Minutes). Demonstration of meaningful efficacy in such a population could be more difficult since symptoms may be more highly variable leading to a high placebo response.

4.5 Screening period

The objectives of the screening period were to ensure that the patient met the inclusion and exclusion criteria. A written informed consent document was signed at this time. Demographic and medical history information was obtained and patients underwent a general physical examination and laboratory tests. Laboratory tests obtained during the screening period and at the end-of-study included: liver function tests (gamma GT, ALT, AST, total bilirubin), lipid tests (HDL cholesterol, LDL cholesterol), hematology (RBC, hemoglobin, hematocrit, MCV, WBC, and differential, platelets), and biochemistry (glucose, urea, total protein, albumin, creatinine, uric acid, sodium, potassium, calcium, alkaline phosphate).

Each patient was given a diary on which to record the number of daily vasomotor symptoms that occurred during the next 14-day period proceeding randomization.

4.6 Baseline period

The baseline period was defined as the 14 consecutive days prior to the first treatment dose. After at least one week of exhibiting at least 60 moderate to severe vasomotor symptoms, the patient was given a gynecological examination including a breast examination, bi-manual pelvic examination, a Pap smear, and a pregnancy test. If these evaluations were within normal limits patients were randomly assigned to one of the two treatment regimens according to a randomization schedule developed before study initiation. Patients were randomized in a ratio of three (3) active to two (2) placebo.

4.7 Treatment period

During the treatment period, patients were seen eight times: randomization (first dose), weeks 1, 2, 4, 6, 8, 10 and 12. Additional visits were scheduled to monitor any adverse event or premature withdrawal from the study for any reason.

Placebo and synthetic conjugated estrogens A tablets were administered orally once daily for the 12-week period. This was a dose titration study. The dose titration visit occurred one week after the first dose (day 7). During this visit the investigator determined vital signs, asked the patient about her symptoms, documented specific vasomotor symptoms as measured by the Kupperman Index[1], checked patient's diary, and performed drug accountability. If the patient's daily hot flashes had not been reduced by at least 50% from her baseline average, the investigator increased the study drug medication to two 0.625 mg tablets per day (for a total daily dose of 1.25 mg) or increased the placebo tablet to two tablets per day. Per the protocol, no increases were allowed during the remainder of the study. If the patient exhibited signs of study drug intolerance (such as breast tenderness, bloating/water retention or persistent headache and/or nausea), the investigator decreased the study medication from 0.625 mg to one 0.3 mg tablet per day. During visits at 2, 4, 6, and 8 weeks, if the patient had been increased to 2 x 0.625 mg at day seven and she demonstrated signs of intolerance, she was returned to a single 0.625 mg tablet per day for the balance of the study. If signs of intolerance persisted, the study medication could be decreased to one 0.3 mg tablet per day. A decrease in dosage, after the dose titration visit at Week 1, was allowed at any time during the remaining 11 weeks of the study. At the end-of-study visit, in addition to the above stated evaluations, the investigator prescribed a progestin if clinically indicated.

4.8 Evaluation period

From data collected and recorded by the patient in a self-evaluation diary, the primary efficacy criterion, the mean number of moderate to severe hot flashes recorded in the 14 days prior to the first dose (baseline) and those recorded during the fourth, eight, and twelfth week of the trial, were determined. Secondary evaluation criterion included changes from baseline in the mean number of moderate to severe vasomotor symptoms recorded daily by the patient throughout the 12 weeks of treatment and changes from baseline in the mean severity score of vasomotor symptoms recorded daily by the patient throughout the 12 weeks of

[1] Kupperman HS, et al, Comparative clinical evaluation of estrogenic preparations by the menopausal and amenorrheal indices, J Clin Endocrin Metab, 1953: 13:688-703.

treatment using the Kupperman Index following an interview of the patient by the principal investigator or his designee.

