Duramed Clinical Study

Synopsis of Study

Duramed sponsored one double-blind, four-center, placebo-controlled clinical study to determine the efficacy of Cenestin™ (synthetic conjugated estrogens) in the treatment of moderate to severe vasomotor symptoms (MSVS). MSVS were recorded by patient self-assessment of daily hot flashes. The primary efficacy analysis was the statistical significance of the difference between drug and placebo treatments in absolute 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.

Extent of Exposure

The extent of exposure to Cenestin™ is that experienced in the pivotal clinical study number 366. In this study, 120 patients were enrolled. Seventy-two (72) patients were randomized to study medication of a single 0.625 mg daily dose and 48 patients randomized to a matched placebo. This was a dose titration study. As specified in the study protocol, after the end of the first week (seven days), the principal investigator could increase the dose to 2 x 0.625 mg (a total daily dose of 1.25 mg) or, at this visit and any time thereafter, lower the dose due to treatment intolerance. The different dosing regimens are presented in the following table.

Table 3

Dosing Regimens that Occurred Over the 12 Weeks of Treatment
Pivotal Study 366

Treatment	0.625 mg (No change)	0.625 mg to 1.25 mg by Week 1	0.625 mg to 0.3 mg	0.625 mg to 1.25 mg to 0.625 mg	Other
Active (n=70)	7 (10%)	54 (77%)	2 (3%)	5 (7%)	2 (3%)
Placebo (n=46)	9 (20%)	34 (74%)	0 (0%)	2 (4%)	1 (2%)

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Duramed Clinical Study, Continued

Demographic Characteristics

The pivotal clinical study number 366 was conducted in the United States in four centers: Lincoln and Omaha, Nebraska, Phoenix, Arizona and Cincinnati, Ohio. Selected baseline demographic characteristics are presented in Table 4.

Table 4

Baseline Demographics of the Efficacy Population
Pivotal Study 366

Characteristic	Synthetic Conjugated Estrogens	Placebo	Overall
Age (years)			
Mean	49	48	48
Range	38-66	39-56	38-66
N	72	48	120
Duration since last menses			
< 6 months	19	15	34
6 – 12 months	6	1	7
≤ 36 months	13	6	19
> 36 months	34	26	60
Mean	87	85	86
Range	0-406	0-320	0-406
N	72	48	120
Race (%)			
Caucasian	67	71	68
Black	29	25	28
Asian/Oriental	0	2	1
Other	4	2	3
Weight (lbs.)			
Mean	163	168	165
Range	109-271	115-238	109-271
N	68	47	115
Height (inches)			
Mean	64	65	64
Range	59-71	59-71	59-71
N	69	48	117
Smoker (%)	29	31	30

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Duramed Clinical Study, Continued

Summary of Efficacy Results

The key efficacy data were obtained from the pivotal clinical study 366. Efficacy was determined by the absolute change from baseline in the number of moderate and severe vasomotor symptoms (MSVS) after 4-, 8- and 12 weeks of treatment with Cenestin™ or a matched placebo. MSVS were determined by a count of hot flashes and an assessment of their severity recorded by each patient in a daily diary. All patients evaluable for efficacy (intent-to-treat population) must have had at least four or more daily doses. Of the 120 patients enrolled, 117 patients were included in the intent-to-treat efficacy analyses. The efficacy results are presented in Table 5.

A secondary efficacy analysis was performed using both a severity score and the Kupperman Index. Overall, there appeared to be no discernable correlation or trend using this Index between the active and placebo treatment groups during the course of this study.

Table 5

Summary of Absolute Change in MSVS at Weeks 4, 8 and 12
Intent-to-Treat Analysis
Pivotal Study 366

	Synthetic Conjugated Estrogens N=70		Placebo N=47			
Study Week	Arithmetic Mean	S.D.	Arithmetic Mean	S.D.	Absolute Difference	Prob>F
Baseline	96.8	42.6	94.1	33.9		
Week 4	68.8	42.8	51.0	43.2	18.0	0.0305
Week 8	78.5	48.7	57.9	44.7	21.2	0.0205
Week 12	80.6	49.8	59.2	44.2	22.1	0.0170

Conclusion of Study

The results of the pivotal study support the efficacy of Cenestin™ in the treatment of moderate-to-severe hot flashes in postmenopausal women.

