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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

ORIG AMENDMENT
BP

October 30, 1998

VIA UPS

Diane Moore
Food and Drug Administration
Division of Reproductive and Urinary Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

Re: **NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens) Tablets 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg and 2.5 mg**

Subject: **Diskette**

Dear Ms. Moore;

Per your request, please find enclosed in this UPS package a diskette containing the letter of today and Excel files containing the pharmacokinetic parameters that are presented in the letter for the convenience of the reviewers.

I am in Bethesda on Monday and Tuesday attending the FDA – Industry Fall Workshop. Should you need anything further, please leave a voice message at 513-458-7325 and I will get back to you.

Sincerely,

Ken Phelps
Vice President Corporate Projects

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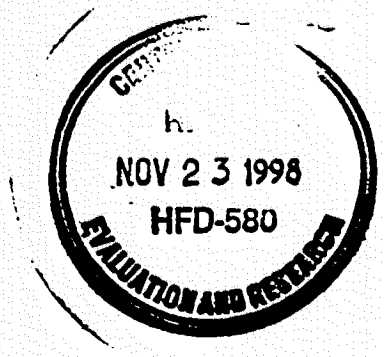
BL

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

November 20, 1998



Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens) Tablets 0.3 mg, 0.625 mg, 0.9 mg, 1.25 mg and 2.5 mg

Subject: Labeling Amendment

Dear Dr. Rarick;

Per a telephone request of Ms. Diane Moore on Thursday, November 19, 1998, we now submit as an amendment labeling that had previously been submitted as a controlled communication on October 26, 1998. The entire October 26 communication is enclosed.

This **Amendment** is submitted in 1 volume and includes two (2) copies, an archival copy and a review copy.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure
Completed 356h

CC: Desk copy for Diane Moore

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS
DATE

BB

DURAmed

ORIGINAL

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

The Art of Leadership...
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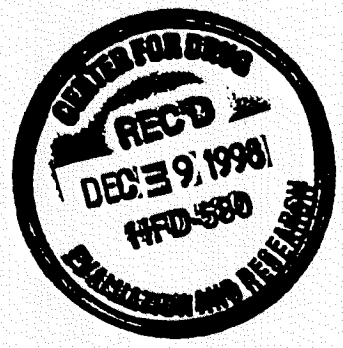
December 8, 1998



Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens) Tablets**

Subject: **Human Pharmacokinetics Amendment**

Dear Dr. Rarick;

Reference is made to a December 4, 1998 telephone conference call between you and members of the Division of Reproductive and Urinary Drug Products and Duramed Pharmaceuticals, Inc. and a subsequent follow-up telephone conversation with Ms. Diane Moore on December 7. In this teleconference Duramed was requested to provide dissolution data on equilin and perform an F2 comparison test of the results between the 0.625 mg NDA bioavailability lot (the F2 reference drug product), the 0.3 mg and 0.9 mg NDA submission lots and the 0.3 mg and 0.625 mg lots used in the pivotal vasomotor clinical trial. In addition, we were requested to provide an F2 comparison test between the two 0.3 mg lots (the green-colored commercial presentation and the pivotal clinical trial formulation incorporating the red color of the 0.625 mg tablet to maintain the blinding), with the NDA submission lot as the reference.

We now submit this amendment to furnish the requested information and F2 comparisons. The dissolution information (individual results, mean, range and RSD, N=12) for each lot is attached on pages 04-06. The detailed F2 calculations are attached on pages 07-11. A statement on the dissolution test method is also attached on page 03. For convenience, the F2 results are summarized in the following table.

Lot #	Description	F2	F2
C-0005	0.625 mg NDA bioavailability lot	Reference	
94850	0.625 mg pivotal clinical trial lot	70.9	
X-0328	0.3 mg NDA submission lot	57.4	Reference
C-0034	0.3 mg pivotal clinical trial lot	72.5	69.6
X-0335	0.9 mg NDA submission lot	96.1	

From these data it is concluded that the dissolution profile of equilin in each of the three (3) dosage strengths (0.3-, 0.625- and 0.9 mg) is similar and that the two 0.3 mg batches have similar dissolution profiles. The same conclusion is reached based on the F1 comparison test results. This conclusion is supported by the dissolution data and F2 comparisons for equilin and that previously submitted for estrone. This conclusion is expected given that the formulations for each of these three (3) dosage strengths is nearly identical and that the manufacturing process has been proven to be reproducible through the dissolution and assay results obtained from over 100 full-scale production batches. This formulation incorporates a coating and gum matrix which, in contrast to an immediate release formulation, causes a delay in the immediate release and then a slow release of the actives. Given the design of the Cenestin™ dosage form we find these dissolution results are extremely consistent and comparatively uniform.