The patient populations on which the efficacy variables were evaluated in the study were as follows:

- The Treatment-Allocated Population (TAP) consisting of all randomized patients who took at least one tablet of the study medication.
- The Per-Protocol Population (PPT) as a subset of the treatment allocated population consisting of those patients who had no major protocol deviations.
- The Intent-To-Treat Population (ITT) as a subset of the TAP population. The data for any patient who completed any of the intervals of treatment (1, 4, or 8 weeks) and had MSVS data recorded for the treatment interval but did not have MSVS data recorded for the next treatment interval had their most recent full week data carried forward for analysis. For example, the data for any patient who had completed at least the 4th week of treatment and had MSVS data recorded for the 4th week but did not have MSVS data recorded for the 8th and 12th week analysis had their most recent full week data carried forward for the 8th and 12th week analysis.

4.9 Withdrawals and compliance

A total of 120 patients were enrolled in the study and 109 patients completed the entire 12 weeks of the study. Seventy-two (72) patients were enrolled into the synthetic conjugated estrogens A active treatment and 48 patients were enrolled into the placebo treatment. Sixty-seven (67) active treatment patients and 42 placebo patients completed the 12 weeks of the study. Table 2 displays the number of patients enrolled by treatment for the entire study, and their disposition during the trial.

Table 2: Number of Patients Planned and Enrolled by Treatment

	Active	Placebo	Total
Planned	72 (100%)	48 (100%)	120 (100%)
Enrolled	72 (100%)	48 (100%)	120 (100%)
Discontinued			
Baseline	2 (3.0%)	1 (2.1%)	3 (2.5%)
Week 4	1 (1.4%)	2 (4.2%)	3 (2.5%)
Week 8	1 (1.4%)	1 (2.1%)	2 (1.7%)
Week 12	1 (1.4%)	2 (4.2%)	3 (2.5%)
Completed			
Baseline	70 (97%)	47 (98%)	117 (97.5%)
Week 4	69 (96%)	45 (94%)	114 (95%)
Week 8	68 (94%)	44 (92%)	112 (93%)
Week 12	67 (93%)	42 (87%)	109 (92%)

Source: Adapted from NDA 20-992, Volume 1.7, Synopsis, Page 07-022

Eleven patients (5 active treatment and 6 placebo) discontinued the study. Of the eleven patients who did not complete the entire 12 weeks, 6 were discontinued by the principal investigators due to adverse events and 5 patients either withdrew for personal reasons or were withdrawn by study management for compliance issues. Only one patient on active treatment (number 074) left the study prematurely due to an adverse event and persistence of menopausal symptoms. The disposition of each discontinued patient is as follows:

Three patients (2 active treatment and 1 placebo) were dropped at baseline for the following reasons:

Patient No. 048 (active): Patient missed week 4 scheduled visit and failed to take four treatment doses. This patient was not included in the efficacy analysis.

Patient No. 076 (active): Patient was withdrawn by principal investigator due to non-serious adverse events (visual difficulty, complaint of "feeling odd," and abdominal cramps).
Patient No. 061 (placebo): Patient requested to be with drawn after medication made her nauseous.

Three patients were withdrawn by week 4 for the following reasons:

Patient No. 092 (active): Patient was withdrawn due to a non-serious adverse event (significant bilateral breast pain).
Patient No. 053 (placebo): Patient was unable to make the titration visit due to personal reasons and was unable to continue the study.
Patient No. 060 (placebo): Patient requested to be withdrawn due to conflict with her job schedule.

Two patients were withdrawn by week 8 for the following reasons:

Patient No. 091 (placebo): Patient requested to be withdrawn, no reason was provided.
Patient No. 130 (active): Patient was withdrawn due to poor compliance.

Three patients were withdrawn by week 12 for the following reasons:

Patient No. 031 (placebo): Patient was withdrawn by principal investigator due to non-serious adverse events (high blood pressure and headache).
Patient No. 074 (active): Patient was withdrawn by principal investigator due to non-serious adverse events (melancholia and persistent complaint of menopausal symptoms [lack of efficacy]).
Patient No. 102 (placebo): Patient was withdrawn by principal investigator due to a non-serious adverse event (intense breast soreness and development of a cystic mass in left breast; patient did not disclose at enrollment her history of four previous cystic breast masses).