Comparison of Duramed Study to Supportive Studies

Study Methodology and Design

The target population of Duramed's pivotal study of Cenestin™ (Cenestin™ Study) was purposely intended to be more inclusive and more representative of the population as a whole, than most vasomotor studies conducted to this point.

Vasomotor symptoms begin occurring at the climacteric – the time of a woman's life, usually spanning several years, when the ovaries cease functioning. While most patients in the Supportive Studies were included only if they had their last menses over 6 months before dosing, no such inclusion criterion was used in the Cenestin™ Study. In fact, in the Cenestin™ Study, several patients were still experiencing an occasional menstrual period.

The Cenestin™ Study had a much higher percentage of Blacks than in any of the Supportive Studies which were generally 100% Caucasian. Further, more concomitant medications were allowed in the Cenestin™ Study to more broadly reflect the typical patient seen clinically for vasomotor symptoms at menopause.

Since there was no weight restriction in the Cenestin™ Study, several obese women (3 in the active treatment group, 2 in the placebo treatment group with a Body Mass Index > 40) were included. With the absence of a weight restriction, the Cenestin™ Study enrolled a broader cross section of the population than did the Supportive Studies.

The duration of treatment in the Cenestin™ Study, 12 weeks, was similar to more recent Supportive Studies. The use of patient diaries for the self-assessment of the count and severity of hot flashes is consistent with most Supportive Studies.

Outcome

The reduction of hot flashes in the active treatment group in the Cenestin™ Study was similar to the reduction achieved in the Supportive Studies – most, but not all patients achieved complete relief of their symptoms. The efficacy of Cenestin™ is consistent with the conclusions reached during FDA's DESI review: all oral, short-acting estrogens are effective for the relief of vasomotor symptoms.

A substantial placebo effect was experienced in the Cenestin™ Study, somewhat greater than the effect experienced in most of the Supportive Studies. In contrast, the dropout ratio was much lower in the Cenestin™ Study than in the placebo-controlled Supportive Studies, especially dropouts due to lack of effectiveness. In these Supportive Studies, many members of the placebo groups dropped out early due to lack of control of their hot flashes. In contrast, in the Cenestin™ Study, no dropouts occurred for this reason.

Dose Selection & Justification

Individualization of Dose

It is well established that the oral dose of estrogen needed to control hot flashes ranges from 0.625 to 1.25 mg daily, having greater than 95% efficacy. The dose necessary to treat atrophic vaginitis may be lower than that needed for control of hot flushes; an oral dose of 0.3 to 0.625 mg of estrogen is usually sufficient. [16]

Since vasomotor symptoms occur during a period of declining endogenous estrogen production and they have a wide range of severity, the dose required is individualized by titration; the common practice to begin at a low dose and increase it until the symptoms are resolved.[17] There is no critical estrogen level below which symptoms will occur.[18,19] As a result of these factors, attempts to demonstrate a generalized dose-response in a population have generally been unsuccessful.[20]

Results from Duramed's pivotal clinical study of Cenestin™ support both an initial starting daily dose of 0.625 mg was well as the need to titrate the dose to eliminate the symptoms or respond to intolerance of the treatment. Most (77%) of the patients on active treatment increased their daily dose to 1.25 mg (2 x 0.625 mg), while about 10% remained on a daily dose of 0.625 mg for the 12 weeks of treatment. Despite this increase, some women did not achieve complete elimination in their symptoms, presumably because the dose was not high enough (the study protocol did not provide for increases beyond 1.25 mg daily). About 10% of those patients in the active treatment group required a reduction in their dose due to intolerance to the higher dose treatment.

The use of the lowest effective dose is consistent with the risks of estrogen replacement therapy. It is well established that the risk of developing endometrial carcinoma is related both to dose and duration of use. Thus, women with intact uteri should also be prescribed a progestin if not contraindicated[21]. While the *Estrogen Class Labeling* suggests that the dose for vasomotor symptoms be administered cyclically, current practice indicates that compliance and convenience are better achieved with continuous therapy[22]. See Safety Summary for further discussion and references.

