CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-992

ADMINISTRATIVE DOCUMENTS

Division Director Memo

MAR 24 1999

NDA: **20-992**

Sponsor: **Duramed Pharmaceuticals, Inc.**

Drug: **Cenestin™ (synthetic conjugated estrogens, A) Tablets**
Oral tablet for once daily dosing
The sponsor requests approval of the 0.3, 0.625, and 0.9 mg tablets

Indications requested:
Treatment of moderate to severe vasomotor symptoms associated with the menopause

Date received: **March 30, 1998**

Date of Memo: **March 24, 1999**

APPLICATION SUMMARY

This section 505(b)(2) submission presents information in support of the safety and efficacy of Cenestin™ (synthetic conjugated estrogens, A) Tablets for the relief of moderate to severe vasomotor symptoms (MSVS) associated with the menopause.

I agree with the primary review team that the results support the safety and effectiveness of the 0.625 mg/day, 0.9 mg/day and 1.25 mg/day (as 2 X 0.625 mg) doses for the treatment of MSVS. I also agree with the conclusion that there is insufficient data to establish the effectiveness of the lowest dose presented (0.3 mg/day) and insufficient data to support the requested indications other than MSVS.

Chemistry

The drug substance for this product is composed of a 9 component estrogen mixture that includes:

Sodium estrone sulfate
Sodium equilin sulfate
Sodium 17α-dihydroequilin sulfate
Sodium 17β-dihydroequilin sulfate
Sodium 17α-estradiol sulfate
Sodium 17β-estradiol sulfate
Sodium 17α-dihydroequilenin sulfate
Sodium 17β-dihydroequilenin sulfate
Sodium equilenin sulfate

Review of the Chemistry, Manufacturing and Controls information reveals that the sponsor has provided adequate information for approval. The labeling and nomenclature committee found the proposed tradename, Cenestin™, acceptable on June 11, 1998.

The established name, "synthetic conjugated estrogens, A" is recommended, after review and discussion, in a January 6, 1999 memo and subsequent, March 15, 1999 memo, from the Center for Drug Evaluation and Research (CDER) "Complex Drug Substances Coordinating Committee/Conjugated Estrogens Working Group".

The strengths assigned to the final tablets (0.625 mg and 0.9 mg) maintain the convention currently in place for labeling of multiple estrogen products. Conjugated estrogens are labeled according to the sum of the three most prevalent components (sodium estrone sulfate, sodium equilin sulfate and sodium 17α-dihydroequilin sulfate) of a multiple component mixture. Esterified estrogens, which are another type of conjugated estrogens product, are labeled according to the sum of the two most prevalent components (sodium estrone sulfate and sodium equilin sulfate) of a multiple component mixture (depending on the product, it may also contain 17α-estradiol and/or 17α-dihydroequilin). Commercially available examples include Estratab® and Menest™ (esterified estrogens tablets, USP) which are available as 0.3, 0.625, 1.25 and 2.5 mg tablets.

Although historically the designation of strength was based on a potency bioassay, as more sophisticated and specific techniques have developed for identifying components, the potency bioassay has been replaced with the current convention (as described above) of measurement of the most prominent ingredients. For conjugated estrogens, the milligram designation determined through the original bioassay measurement correlated to the sum of the three most prevalent components, and thus this system was adopted.

Specifications for Cenestin™ maintain the convention applied to other conjugated estrogens. The milligram designation is based on the "sum of three" convention in place for other conjugated estrogens with multiple components. The established name in this case encompasses products with multiple components. To apply the convention used in other product classes of naming each ingredient, along with its strength, in either the established name or its description is not practical and would be confusing. In the case of conjugated estrogens, including esterified estrogens, the established name would become a long string of specific estrogen components along with the individual strength of each—an unwieldy, confusing and impractical labeling solution. Thus, for these multiple component products, CDER will continue the "sum of three" practice for the milligram designation of the conjugated estrogens products.

Pharmacology/Toxicology

Because of the vast long-term clinical experience with conjugated estrogens and estrogens in general, and because of the availability of published literature on the animal and human toxicology of conjugated estrogens (particularly carcinogenicity), no new pharmacology/toxicology information is required for new drug applications for known estrogens for MSVS. Because this application includes only known estrogens, it contains no new pharmacology/toxicology information, but instead contains references to the relevant literature.

Animal safety data on estrogens, either *in vitro* or *in vivo*, have not proven to be quantitatively predictive of the effects of these products found in women.[1] The most confident conclusions can be drawn from human experience. There is extensive animal safety data available in the published literature on estrogens. Animal data is designed as a screen to identify gross toxicities, such as whether or not a drug product is a potential human carcinogen. Animal tests cannot be used to definitively assign human clinical effects, but they are useful in screening compounds for activity.