Patient Numbers 048 (active), 061 (active), and 076 (placebo) were excluded from the per-protocol population data set and from the intent-to-treat population. Patient Numbers 061 and 076 took study medication on only 3 and 2 days, respectively, which was judged inadequate to achieve a clinically significant response. Patient Number 048, who completed 1 week of treatment, recorded 1137 hot flashes for the first week of treatment and failed to record any adverse events or concomitant medications. She was considered unreliable and the FDA concurred with her exclusion from the data set. All other discontinued patients had their last observations carried forward.

4.10 Protocol deviations

Overall, 100 % of the patients met all inclusion and exclusion criteria as specified in the protocol. Protocol deviations were classified into five categories:

1) Patients who did not complete all 14 days of baseline or had an extra day of baseline: Of the total patients who completed through week 12 of the study, 13 of 109 (13%) did not complete all 14 days of baseline and one patient had an extra day of baseline recorded;
2) Patients who did not complete at least 5 days of vasomotor symptom diary during a week: Four of 120 (3%) enrolled patients did not complete at least 5 days of vasomotor symptom diary during the week (three placebo patients and one active treatment patient);
3) Patients who did not have final clinical laboratories recorded: Six of the 120 patients (5%) did not have final clinical laboratories recorded on their final visit (two placebo patients and two active treatment patients);
4) Patients who did not have a "final" Kupperman evaluation: One placebo and one active treatment patient did not have a final Kupperman evaluation performed on their last visit; and
5) Dosing errors: Five (4.2%) of 120 randomized patients had dosing errors (four active treatment and one placebo patient). Per the sponsor the dosing errors were not felt to significantly impact the primary efficacy outcome with the exception of Patient No. 011 who received a sub-optimal dose Weeks 2 – 8 and may not have achieved maximal symptom relief (NDA 20-992, Volume 1.7, Page 60). See the following Table 3 for a complete explanation of all five dosing errors.

Table 3: Dosing Errors

Patient Number (Randomized) Treatment)	Period	(Actual Treatment Received)	Dosing Regimen	Explanation/Outcome
011 (Active)	Randomization Visit W1 W2-W8 W10 W11-W12	 (Active) (Active) (Active) (Active) (Active)	 0.625 mg 2 x 0.625 mg 0.625 mg 2 x 0.635 mg 0.625 mg	Patient qualified for increase in dosage regimen for Week 1. At the Week 2 visit the dosage was erroneously decreased to 0.625 mg. Week 10 the patient made an error and took 2 tabs of 0.625 mg. Patient remained in the Intent-to-Treat (ITT) population as an Active patient at the 0.625 mg dose level.
035 (Active)	Randomization Visit – W5 W6 W8 - W12	 (Active) (Active) (Active)	 0.625 mg 2 x 0.625 mg 0.625 mg	At week 6 the patient was dispensed a bottle with the wrong dosing instructions and took 2 x 0.625 mg (active treatment) daily for 2 weeks. Patient resumed original dose at Week 8. Patient remained in the ITT population as an Active patient at the 0.625 mg dose level.
074 (Active)	Randomization Visit W1 – W3 W4 – W6 W7 – W12	 (Active) (Active) (Placebo) (Active)	 0.625 mg 2 x 0.625 mg 2 x 0.625 mg 2 x 0.625 mg	Patient was dispensed the wrong patient's medication for Weeks 4 to 6. During this time she received placebo instead of active treatment. She received the correct medication at Week 7 and throughout the remainder of the study. Patient remained in the ITT population as an Active patient at the 2 x 0.625 mg dose level.
096 (Placebo)	Randomization Visit – W1 W2 – W3 W4 – W12	 (Placebo) (Placebo) (Placebo)	 0.625 mg 1.25 mg 0.625 mg	Patient was erroneously dispensed a bottle with the wrong dosing instructions and took 2 x 0.625 mg (Placebo) for weeks 2-4. This was corrected by the week 4 visit. Patient remained in the ITT population as a Placebo patient at the 0.625 mg dose level.
126 (Active)	Randomization Visit – W1 W2 – W4 W5 – W12	 (Active) (Placebo) (Active)	 0.625 mg 2 x 0.625 mg 0.625 mg	Patient was dispensed the wrong patient's medication (placebo) at Week 2. She took placebo for two weeks (Weeks 2 – 4) before returning to active treatment with 0.625 mg Weeks 5-12. Patient remained in the ITT population as an Active patient at the 0.625 mg dose level.