We have previously submitted proposed dissolution specifications based on estrone alone. There is no reason to believe that rate of the release of equilin should be different than that of estrone. Therefore, we are proposing to apply the same dissolution specifications for the release of both estrone and equilin. These specifications are the same as proposed in the NDA except that equilin is now added to the dissolution specifications as follows (USP L1 specifications).

Drug	2 hours	5 hours	8 hours
Estrone			
Equilin			

This **Amendment** is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy for the pharmacokinetic reviewers. A desk copy is also being sent to the attention of Ms. Diane Moore.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Attachments:
Completed Form FDA 356h
Statement on Dissolution Test Conditions and Dissolution Test Solution Method Used
Dissolution Data
Dissolution F2 Comparisons

CC: Desk copy, Ms. Diane Moore

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

BZ

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Duramed Pharmaceuticals, Inc.
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Cincinnati, Ohio 45213
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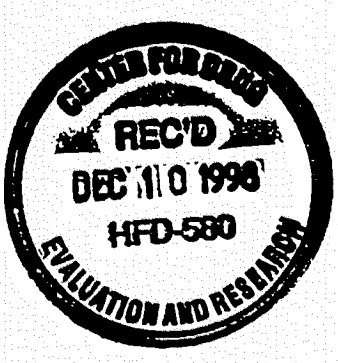
CONFIDENTIAL



December 9, 1998

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: **NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens) Tablets**

Subject: **Amendment to Withdraw the 1.25 mg and 2.5 mg Dosage Strengths**

Dear Dr. Rarick

Reference is made to a December 4, 1998 telephone conference call between you and members of the Division of Reproductive and Urinary Drug Products and Duramed Pharmaceuticals, Inc. In this teleconference Duramed was informed that the 1.25- and 2.5 mg dosage strengths would not be approved since the 1.25 mg dosage strength was determined to be not bioequivalent to the 2 x 0.625 mg dosage treatment used in the pivotal clinical trial. Since the 2.5 mg dosage strength is dose proportional to the 1.25 mg, it too cannot be approved.

We now amend the NDA to withdraw these two (2) dosage strengths, 1.25 mg and 2.5 mg, as formulated.

This **Amendment** is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Attachment: Completed Form FDA 356h

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-992

DEC 14 1998

Duramed Pharmaceuticals, Inc.
Attention: Mr. John Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs
5040 Duramed Drive
Cincinnati, OH 45213

Dear Mr. Rapoza:

Please refer to your pending March 27, 1998, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cenestin (synthetic conjugated estrogens tablets) 0.3, 0.625, 0.9, 1.25, 2.5 mg.

We also refer to your submissions dated April 8 and 23, May 7 and, 27, June 19, September 22, October 30 (2), and November 20, 1998.

We are reviewing the Clinical, Chemistry, Manufacturing and Quality Control, Pharmacology, Biometrics, and Clinical Pharmacology and Biopharmaceutics sections of your submission and have the following comments and information requests:

Chemistry and Manufacturing and Quality Control

Drug Substance

1. The following revisions to the drug substance specifications should be made:

   a. The three Identification Tests should be combined together into one Identification Test. However, before combining the Identification C specification, the term, "exhibits" should be inserted after, "The chromatogram" so that the sentence reads,

      "The chromatogram exhibits additional peaks corresponding to 17β-estradiol, 17α-dihydroequilenin, 17β-dihydroequilenin and equilenin at R_ts of about 0.29, 0.56, 0.64 and 1.3 relative to 3-O-methylestrone."

   b. The heading "Primary Estrogens" and "Other Estrogenic Substances" should be replaced with the heading, "Estrogens."

   c. Based on the batch data from the following specifications should be revised as follows:

      1. Sodium 17β-dihydroequilin sulfate: of labeled content

      2. Sodium 17α –estradiol sulfate of labeled content

3. Sodium 17β-estradiol sulfate: of labeled content
4. Sodium equilenin sulfate: of labeled content
5. Sodium 17 α–dihydroequilenin sulfate: of labeled content
6. Sodium 17β-dihydroequilenin sulfate: of labeled content
7. Free steroids:

Drug Product

1. The specifications and test methods used to release the bulk drug substance solution for use in the manufacture of the drug product tablets should be provided. A statement is needed specifying that the test methods comply with USP 23, supplement 7.

2. The following revisions to the drug product in-process specifications should be made:

   a. The subheadings "Primary Estrogens Assay" and "Other Estrogenic Substances Assay" should be replaced with "Assay."

   b. The following specification should be added to the Identification Test: "The chromatogram exhibits additional peaks corresponding to 17β-estradiol, 17α-dihydroequilenin, 17β-dihydroequilenin and equilenin at R_fs of about

   c. The total estrogens assay specification should be revised to total of sodium estrone sulfate, sodium equilin sulfate, and sodium 17α-dihydroequilin sulfate.

   d. The assay specifications should be revised to those of the assay specifications for the drug product.

