DRAFT

Minutes of Telecon

Date: March 12, 1999 **Time**: 2:30 - 2:40 PM **Place**: Parklawn: Dr. Rarick's Office

NDA: 20-992 **Drug Name**: Cenestin (synthetic conjugated estrogens, A) Tablets

Indication: Treatment of moderate-to-severe vasomotor symptoms of the menopause

External Constituent: Duramed

Type of Meeting: Guidance

FDA Lead: Dr. Lisa Rarick **External Participant Lead**: Mr. Ken Phelps

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580) (via telephone)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)

External Participants:
Mr. Ken Phelps, V. P., Corporate Projects, Duramed

Meeting Objective:
To discuss the indications to be included in the Cenestin™ label.

Discussion Items:
- reference listings should be submitted for the Pharmacology section of the NDA
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- FDA requests that the sponsor send a copy of their press release for discussion
- FDA plans to supply a Question and Answer press release upon action on the application
- the comments to be conveyed at the Teleconference scheduled for Monday, March 15, 1999, may have an impact on the estrogens class labeling guidance

Decisions Reached:
- the sponsor plans to confirm the launch materials for the Cenestin product after the final comments on the Cenestin label have been received

Action Items:

• **Item**	**Responsible Party**	**Due Date:**
• submit press release information	Duramed	when available

Signature, recorder

Signature, Chair

drafted: dm/2.15.98/n20992TCA2499.doc
cc:
HFD-580
HFD-580/LRarick/Tvan der Vlugt/MRhee/DLin/AParekh/JLau/AJordan

Concurrences:
TRumble 03.15.99

DRAFT

Minutes of Telecon

Date: March 15, 1999 **Time**: 9:20 - 9:40 AM **Place**: Parklawn: Dr. Rarick's Office

NDA: 20-992 **Drug Name**: Cenestin (synthetic conjugated estrogens, A) Tablets

Indication: Treatment of moderate-to-severe vasomotor symptoms of the menopause

External Constituent: Duramed

Type of Meeting: Guidance

FDA Lead: Dr. Lisa Rarick **External Participant Lead**: Mr. John Rapoza

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580) (via telephone)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Alexander Jordan, Ph.D. - Pharmacology Team Leader, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R. Ph., Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

External Participants:
Mr. John Rapoza, V. P., Regulatory Affairs, Duramed
Mr. Ken Phelps, V. P., Corporate Projects, Duramed

Meeting Objective:
To discuss FDA revisions to the Cenestin™ labeling submission dated March 1, 1999.

Discussion Items:
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Decisions Reached:
- Pharmacology section
  - a list of pharmacology/toxicology references should be submitted to this section of the NDA to fulfill 505(b)(2) requirements

- Clinical Pharmacology and Biopharmaceutics section
  - the stability data from 113 clinical batches was referenced for dissolution calculations
  - the dissolution specifications for the 0.625 mg and 0.9 mg Cenestin™ tablets should be as follows:

Time, hour	Sodium Estrone Sulfate % dissolved	Sodium Equilin Sulfate % dissolved
2		
5		
8		

  - the sponsor will discuss the new dissolution specifications and inform the FDA of their decision regarding the acceptance of the new tighter specifications

Physicians Package Insert

- the title should be revised to read, "Cenestin™ (synthetic conjugated estrogens, A) Tablets
- **DESCRIPTION** section
  - in the first sentence, the established name should be placed in lower case letters and the word and number "nine (9)" should be inserted after the word, "of" so that the sentence reads, "Synthetic conjugated estrogens, A tablets contain a blend of nine (9) synthetic estrogenic substances."
  - in the second sentence, the word, "and" between "sodium equilin sulfate" and "sodium 17 α-dihydroequilin sulfate" should be deleted
  - in the first sentence of the second paragraph, the word, "and" should be inserted between "0.625 mg" and "0.9 mg"
  - **Clinical Studies** subsection
    - the first sentence refers to 120 menopausal women in the clinical study; however, 117 women are included in the intent-to-treat population described in Table 2; the narrative and Table 2 should be revised to explain this difference
    - Table 2
      - an asterisk (*) should be placed in the title after Clinical Response to refer to a footnote at the bottom that should say "*intent-to-treat population"
      - in the left column that starts with "Baseline," the term "(S.D.)" should be inserted after "Mean #" for Baseline, Week 4, Week 8 and Week 12
      - in the second footnote, the term, "Synthetic Conjugated Estrogens" will be replaced by "Cenestin)
- **INDICATIONS AND USAGE** section
  - the established name should be revised to put the parenthesis around "synthetic conjugated estrogens, A" and not include "tablets"; tablets should be capitalized
  - items 2 and 3 referring to vulvar and vaginal atrophy and hypoestrogenism should be deleted
  - the number 1 in the first indication should be deleted
- **ADVERSE REACTIONS**
  - in the additional adverse reactions subsection, item number 3, the term, "Gastrointestina" should be revised to read, "Gastrointestinal"
- **DOSAGE AND ADMINISTRATION** section
  - in the first sentence, the number "1." and the terms, vaginal and vaginal atrophy" should be deleted; the last sentence of the first paragraph that begins, "vasomotor symptoms – 0.625" should be deleted
  - the entire section under item 2 should be deleted