[1] Stern MD, "Pharmacology of Conjugated Oestrogens," *Maturitas*, 4:285-290, Elsevier Biomedical Press, 1982.

Conjugated estrogens and estrogens in general have been the subject of substantial toxicological evaluation.[2] Safety studies in humans, animals, and *in vitro* have examined the mechanism of action of estrogens, their binding to estrogen receptors, activation of estrogen response elements metabolism, pharmacokinetics, and relative potencies. It is known from both animal, and more importantly, human data that estrogens are carcinogenic.

Because of the volume of available data on estrogens for menopausal symptoms, CDER does not require new safety studies in animals prior to testing in humans or prior to drug product approval. For example, no long-term animal safety testing has been required for any of the estrogen-alone products for menopausal therapy approved through the NDA or abbreviated NDA (ANDA) process. Estrace (estradiol tablets) was approved in 1975 and Ogen (estropipate tablets) in 1977 through the ANDA process and thus were not required to provide animal safety data. Several transdermal estradiol delivery systems and one vaginal estradiol delivery product were approved through the NDA process since Premarin®'s approval in 1942. Although short-term animal safety data relevant and specific to the delivery systems were included in these applications, no new long-term animal safety studies were required for these approvals.

As is the case with other approved drug products in this class, existing animal safety data for estrogens is appropriately extrapolated to new estrogen drug products, including Duramed's synthetic conjugated estrogens drug product.

Clinical Pharmacology/Biopharmaceutics

As per Dr. Lau's initial review and subsequent amendment reviews, the sponsor has provided sufficient pharmacokinetics and bioavailability information to support the approval of the 0.3, 0.625 and 0.9 mg tablet strengths. However, because the submitted clinical trial does not establish the effectiveness of the lowest strength (see Medical Officer review and clinical comments below), the 0.3 mg tablet strength will not be approved at this time.

Clinical/Statistical

In the submitted clinical trial, a total of 120 women were randomized (72 to receive active drug and 48 placebo) in a double blind, placebo-controlled, dose-titration designed study. The primary efficacy endpoint was the reduction in the mean number of moderate to severe vasomotor symptoms (MSVS) during the fourth, eighth and twelfth weeks of treatment compared to placebo.

Of the 120 women enrolled, 109 completed the entire 12-week study. Analysis of results revealed significant improvement as compared to placebo at each pre-specified time point ($p= 0.02$, 0.01 and 0.01 at 4, 8 and 12 weeks, respectively).

Subject withdrawals, discontinuations, protocol violations and impact are described and discussed in the clinical and statistical reviews.

The intent-to-treat analysis of 117 subjects (Cenestin™ n=70, placebo n=47) included data for any patient who completed at least the first week of treatment, with the last treatment observation carried forward, as needed. Results of this analysis revealed that, overall, Cenestin™ resulted in a significant improvement in MSVS at weeks 4, 8, and 12 when compared to placebo. By the end of the 12-week study, 94% of Cenestin™-treated subjects were taking either 0.625 mg or 2 X 0.625 mg tablets for relief of symptoms. Four subjects were taking 0.3 mg Cenestin™ at the end

[2] Westerholm, Pharmacol. Ther., 10:337-349, 1980; Hart, Pharmacol. Ther., 47: 203-218, 1990.

of the study, therefore making any reasonable determination of effectiveness compared to placebo at this dose impossible.

Appropriate safety monitoring during the study was performed and included baseline, end-of-study, and, where necessary, during-study collection of physical examination results. Exams included breast exam, gynecologic exam, Pap smear and pregnancy testing, vital sign monitoring (blood pressure, heart rate) and laboratory tests. Laboratory tests obtained at baseline and end-of-study included liver function tests, lipid tests, hematology and standard biochemistry measurements (see Medical Officer review for full discussion). Subjects enrolled were required to have a normal mammogram within six months before entering the study. Adverse events were monitored throughout the study. Patients received progestin treatment post-study as appropriate.

The safety analyses revealed comparable safety profiles for Cenestin™ versus placebo with the exception of events typically seen with estrogen replacement therapy. For example, there was a higher incidence of breast pain (29% Cenestin™ versus 15% placebo) and metrorrhagia (14% Cenestin™ versus 6% placebo) in the active drug group.

Along with review of the submitted clinical trial results, as well as reconsideration of the DESI determination and referenced publications pertaining to the 1972 DESI notice, the division has also searched the published literature for relevant references containing assessment of safety and effectiveness of estrogens for MSVS. We agree that estrogens are appropriate therapy and have a favorable benefit to risk ratio in the management of MSVS associated with the menopause.