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Dose Selection & Justification, Continued

Dose Recommendations

In order to achieve an individualized approach to relief from postmenopausal symptoms and to minimize patient discomfort, we recommend the following dose regimens:

For vasomotor symptoms:
Vasomotor symptoms- 0.625 mg daily initially; increase as needed to lowest effective dose.
For atrophic vaginitis:
0.3 mg to 1.25 mg or more daily, depending upon the tissue response of the individual patient. Administer cyclically (e.g., 3 weeks on and 1 week off).

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Table of Contents

Introduction

Organization

In this section we present:

- An overview of the safety of estrogens as a class
- A summary safety information from Duramed's pivotal trial of Cenestin™
- A summary of the safety information from the pharmacokinetic studies (Ancillary Studies) which is presented separately due to the different population studied

Safety of Oral Short-Acting Estrogens

Overview

The determination of the relative risks of estrogen therapy has been complicated since the dose, duration of exposure, indications and practice of use of estrogens has changed substantially over the last 20-30 years. Short-term risks, i.e., less than a few years, are generally more certain than long-term (>5-10 years) risks since most of the change has occurred over the last 10 years, in large part since the prevention of osteoporosis indication was granted in 1986.

Initially, estrogens were used short-term (< 5 years) for the relief of vasomotor symptoms and the dose used was about twice the current dosage[1]. During the 1970's the relationship between dose and duration of use of estrogens and endometrial cancer was firmly established. To counter this risk, clinicians began prescribing estrogen on a cyclic basis (3 weeks on, 1 week off) believing that this regimen would induce bleeding and cause a shedding of the endometrial lining. Because of the limited acceptance of bleeding, physicians began co-administering a progestin, also in cyclic fashion. In the1990's it has become accepted practice to administer both the estrogen and progestin continuously because there is no apparent benefit to cyclic administration for most patients[3].

Thus, retrospective studies have been confounded by these many co-variables, many uncontrolled. Long-term prospective studies are on-going that will provide a clearer understanding of the long-term risks of estrogen use with current clinical practice.

Based on studies that had been conducted up to mid-1995, in July1995 FDA's Fertility and Maternal Health Drugs Advisory Committee concluded that, in regard to safety, there was no clinical evidence to significantly differentiate one approved estrogen for the treatment of vasomotor symptoms from another.[2] A review of the published literature since that date did not uncover any further safety issues not already reflected in the current class labeling. Class labeling for oral, short-acting estrogen-containing compounds includes the following warnings: endometrial carcinoma, breast carcinoma, congenital lesions with malignant potential, gallbladder disease, elevated blood pressure, and hypercalcemia. Additionally, Grady et al[3] stated that no significant differences in the clinical safety profile of any marketed drug covered by the non-contraceptive estrogen drug product class labeling guidelines has been found.

In the following sections we provide reports of the effect of estrogens on carcinoma of the endometrium and breast made since the 1995 findings of FDA's Fertility and Maternal Health Drugs Advisory Committee.

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Safety of Oral Short-Acting Estrogens, Continued

Endometrial Carcinoma

It has been widely accepted that the use of unopposed estrogen therapy increases the risk of developing endometrial cancer in postmenopausal women. Grady et al[4] reported in 1995 the results of a meta-analysis of 37 studies discussing hormone therapy and endometrial cancer. These authors made the following conclusions:

- The risk of endometrial cancer is substantially increased with prolonged use at current dosages of any estrogen product;
- Endometrial cancer risk increases somewhat with higher doses of unopposed estrogen;
- Users of natural conjugated estrogens have a greater risk of endometrial cancer than users of synthetic estrogens (relative risk 2.5 and 1.3, respectively).