- **HOW SUPPLIED** section
  - the established name should be revised to read, "Cenestin (synthetic conjugated estrogens, A) Tablets

INFORMATION FOR THE PATIENT

- the title should be revised to read, "Cenestin™ (synthetic conjugated estrogens, A) Tablets"
- **USES OF CENESTIN** section
  - the second and third subsections that begin, " To treat vulvar and avaginal atrophy . . ." and to treat certain conditions . . ." should be deleted
- **HOW SUPPLIED** section
  - the established name should be revised to read, "Cenestin (synthetic conjugated estrogens, A) Tablets"

Action Items:

• **Item**	**Responsible Party**	**Due Date:**
• fax a list of references to sponsor	Ms. Moore	1 Day
• submit list of references to NDA	Duramed	1-2 Days
• submit revised label	Duramed	1-2 Days
• send a copy of press release via telefacsimile	Duramed	2 Days
• send sponsor Q and A sheet	Ms. Moore	on action date

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Signature, recorder Signature, Chair

drafted: dm/2.15.98/n20992TCA2499.doc
cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/SAllen/Tvan der Vlugt/MRhee/DLin/AParekh/JLau/AJordan

Concurrences:
TRumble 03.15.99

NDA 20-992
Cenestin™ (synthetic conjugated estrogens, Composition, A) Tablets
Duramed Pharmaceuticals, Inc.

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 20-992
Cenestin™ (synthetic conjugated estrogens, Composition, A) Tablets
Duramed Pharmaceuticals, Inc.

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 20-992
Cenestin™ (synthetic conjugated estrogens, Composition, A) Tablets
Duramed Pharmaceuticals, Inc.

Advertising Material

No advertising material has been submitted.

Table of Contents

Introduction

Organization

In this section we present:

- In this section we present recent controlled and non-controlled studies (since 1970) documenting the efficacy of estrogens as a class for the treatment of vasomotor symptoms (Supportive Studies).
- A summary of Duramed's pivotal trial of Cenestin™ (synthetic conjugated estrogens) which shows its effectiveness for the treatment of vasomotor symptoms
- A comparison of the Cenestin™ pivotal trial with the Supportive Studies
- Dose selection and justification
- Copies of the references to the scientific literature

Rationale for efficacy

Estrogen has classically been used to describe any estrus-producing compound.[1] However, more recent studies indicate that an estrogen is any compound that is capable of binding to and activating the nuclear estrogen receptor leading to the observed effects. The three major naturally occurring estrogens in humans are estrone, estradiol (the commonly used term used to refer to 17β-estradiol) and estriol. The primary source of estrogen in normally cycling adult women is the ovarian follicle[2], which secretes 70 to 500 micrograms of estradiol daily, depending on the phase of the menstrual cycle. This is converted primarily to estrone, which circulates in roughly equal proportion to estradiol, and to small amounts of estriol.[3]

Loss of ovarian function is associated with various symptoms, but in the natural aging process estrogen production by the ovary begins to decline in the perimenopausal years. During this period of life, two major symptoms may appear vasomotor symptoms ("hot flashes") and urogenital atrophy.

The hot flash is the most common menopausal symptom for which patients seek treatment.[4] The hot flash is a localized raising of skin temperature due to vasodilation.[5,6] This may be followed by a sensation of pressure within the head and is frequently accompanied by weakness, faintness, or vertigo. This episode usually ends in profuse sweating and a cold sensation.[7] Hot flashes typically occur more frequently at night, thus awakening patients from sleep. This reduced quality of sleep results in fatigue, which then may lead to symptoms such as irritability, poor concentration, and impaired memory. [8]

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Introduction, Continued

Rationale for efficacy – con't

The tissues of the lower portion of the vagina, labia, urethra, and bladder trigone are of common embryonic origin, derived from the urogenital sinus, and are all estrogen dependent.[9] Following the loss of estrogen at menopause, the vaginal walls become pale, due to diminished vascularity, as well as thin, leading to vaginal atrophy. The vaginal epithelial cells contain less glycogen, which prior to menopause has been metabolized by lactobacilli to create an acidic pH, thereby protecting the vagina from bacterial overgrowth. Loss of this protective mechanism leaves the tissue vulnerable to infection and ulceration.

Since both hot flushes and atrophic vaginitis are a consequence of estrogen withdrawal, the most effective form of therapy is estrogen replacement.

Supportive Studies

Overview

In this section we present a summary of the most relevant of the many clinical trials that have evaluated estrogens for the relief of vasomotor symptoms. These studies support the efficacy of estrogens and thus, Cenestin™ for the treatment of vasomotor symptoms.

Studies Reviewed

To reflect current therapeutic levels of estrogen employed in clinical practice, the literature search was limited to studies conducted since 1970. The search was conducted using Medline, the on-line search capability of the National Library of Medicine's computer database. The review is focused on the so-called "natural" estrogens (estrogens endogenous to animals). A wide variety of the "synthetic" estrogens (chemical derivatives and analogs of the endogenous estrogens) have also been shown effective for these symptoms.[10] The studies were further limited to the use of 'unopposed' estrogen, that is, without use of a concurrent progestin.

