CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-992

CORRESPONDENCE

DURAmed

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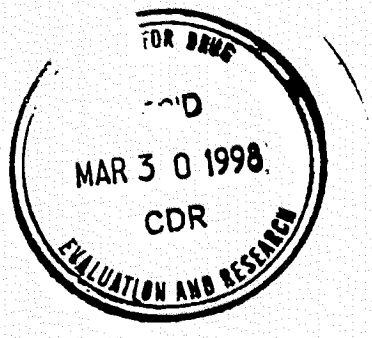
Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

March 27, 1998



Lisa Rarick, M.D.
Director, Div. Of Reproductive
& Urological Drug Products (HFD-580)
c/o Dockets Management Branch
Document Control Room
Food and Drug Administration
12229 Wilkens Avenue
Rockville, MD 20852

Re: NDA 20-992

Subject: Original New Drug Application Filing
Cenestin™ (Synthetic Conjugated Estrogens) Tablets
0.3, 0.625, 0.9, 1.25 and 2.5 mg

Dockets Management Branch:

Please find attached an original New Drug Application (NDA) for Cenestin™ (synthetic conjugated estrogens) tablets 0.3, 0.625, 0.9, 1.25 and 2.5 mg prepared in accordance with 21 CFR 314.50 and submitted under part 505(b)(2) of the Federal Food, Drug and Cosmetic Act.

We would like to inform you that we have been granted a **Small Business Waiver for the NDA filing fee** required under the Prescription Drug User Fee Act. Authorization for this waiver is provided in the attached letter, dated March 17, 1998, from the Office of the Chief Mediator and Ombudsman, and signed by Suzanne M. O'Shea, Deputy User Fee Waiver Officer.

We request an expedited review of this NDA submission. This request is justified given the extraordinary regulatory delay associated with the FDA prior review of this drug product and the resultant financial burden that delay has caused Duramed. Expeditious review of the NDA is warranted as a matter of fairness to Duramed and American women who seek and need an economic alternative estrogenic therapy.

In this NDA submission, we have complied with the requirement to conduct one essential adequate and well-controlled clinical trial for approval and now officially request, under 21 CFR 314.108(b)(4), **a three-year non-patent market exclusivity for synthetic conjugated estrogens tablets**.

This original NDA is being filed for synthetic conjugated estrogens tablets 0.3, 0.625, 0.9, 1.25 and 2.5 mg for the oral treatment of postmenopausal symptoms. The filing consists of 27 volumes with applicable copies, which total 87, and are divided for FDA review as follows:

No. of Volumes	Color	Review Section
27	Blue	Archival
6	Red	Chemistry
2	Red	Validation (extra copies)
4	Yellow	Pharmacology
3	Orange	Pharmacokinetics
22	Light Brown	Clinical
23	Green	Statistics
87 TOTAL		

For detailed information on the organization of this application, please refer to the following "EXECUTIVE SUMMARY - Organization of the NDA."

We certify that a true copy of the technical section described in 21 CFR 314.50(d)(1), the chemistry, manufacturing, and controls section of this submission, has been provided to the Food and Drug Administration, Cincinnati District Office, Cincinnati, Ohio.

Please direct any written communications regarding this NDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, 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

JRR/nam
Attachment

1) Completed 356h FDA Form
2) Desk Copies of Volume 1 only:
   a) Ms. D. Moore, DRUDP (HFD-580)
   b) Office of Scientific Investigation via Ms. Moore

NDA 20-992

APR - 2 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:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Cenestin™ (synthetic conjugated estrogens) Tablets 0.3, 0.625, 0.9, 1.25, and 2.5 mg.
Therapeutic Classification:	Standard
Date of Application:	March 27, 1998
Date of Receipt:	March 30, 1998
Our Reference Number:	20-992

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on May 29, 1998, in accordance with 21 CFR 314.101(a).

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

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

4/2/98

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-992
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/MMann/MRhee/AJordan/LKammerman/ADorantes
DISTRICT OFFICE

Drafted by: dm/April 2, 1998/n20992ak. 9/2/98

Concurrence:
LPauls 04.02.98

ACKNOWLEDGEMENT (AC)

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

ORIG AMENDMENT
BC

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

CENTER FOR DRUG
REC'D
MAY 8 1998
HFD-580
EVALUATION AND RESEARCH

May 7, 1998

Lisa Rarick, M.D.
Director, Div. Of Reproductive
& Urologic 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, 0.625, 0.9, 1.25 and 2.5 mg

Subject: Chemistry Amendment

Dear Dr. Rarick:

Reference is made to a telephone conference on May 6, 1998 between Ms. Diane Moore, Dr. David Lin and Dr. Moo-Jhong Rhee of your Division and Mr. John Rapoza, Mr. K. Phelps, Ms. Annette Arlinghaus and Mr. J. Banschbach from Duramed concerning clarification in the Chemistry, Manufacturing and Controls section in our New Drug Application #20-992 for Cenestin™ (Synthetic Conjugated Estrogens) Tablets 0.3, 0.625, 0.9, 1.25 and 2.5 mg.