A 1993 report by Herrinton and Weiss[5], who reviewed 19 published studies pertaining to unopposed estrogen use and endometrial cancer concluded that there was an increased risk (range 1.8 to 36) in endometrial cancer in women on estrogen therapy for greater than 5 years. However, they further concluded that all dose levels of conjugated estrogens increased risk of endometrial cancer substantially; and no increased risk in endometrial cancer was seen between women on oral synthetic estrogens compared to natural conjugated estrogens.

Breast Cancer

Up to 1994, the data regarding the use of estrogens in postmenopausal women was inconclusive. While some studies had found a slight increase in the risk of breast cancer, other studies found no increased risk. Studies published since 1994 have not resolved this question. For example, Colditz and his colleagues reported results of the Nurses' Health Study, a prospective cohort study in female registered nurses[6]. They observed an elevated risk of breast cancer in postmenopausal women taking estrogens alone. The difference between women taking natural conjugated estrogens alone versus 'other' estrogens alone was not significant (adjusted relative risk was 1.32 and 1.28, respectively). On the other hand, a population-based case-control study of 537 women with in situ or invasive disease and 492 controls concluded that the long-term use of estrogens (>20 years) did not increase the risk of breast cancer. Furthermore, they observed that although the most frequent type of menopausal ERT used was oral conjugated estrogens, the "risk of breast cancer did not vary according to estrogen type or dose of [natural] conjugated estrogens used."[7]

The risk of breast cancer may increase with duration of use. Kenemans et al conclude from their review of the literature that "breast cancer risk does not seem to be increased by the use of estrogens for 5 years or less".[8] In contrast, Ettinger et al conducted a retrospective cohort study of the incidence of breast cancer in women who had taken long-term estrogen (average 17.2 years), compared to women who had not taken estrogens.[9] These authors concluded that after certain adjustments, the relative risk for estrogen use was 2.0 (95% CI -.9-4.5), and therefore long-term estrogen use is associated with a substantially increased risk of breast cancer.

Duramed Clinical Study

Synopsis

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Overall Extent of Exposure

The extent of exposure to Cenestin™ is that experienced in the pivotal clinical study number 366. In this study, 120 patients were enrolled. Seventy-two (72) patients were randomized to study medication of a single 1 x 0.625 mg tablet daily dose and 48 patients randomized to a matched placebo. This was a dose titration study. As specified in the study protocol, after the end of the first week (seven days), the principal investigator could increase the dose to 2 x 0.625 mg (a total daily dose of 1.25 mg) or, at this visit and any time thereafter, lower the dose due to treatment intolerance. The different dosing regimens are presented in the following table.

Table 1

Dosing Regimens that Occurred Over the 12 Weeks of Treatment
Pivotal Study 366

Treatment	0.625 mg (No change)	0.625 mg to 1.25 mg by Week 1	0.625 mg to 0.3 mg	0.625 mg to 1.25 mg to 0.625 mg	Other
Active (n=70)	7 (10%)	54 (77%)	2 (3%)	5 (7%)	2 (3%)
Placebo (n=46)	9 (20%)	34 (74%)	0 (0%)	2 (4%)	1 (2%)

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Duramed Clinical Study, Continued

Demographic Characteristics

The pivotal clinical study number 366 was conducted in the United States in four centers: Lincoln and Omaha, Nebraska, Phoenix, Arizona and Cincinnati, Ohio. Selected baseline demographic characteristics are presented in Table 2.

Table 2

Characteristic	Synthetic Conjugated Estrogens	Placebo	Overall
Age (years)			
Mean	49	48	48
Range	38-66	39-56	38-66
N	72	48	120
Duration since last menses			
< 6 months	19	15	34
6 – 12 months	6	1	7
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Mean	87	85	86
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N	68	47	115
Height (inches)			
Mean	64	65	64
Range	59-71	59-71	59-71
N	69	48	117
Smoker (%)	29	31	30

Discontinuations

Of the 120 patients enrolled in the pivotal study, 109 completed the 12 weeks of treatment. Of the 11 patients who did not complete the entire 12 weeks, 6 were discontinued by the principal investigators or designates due to adverse events and 5 patients either withdrew for personal reasons or were withdrawn by study management for compliance issues. The disposition of each discontinued patient is presented in Table 3.

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