Source: NDA 20-992, Volume 1.7, Table 10.2-4, Page 07-060.

4.11 Efficacy analysis

The primary efficacy variable was the change from baseline in moderate to severe vasomotor symptoms (MSVS) at weeks 4, 8, and 12. MSVS for the baseline period was calculated for each patient by adding up the moderate and severe symptoms recorded each day for each week and then averaging the two weekly totals. When data was missing during the baseline period, a weighted average was calculated by adding the MSVS recorded for each day there was data, dividing by the number of days that data were available and multiplying by 7. MSVS for each subsequent week was calculated for each patient by adding up the moderate and severe symptoms recorded each day for that week. The change in MSVS for weeks 4, 8, and 12 was calculated for each patient by subtracting the baseline total from the total for that week.

The treatment-allocated population (TAP) consisted of all randomized patients who took at least one tablet of the study medication and totaled 120 patients (72 active treatment and 48 placebo patients).

The per-protocol population (PPT) consisted of those patients who had no major protocol deviations and consisted of 117 patients with 70 active treatment patients and 47 placebo patients. Three patients were excluded from this subset (patients 048 [active], 061 [placebo], and 076 [active]). Patient Numbers 061 and 076 took study mediation on only 3 and 2 days, respectively. Patient Number 048 was excluded from the PPT data set after 1 week of active treatment

For the intent-to-treat (ITT) data, data for any patient who had completed at least the 1st week of treatment but did not have data for other weeks had their most recent full week of data carried forward to the remaining study weeks. The ITT population consisted of 117 patients with 70 in the active treatment group and 47 in the placebo treatment group. Patient Numbers 061(placebo) and 076 (active) were excluded from this patient population because they did not complete one week of treatment. The data for Patient 048 (active) were not included in the efficacy or secondary analysis even though Patient 048 completed week one of treatment and met the requirements of the ITT population. Patient 048 entered the study with 453 MSVS at baseline. During Week one this patient reported 1137 MSVS. In addition to this dramatic increase in hot flashes from baseline, Patient 048 failed to report any adverse events or concomitant medications and did not report to the clinic for appointments. In a telephone conference with the FDA on February 9, 1998, it was agreed that the data for Patient 048 could be dropped from the efficacy analysis.

An analysis of variance was performed for weeks 4, 8, and 12. T-tests for significantly different change from baseline within each treatment group were applied. The ITT data analysis was the primary analysis. All other data analyses were considered supportive.

This submission, as amended on December 9, 1998, proposed approval of 3 dose levels of Cenestin™: 0.3 mg, 0.625 mg, and 0.9 mg. In the clinical trial conducted, the 3 different dosing regimens used over the 12 week duration of the study were: 0.3 mg, 0.625 mg, and 2 x 0.625 mg (total of 1.25 mg). The 0.9 mg dose, not included in the clinical trial, is compositionally similar to the 0.625 mg tablet.

Per the protocol, all patients were started on 0.625 mg of synthetic conjugated estrogen tablets or placebo daily. After 7 days of treatment, patients not receiving sufficient symptomatic relief (defined as a 50 % reduction in baseline MSVS levels) were dose titrated up to 1.25 mg daily (patients took 2 x 0.625 mg tablets). No additional increase was allowed per protocol. Patients who exhibited intolerance to the 0.625 mg tablet or to placebo at any time had their dose decreased to a minimum of 0.3 mg tablet daily (see Table 4). All doses (0.3 mg, 0.625 mg, and placebo) were red film coated round tablets provided by Duramed.