The search results are summarized in Table 1 (drug products with a single active ingredient) and Table 2 (drug products with multiple active ingredients). Following these two tables, a brief summary is given for each study as it relates to the treatment of vasomotor symptoms.

Products Studied

The dosage forms reviewed included oral tablets and transdermal patches. The estrogens delivered by these dosage forms include estradiol, estrone, 17α-dihydroequilin, equilin, conjugated estrogens, esterified estrogens and ethinyl estradiol. The latter was the only 'synthetic' estrogen reviewed and only because it was studied in conjunction with a 'natural' estrogen.

Study Designs - Dose

Oral doses studied are 1.25 mg (or estrone equivalent) conjugated estrogens or 1 – 2 mg micronized estradiol. Transdermal estradiol doses in the 20 – 100 mcg range were common. Several studies noted that a general dose response was present, with greater amounts of estrogen having a greater tendency to eliminate symptoms. However, the same authors noted that there are exceptions. To address this issue, several studies titrated the dose, some based on entry criteria (higher dose for more hot flashes) others based on response after treatment. For most studies, even the highest dose did not alleviate all patients' symptoms. It was postulated that higher doses might have been required to completely eliminate the symptoms of some women.

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Supportive Studies, Continued

Study Designs - Duration

The duration of treatment in the studies ranged from 20 days to 2 years, with the most common treatment period being 6 – 12 weeks. Most studies noted that the reduction in hot flashes commenced one or two weeks after the initiation of therapy and that differences from placebo, when used as a control, were not significant until 3 – 4 weeks. Thus, in recent studies, the duration of the treatment phase is typically 12 weeks.

Study Designs - Methodology

Studies designs included active controls, placebo controls and no controls. A review of the placebo-controlled studies indicates that the placebo effect can be substantial. Several studies (Coope, Haas, Good, and Laufer) note that the placebo effect is due to the subjective nature of the measurement, hot flashes. However, a considerable, but reduced, placebo effect is observed using objective measurement techniques such as thermography (Laufer).

In general, studies using active controls show that all treatments (type, formulation and route of administration) yield a reduction in vasomotor symptoms by similar amounts. Some active control studies used a crossover design in an attempt to show a statistical difference between treatments. In light of the placebo effect, these studies may be considered supportive but not conclusive.

Study Designs - Demographics

Most of the studies were conducted in the setting of a clinical practice, recruiting from women who were among the general client registry. The typical patient was a Caucasian in good health except for the presence of moderate to severe vasomotor symptoms. Generally, patients enrolled in the reviewed studies were confirmed postmenopausal, that is, 6 or more months since their last menses. Of those studies reporting an entry criterion of weight, all restricted weight to a standardized weights table. Smokers are generally excluded from these studies.

Study Designs - Efficacy Measurements

The most common menopausal symptoms are vasomotor (hot flashes) and, to a much lesser degree, vaginal atrophy (vaginal dryness). Due to the physical and emotional impact of hot flashes, patients seek early treatment of this symptom. Thus, it is most common to measure hot flashes. The very few studies that measure both hot flashes and vaginal atrophy have met with varying success; there is no direct correlation between hot flashes and vaginal atrophy (Coope). Reasons for this may include the fact that the patient population presenting with vaginal atrophy is older than that presenting with hot flashes; hot flashes begin to wane as dryness of the vagina begins to become clinically significant.

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Supportive Studies, Continued

Study Designs - Efficacy Measurements – continued

Two broad strategies are used for evaluating hot flashes. The most common is the subjective measurement by patient diary entries. Patients are informed of the definitions of mild, moderate and severe hot flashes and asked to record the number of episodes in a daily diary. Alternatively, an objective measurement may be made using thermography - a thermo-sensitive device is attached to a finger and temperature readings are made at selected intervals, often in conjunction with a means to allow the patient to indicate the initiation and cessation of her sensation of a hot flash. This latter technique has not found wide use, presumably due to cost and inconvenience. Moreover, since its use is limited to a clinical laboratory setting, it may not be representative of the response to treatment since night sweats are not be measured. However, careful experiments have shown that, at least during the (daytime) periods measured, there is a good correspondence between thermography and self-assessment diaries.[11]

A few early studies relied on a weighted index of many menopausal symptoms as a primary measurement. The menopausal index is based on an interview between the patient and a blinded investigator. Unfortunately, due to a large placebo response the results were difficult to interpret because the differences between active and baseline and/or placebo were not statistically insignificant. The large placebo response in such settings has been attributed to the attention given by the medical practitioner (Wiklund).

A few studies measured various biological parameters, including blood concentrations of the estrogens and gonadotropins, FSH and LH. It was observed in these studies that higher estrogen levels were consistent with the observations of fewer and less severe hot flashes, but no direct cause and effect was determined. Similarly, the levels of gonadotropins decrease with increasing estrogen doses. However, no specific level of gonadotropins has been found at which hot flashes will be eliminated.

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