3. Please provide the sampling plan that will be used to test each production batch of drug product.

4. The following revisions to the drug product specifications should be made:

   a. The "ratio of sodium equilin sulfate to sodium estrone sulfate" should be added as in the original submission of the NDA.

   b. The following specification should be added to the Identification Test: "The chromatogram exhibits additional peaks corresponding to 17β-estradiol, 17α-dihydroequilenin, 17β-dihydroequilenin and equilenin at R_fs of about

c. The specifications should be revised as follows:

Assay (SS-0187)	*Specifications*
total of sodium estrone sulfate, sodium equilin sulfate, and sodium 17α-dihydroequilin sulfate	
Sodium estrone sulfate	
Sodium equilin sulfate	
Sodium 17α-dihydroequilin sulfate	
Ratio of sodium equiline sulfate to sodium estrone sulfate	
Sodium 17β-dihydroequilin sulfate	
Sodium 17α –estradiol sulfate	
Sodium 17 β–estradiol sulfate	
Sodium equilenin sulfate	
Sodium 17α-dihydroequilenin sulfate	
Sodium 17β-dihydroequilenin sulfate	

5. Please comment as to why the acceptance criteria for the dissolution test are not the same for all five strength tablets. A simple statement that the dissolution test must conform to Acceptance Table 1 in USP 23<724> (drug release for extended release drug products) is sufficient.

6. The description section of the package should be revised as follows:

"Synthetic Conjugated Estrogens Tablets contain a blend of synthetic estrogenic substances

The estrogenic substances include sodium estrone sulfate, sodium equilin sulfate, and sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, Sodium 17α-dihydroequilenin sulfate, Sodium 17β-dihydroequilenin sulfate sodium equilenin sulfate and sodium 17β-estradiol sulfate.

The structural formulae for estrogens are:"

7. In the **DESCRIPTION** section of the package insert the structural formulas, established names, molecular formulas, and molecular weights of all the estrogen substances should be included with the structural formulae.

8. In the HOW SUPPLIED section of the package insert, the storage condition statement should be revised to "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature.]"

9. The storage statement on the container and carton labels should be revised to "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature.]"

Clinical Pharmacology and Biopharmaceutics

1. Separate bioavailability studies have been conducted on the 0.625 mg and 1.25 mg Cenestin tablet strengths. Studies BN038 and BN037 provide data for 2 x 0.625 mg and 1x 1.25 mg tablets under fasted conditions, respectively, while Studies 930125 and 941817 provide data for corresponding strengths under fed conditions. The daily dose of 2x 0.625 mg tablets has been studied clinically, but the 1.25 mg tablet strength was not included in the clinical trial.

   A bioavailability or bioequivalence study comparing the 01.625 mg and the 1.25 mg tablets is warranted because of the following:

   a.) the 0.625 mg and 1.25 mg tablets are not compositionally similar,

   b.) the clinical efficacy and safety data were based on only the 0.625 mg tablets, and

   c.) the bioavailability for the 1.25 mg tablet strength, relative to the 0.625 mg tablet strength is questionable.

2. The 0.3 and 0.9 mg tablets, which are compositionally similar to the 0.625 mg tablet strength, have similar dissolution profiles/data for sodium estrone sulfate. However, in order to meet the bioavailability waiver criteria as outlined in 21 CFR 320.22, comparative *in vitro* dissolution data are also needed for sodium equilin sulfate for the 0.3, 0.625 and 0.9 mg tablet strengths.

4. To support the color change for the to-be-marketed 0.3 mg tablet, comparative *in vitro* dissolution profile data for the clinically-tested and to-be-marketed 0.3 mg tablets should be provided for sodium equilin sulfate.

Labeling

DESCRIPTION section (see Chemistry, Manufacturing and Quality Control comments.)

CLINICAL PHARMACOLOGY section

Pharmacokinetics subsection

Absorption subsection

1. The second sentence that begins, "The Cenestin™ formulation . . ." should be deleted.

2. In the third sentence that begins, "Maximum plasma concentrations . . . ," the term, "Cenestin" should be inserted before the word, "maximum" so that the sentence reads, "Cenestin maximum plasma concentrations of the conjugated and unconjugated estrogens are attained within 4 to 10 hours after dose administration."

3. The table entitled, "Pharmacokinetic Parameters For Unconjugated and Conjugated Estrogens" should include total equilin and baseline-corrected total estrone for the 2x0.625 mg dose and be labeled as such. In addition, concentration versus time profiles for unconjugated equilin and unconjugated estrone **not** corrected for baseline for the 2x0.625 mg dose should be included and labeled as such.