Table 4: Dosing Regimens That Occurred Over the 12 Week Clinical Trial, Intent-to Treat Population

	Cenestin™ (n=70)		Placebo (n=47)	
	N	%	N	%
Remained on 0.625 mg dose	7	10%	9	20%
Increased to 1.25 mg dose at week 1 (no further change)	54	77%	34	74%
Increased to 1.25 mg dose at week 1; Returned to 0.625 mg after week 1 (no further change)	5	7%	2	4%
Increased to 1.25 mg dose at week 1; Returned to 0.625 mg dose at week 2 or later; Decreased to 0.3 mg dose at week 4 or later; (no further change)	2	3%	0	0%
Decreased to 0.3 mg at week 1 or later (no further change)	2	3%	0	0%
Decreased to 0.3 mg dose at week 1 or later; Returned to 0.625 mg dose at week 2 or later (no further change)	0	0%	1	2%
Missed titration visit (stayed at 0.625 mg)	0	0%	1	2%

Source: Statistical Review and Evaluation (Volume 4.2 and 1.13, Table 11.4.1.3-1, Appendix 16.2.5.3.1)

Composite change in MSVS at weeks 4, 8, and 12 in the intent-to-treat population for all of the dosing regimens used in the 12 week study is displayed in Table 5.

Table 5: Summary of Change in Mean Number MSVS at Weeks 4, 8, and 12; Intent-to-Treat Analysis

	Synthetic Conjugated Estrogens A (n=70)	Placebo (n=47)	Difference	P-value
Baseline Mean #	96.8 (42.6)	94.1 (33.9)	-	-
Week 4 Mean #	28.7 (28.8)	45.7 (36.8)	-	-
Mean Change	-68.1 (43.9)	-48.4 (46.2)	-19.9	0.0224
Week 8 Mean #	18.6 (25.0)	39.8 (39.1)	-	-
Mean Change	-78.3 (49.0)	-54.3 (49.2)	-24.6	0.0101
Week 12 Mean #	16.5 (25.7)	37.8 (38.7)	-	-
Mean Change	-80.3 (50.3)	-56.3 (48.0)	-24.7	0.0102

Mean # = Arithmetic Mean of Hot Flashes/Week (Standard Deviation)
Mean Change = Difference between treatment LSMeans (Standard Deviation)
Source: NDA 20-992, Amendment 1, Volume 2, Page 02-065; Excludes Patients: 048, 061, and 076

From this reported data, the mean number of moderate to severe hot flashes at baseline averaged 96.8 (S.D.=42.6) for the active treatment group and 94.1 (S.D.=33.9) for the placebo treatment group. By Week 4 the mean number of MSVS for the active treatment group was 28.7 representing a mean change of –68.1 (S.D.=43.9); the mean number at Week 4 for the placebo group was 45.7 representing a mean change of –48.4 (S.D.=46.2). The –19.9 difference in MSVS between the active and placebo treatments at Week 4 is statistically significant (p=0.0224) using an analyses of variance performed on the primary efficacy variable in the intent-to-treat population.

By week 8 the mean number of MSVS for the active treatment group was 18.6 representing a mean change of –78.3 (S.D.=49.0); the mean number for the placebo group at Week 8 was 39.8 representing a mean change of –54.3 (S.D.=49.2). The –24.6 difference in MSVS between the active and placebo treatments at Week 8 (p=0.0101) is statistically significant. By Week 12 the mean number of MSVS for the active treatment group 16.5 representing a mean change of –80.3 (S.D.=50.3); the mean number at Week 12 for the placebo group was 37.8 representing a mean change of –56.3 (S.D.=48.0). The documented difference in MSVS at Week 12 between the active and placebo treatment (-24.7 MSVS) is statistically significant (p=0.0102).

The Intent-to-Treat population analysis is appropriate and represents the planned analysis from the protocol. In the sample size calculations submitted, the sponsor proposed 4 MSVS per day or 28 per week as a clinically meaningful difference between active treatment and placebo for the mean change from baseline in the number of MSVS per week. From Table 5, the observed difference at all 3 time points was actually less than 28: -19.9 at 4 weeks, -24.6 at 8 weeks, and –24.7 at 12 weeks.

Reviewer's comments

Although the clinically meaningful difference of 28 MSVS per week was not met, the observed difference in mean number of MSVS between treatment and placebo, along with the statistical significance of this difference, provides evidence for the efficacy of Cenestin™ in relief of vasomotor symptoms associated with the menopause by Week 4, which continued through Week 12.

The observed placebo effect was greater than the sponsor's anticipated decrease of 15 MSVS from baseline used for planning (-48.4 mean change at Week 4, -54.3 at Week 8, and –56.3 at Week 12).