We acknowledge agreement to the clarification of the definition of synthetic conjugated estrogens and are now amending the NDA. As a result of our agreement, the specifications for the drug substance solution and drug product are revised and the following documents are attached:

- Raw Material Specification Sheet for Synthetic Conjugated Estrogens Solution (02-005*)
- In-Process Specification Sheet for Synthetic Conjugated Estrogens Granulation (02-089*)
- Finished Drug Product Specification Sheet (02-091*)
- Post Approval Marketed Product Stability Protocol (03-006*)

* NDA page where the original document is located

This information will be included as part of an electronic submission of a clinical amendment which is to be filed within three weeks.

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

We certify that a true copy of this submission has been provided to the Food and Drug Administration, Cincinnati District Office, Cincinnati, Ohio.

Please direct any written communications regarding this NDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, 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

cc: David Lin (desk copy via Diane Moore)

DURAmed

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

ORIGINAL

May 27, 1997

ORIG AMENDMENT

BNL

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

Subject: Clinical Efficacy Amendment

Dear Dr. Rarick:

Reference is made to a telephone conference on May 4, 1998 between Ms. Diane Moore of your Division and Mr. Ken Phelps from Duramed concerning the computation of the primary efficacy endpoint in the Clinical section in our New Drug Application #20-992 for Cenestin™ (Synthetic Conjugated Estrogens) Tablets 0.3, 0.625, 0.9, 1.25 and 2.5 mg. Initially, the Division had requested that the primary efficacy be determined by computing the absolute difference in moderate and severe vasomotor symptoms (MSVS) between baseline and 4-, 8 and 12 weeks and comparing these results between Cenestin™ and placebo treatments. Ms. Moore indicated that upon initial review of our application, the medical officer indicated the use of the actual (arithmetic) difference rather than the absolute difference would more accurately reflect the efficacy of Cenestin™.

Accordingly, the primary efficacy computations have been revised to remove the results based on calculations involving the absolute differences and replace these with results based on actual differences. This re-analysis has been incorporated into the following documents which are being submitted in their entirety for clarity and convenience:

Enclosed Volume	Location in Original NDA Volume	NDA Item	Revisions
1	1	Item 3: Application Summary[1]	A. Annotated Labeling: Revised summary table for clinical study. H. Clinical Data Summary and Results of Statistical Analysis: Revised discussion of efficacy computations, results and summary table.
2	7	Item 8: Clinical Data Section	Clinical Report: Revised discussion of efficacy computations, results, summary tables, figures
3	8		Statistical Tables
4	9		Statistical Tables
5	22		Individual Patient Listings
6	23		Integrated Clinical Efficacy (excluding references)

Additionally, it was agreed to provide essential sections of the NDA in electronic format as a review aid. A CD-ROM and a discussion of its contents is attached immediately following this cover letter.

This **Amendment** is submitted in six (6) volumes and includes three (3) copies, an archival copy and a review copy for the clinical and statistical reviewers.

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

cc: Diane Moore (desk copy)

[1] Section D: Chemistry, Manufacturing and Controls Summary has also been updated to reflect the changes made in the Amendment dated May 7, 1998.

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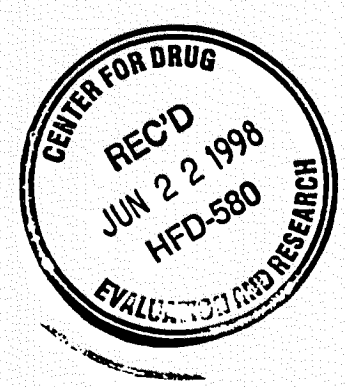
ORIG AMENDMENT
BC

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

June 19, 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: **Chemistry Amendment**

Dear Dr. Rarick:

Reference is made to a telephone conference on June 16, 1998, between Ms. Diane Moore, Dr. David Lin and Dr. Moo-Jhong Rhee, of your Division, and Mr. John Rapoza, Mr. Ken Phelps and Ms. Annette Arlinghaus, of Duramed, concerning the definition of specifications for synthetic conjugated estrogens.

In follow-up to this conference we now submit this amendment to establish new specifications for synthetic conjugated estrogens. Specifically, we have reviewed our production history and defined the label claim to be 100% of the estrogenic composition. This definition requires an adjustment in the calculation of label claim with changes in estrogen ranges, as well as including, for each estrogen, an upper and lower limit specification.

To support these new synthetic conjugated estrogens specifications, we have included the following tables:

1. Drug product lot history in which the label claim is adjusted for nine estrogens.
2. Drug product lot history in which the estrogens ranges have been adjusted for 100% label claim.
3. Summary table of the maximum/minimum ranges and average from Table 1.
4. Summary table of the maximum/minimum ranges and average from Table 2.
5. Summary table of previous assay specifications for individual and total estrogens.
6. Summary table of proposed assay specifications.

REVIEW COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

In addition, we have included a brief narrative outlining how, in the analytical method, the percent label claim of each estrogen is calculated.

We have also included revised release specifications for the drug product. Given this new definition for synthetic conjugated estrogens and how the specifications are characterized, we propose to delete the requirement for the sodium equilin sulfate/sodium estrone sulfate ratio in the finished drug product. These new release specifications for synthetic conjugated estrogens now have a 100% label claim consisting of all nine estrogens.

As an aid in the review process, we have placed the tables on a 3.5" diskette which is also enclosed.

Please direct any written communications regarding this NDA to me at the above address. If you have any questions, or require any additional information, please feel free to contact Ms. Annette Arlinghaus at (513) 731-9900 or myself at (513) 458-7274, or by fax at (513) 731-6482.

Sincerely,

Annette Arlinghaus /for

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

JRR/nam
Enclosures
1) Completed 356h

CC: David Lin (desk copy via Diane Moore)

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ORIGINAL

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

September 22, 1998

NEW CORRESP

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: **Established Name**

Dear Dr. Rarick:

Reference is made to a telephone call on September 21, 1998 between Ms. Moore and Drs. Rhee and Lin of the Division of Reproductive and Urinary Drug Products and Mr. Ken Phelps and Mr. John Rapoza of Duramed Pharmaceuticals, Inc. During this teleconference, Dr. Rhee reviewed the efforts by the Center's Conjugated Estrogens Working Group regarding the established name for Cenestin™. We understand this Group recommends the established name of Synthetic Conjugated Estrogens Mixture A, but they invited Duramed to accept or propose alternatives.

We have reviewed the proposed name, however, we are concerned that the use of the word 'Mixture' implies derivation from a natural source. To better support the synthetic source of our product, we prefer the word 'Composition' or, alternatively, 'Compound'. Thus, we propose Synthetic Conjugated Estrogens Composition A as the established name for Cenestin™.

This **Amendment** is submitted in one (1) volume and includes two (2) copies, an archival copy and a review copy for the chemistry reviewers. A copy is also being faxed to the attention of Ms. Diane Moore at (301) 827-4267.

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

DURAmed

October 30, 1998
The Art of Leadership...
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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

VIA FAX

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: **Draft labeling**

Dear Ms. Moore;

Per our telephone conversation today, I am attaching the following information:

1. The 0.3 mg tablet used in the vasomotor clinical trial is identical to the proposed commercial product except that the coat contained the same red colorant as used in the 0.625 mg tablet to maintain blinding. The 0.625 mg tablet is identical in all respects to the proposed commercial product.
2. F2 dissolution comparisons between the 0.3-, 0.9, 1.25- and 2.5 mg tablets versus the 0.625 mg tablet are attached as Attachment I.
3. A comparison of the bioanalytical methods used in each of the fed and fasted studies is included as Attachment II.
4. The pharmacokinetic parameters, AUC_{0-72}, AUC_{0-inf} and C_{max} for each subject for all analytes, including baseline corrected where indicated, are presented in Attachment III . We understand that you will refer to the ANDA filing for individual graphic profiles. At this writing, I am only including the data for the 1.25 mg fasted study. The balance will be forwarded later today.
5. The table presenting the results of the vasomotor clinical study for use in the proposed labeling, based on the revised computation used in Amendment 1 (arithmetic difference), is presented in Attachment IV.

Please contact me should you have comments or further requirements.

Sincerely,

Ken Phelps
Vice President Corporate Projects