LABELING

Class labeling indications and discussion

Non-contraceptive estrogen products have been the subject of class labeling for many years. Since the 1972 Drug Efficacy Study Implementation (DESI) report, which described multiple indications for short-acting oral or parenteral estrogens, this class labeling has undergone updates and revisions to its present form. The August 1992 non-contraceptive estrogen labeling guidance, and the 1998/99 revised guidance recently published for review and comment, allows for the following indications for the short-acting oral estrogens:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause

Since the 1972 DESI report, estrogen products, when approved for the treatment of moderate to severe vasomotor symptoms associated with the menopause, have generally been granted the second and third indications. The prevention of osteoporosis indication, which is the subject of a 1986 FR notice, is not being requested for Cenestin™.

Specific Cenestin™ label comments were conveyed to the sponsor and accepted on March 15, 1999.

OTHER REGULATORY ISSUES

Acceptance of Single Study

A "Guidance for Industry" published May 1998, entitled "Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products," includes discussion of the Food and Drug Administration's (FDA) considerations regarding the quantity and quality of evidence necessary to support effectiveness. The document includes a discussion of replacement therapy as an example where "a single clearly positive trial can be sufficient to support approval." Therefore, the acceptance of a single clinical trial to support the approval of Cenestin™ for the indication of MSVS is supported by this FDA guidance.

Exclusivity

Duramed has requested non-patent marketing exclusivity for a period of three years as per 21 CFR 314.108. This exclusivity should be granted as this application contains the report of new clinical investigations conducted by the applicant, which were required and essential to the approval of this application for the nine-component estrogen product described above for treating MSVS.

Combination Drug Policy

Under 21 CFR 300.50(c), fixed-combination prescription drugs for humans that have been determined to be effective for labeled indications by the FDA, based on evaluation of the NAS-NRC report on the combination, are considered to be in compliance with the requirements of the fixed-combination drug policy in 21 CFR 300.50.

The 1972 DESI findings for short-acting estrogens, including conjugated estrogens, are applicable to the combination of conjugated estrogens found in Cenestin™ for the purposes of 21 CFR 300.50(c). Therefore, Cenestin™ is considered to be in compliance with the requirements of the fixed-combination drug policy in 21 CFR 300.50 (see also March 22, 1999 memo to the file by the Director of the Center for Drug Evaluation and Research).

RECOMMENDATIONS

Approval of Cenestin™ (synthetic conjugated estrogens, A) Tablets in 0.625 mg and 0.9 mg strengths for use in the treatment of moderate to severe vasomotor symptoms associated with the menopause (as doses of 0.625 mg, 0.9 mg and 2 X 0.625 mg). Non-approval for the further indications and strengths requested.

3/24/99

Lisa Rarick, MD
Director
DRUDP, HFD-580

cc: NDA 20-992
HFD-580/Mann/VanderVlugt/Moore/Kammerman/Meaker/Rhee/Lin/Parekh/Lau/Jordan
HFD- /Houn/Bilstad
HFD- /Lumpkin/Woodcock

PATENT CERTIFICATION

As required by 21 CFR §314.50(i)(1)(ii), Duramed Pharmaceuticals, Inc., hereby certifies as follows: In the opinion and to the best knowledge of Duramed Pharmaceuticals, Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

William P. Stoltman 3/6/98

William P. Stoltman, Esq.
Director, Regulatory Compliance

01- 030

PATENT INFORMATION

As required by 21 CFR §314.53(a) and as specified by 21 CFR §314.53(c)(4), Duramed Pharmaceuticals, Inc. declares that in its opinion and to the best of its knowledge, that there are no relevant patents which claim the drug or drug product as specified in this application, or which claim a method of using the drug product as specified in this application.

William P. Stoltman 3/24/98

William P. Stoltman, Esq.
Director, Regulatory Compliance

01- 029

EXCLUSIVITY SUMMARY for NDA # _20-992_____ SUPPL #_____

Trade Name __Cenestin™___ Generic Name __(synthetic conjugated estrogens, A) Tablets

Applicant Name _Duramed Pharmaceuticals, Inc.__ **HFD-580**_____

Approval Date, if known _____

PART I <u>IS AN EXCLUSIVITY DETERMINATION NEEDED?</u>

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /_X__/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X__/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /_X__/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

__3 _____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /_X__/ OTC Switch /___/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _ 4-782 _____ __Premarin_____

NDA# _20-303_____ ___Prempro_____

NDA# _20-527_____ __Prempro_____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

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(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol 366

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /____/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

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b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/
Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

__ Protocol 366_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ ___ YES /_X__/ ! NO /___/ Explain: _ under individual

Investigation #2

YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

Diane Moore
Signature

Date 3/12/99

_Diane Moore_____
Name (type or print)

_Project Manager_____
Title

Signature of Division Director

Date 3/15/99

__Dr. Lisa Rarick_____
Name (type or print)

cc: Original NDA Division File HFD-93 Mary Ann Holovac