4. A statement should be included in the package insert that states the following: "The effect of food on the 0.3, 0.625 and 0.9 mg tablets has not been studied." If any of these tablet strengths are not approved, the appropriate tablet strength(s) should be deleted from this statement.

Distribution subsection

Specific half-lives should be provided for the estrogen components of Cenestin rather than the general range of half-life values, as proposed.

Clinical Studies section

1. The patient population should be referred to as simply "menopausal."

2. The second paragraph that begins, "The incidence of reported . . . " should be deleted.

3. The first paragraph that begins, "A randomized, placebo. . ." should be revised to read,

   "A randomized, placebo-controlled multicenter clinical study was conducted evaluating the effectiveness of Cenestin for the treatment of vasomotor symptoms in 120 menopausal women. Patients were randomized to receive either placebo or 0.625 mg Cenestin daily for 12 weeks. Dose titration was allowed after one week of treatment. The starting dose was either doubled (2 x 0.625 mg Cenestin or placebo taken daily) or reduced (0.3 mg Cenestin or placebo taken daily), if necessary. Efficacy was assessed at 4, 8 and 12 weeks of treatment. By Week 12, 10% of study participants remained on a single 0.625 mg Cenestin tablet daily while 77% required two (0.625 mg) tablets daily. The results in Table 2 indicate that compared to placebo, Cenestin produced a reduction in moderate-to-severe vasomotor symptoms at all time points (4, 8, and 12 weeks).

4. No p-values should be included in the Clinical Response table; actual numbers should be included instead.

WARNINGS section

The heading under item #2 Venous thromboembolis should be revised to read, "Venous thromboembolism."

ADVERSE REACTIONS section

1. The following sentence should be inserted before the first paragraph of this section, "In a 12-week clinical trial that included 72 women treated with Cenestin and 48 women treated with placebo, the following adverse events occurred at a rate $\geq$ 5% (see Table 3)."

2. Table 12.2.1-1 from volume 2, page 02-074 of the NDA entitled, "Number (%) of Patients with Adverse Events with a > 5% Occurrence Rate by Body System and Treatment Group" should be inserted after the above sentence in this section.

DOSAGE AND ADMINISTRATION section

1. This section should be revised to indicate that an initial dose of 0.625 is recommended with titration up to 1.25 mg. The first sentence that begins, "Vasomotor symptoms- 0.625 mg daily initially . . ." should be revised to read, "0.625 mg daily initially; increase as needed up to 1.25 mg.

2. The paragraph that begins, "Atrophic vaginitis- 0.3 to 1.25 mg . . ." should be deleted.

3. In item #2, "For treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure" subsection, the sentence, "Cenestin has not been studied in this dose, but the following general guidance is given for estrogen" should be added to the first sentence in this item.

HOW SUPPLIED section

The 0.3 mg, 1.25 mg and 2.5 mg doses should be deleted from this section.

Patient Package Insert

DESCRIPTION section

In the **DESCRIPTION** section of the patient package insert, the structural formulas, established names, molecular formulas, and molecular weights of all the estrogen substances should be included with the structural formulas.

USES OF ESTROGEN section

1. The title of this section should be revised to read, "**USES OF CENESTIN.**"

2. The sections entitled, "To treat certain types of abnormal vaginal bleeding . . . ," To treat certain cancers . . . ," and "To prevent thinning of bones . . ." should be deleted.

WHO SHOULD NOT USE ESTROGENS section

The title of this section should be revised to read, "**WHO SHOULD NOT USE CENESTIN.**"

REDUCING THE RISKS OF ESTROGEN USE section

A space should be inserted between the words, "THE" and "RISKS" in this title.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, contact Ms. Diane Moore at (301) 827-4260.

Sincerely,

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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ORIG AMENDMENT

December 15, 1998

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urological Drug Products (HFD-580)
Document Control Room 17B-20
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-992 Cenestin™ (Synthetic Conjugated Estrogens) Tablets 0.3 mg, 0.625 mg and 0.9 mg**

Re: **Amendment**

Dear Dr. Rarick:

Reference is made to a letter from Lana Pauls, M.P.H., dated December 14, 1998 requesting information to continue the review of NDA 20-992 for Cenestin™ Tablets. This amendment contains revisions to drug substance and drug product specifications and to the labeling (physician and patient package inserts) as requested.

This **Amendment** is submitted in 1 volume and includes three (3) copies, an archival copy and two review copies. Please note that one copy each of the 'marked-up' and 'clean' version of the draft package inserts is included each copy. In addition a desk copy to Ms. Diane Moore is provided.

If you have any questions or require any additional information, please contact Mr. Ken Phelps at (513) 458-7325, by fax at (513) 731-6482, or the undersigned at (513) 458-7274.

Sincerely,

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

Enclosure: completed FDA 356h

CC: Desk copy to Diane Moore

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE