# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA #_NDA 20-992_____ Supplement # _____Circle one: SE1 SE2 SE3 SE4 SE6

HFD-580____ Trade and generic names/dosage form: _Cenestin™ (synthetic conjugated estrogens, Composition A, USP) _0.625 mg, 0.9 mg and 2 X 0.625 mg.____Action: AP AE NA

Applicant _Duramed Pharmaceuticals, Inc._____ Therapeutic Class_____3S_____

Indication(s) previously approved __none_____
Pediatric information in labeling of approved indication(s) is adequate _X_ inadequate __
Proposed indication in this application__Reduction of Vasomotor Symptoms associated with the Menopause_____

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTINS IN RELATION TO THE PROPOSED INDICATION.
**IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS?** ___Yes (Continue with questions) _X__ No (Sign and return the form)
**WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED?** (Check all that apply)
___Neonates (Birth-1 month) __ Infants (1month-2yrs) __Children (2-12yrs) ___ Adolescents (12-16 yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing.
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

_X__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

**ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER?** ___ Yes _X__ No
**ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.**

This page was completed based on information from the Medical Officer_____

Diane Moore, Project Manager — March 4, 1999
Signature of Preparer And Title — Date

CC: ORIG NDA/BLA # _NDA 20-992_____
HFD-580_____/DIV FILE
NDA/BLA ACTION PACKAGE
HFD-OO6/ KROBERTS

(revised 10/20/97)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)**

Memorandum

TO: NDA 20-992 Division File

THROUGH: Shelley Slaughter, M.D.
Team Leader

FROM: Theresa H, van der Vlugt, M.D., M.P.H.
Medical Officer

SUBJECT: Pediatric Studies with Cenestin™

DATE: March 4, 1999

Cenestin™ (Synthetic Conjugated Estrogens, A) is a drug product to be used in a postmenopausal population, aged 45 to 65, for the relief of vasomotor symptoms associated with the menopause. Synthetic Conjugated Estrogens, A drug product has no potential for use in pediatric patients.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-992
MOORE
HFD-580 - Doc Rm

OCT 13 1998

James C. Kisicki, M.D.
MDS Harris Laboratories
621 Rose St.
Lincoln, Nebraska 68501

Dear Dr. Kisicki:

Between may 19-22, 1998, Ms. Jane E. Nelson, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of a clinical study (protocol # ; of the investigational drug Cenestin (synthetic conjugated estrogens), performed for Duramed Pharmaceuticals, Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From an evaluation of the inspection report and of the documents collected during the inspection, we conclude that you did adhere to all federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Ms. Nelson during the inspection.

Sincerely yours,

Bette L. Barton, Ph.D., M.D.
Chief
Clinical Investigations Branch
Division of Scientific
Investigations, HFD-344
Office of Compliance
Center for Drug Evaluation
and Research

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

**Group Leader's Memo**

No Group Leader's memo will be prepared; the memo will be prepared by the Division Director; no Group Leader memo is required.

# MEETING MINUTES

**Date:** June 19, 1997 **Time:** 3:30 - 5:00 **Location:** Woodmont II: Conference Room "G"

**Pre-NDA** **Drug Name:** Synthetic Equine Estrogens

**External Participant:** Duramed Pharmaceuticals, Inc.

**Type of Meeting:** Pre-NDA

**Meeting Chair:** Dr. Lisa Rarick **External Participant Lead:** Mr. John R. Rapoza

**Meeting Recorder:** Mrs. Diane Moore

**FDA Attendees:**

- Jane Axelrad - Associate Director for Policy, CDER (HFD-005)
- James Bilstad, M.D. - Director, Office of Drug Evaluation II (ODE II; HFD-102)
- Leah W. Ripper - Assistant to Director, ODE II (HFD-102)
- Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
- Heidi Jolson, M.D., M.P.H. - Deputy Director, DRUDP (HFD-580)
- Lana L. Pauls, M.P.H. - Chief, Project Management Staff, DRUDP (HFD-580)
- Diane Moore - Consumer Safety Officer, DRUDP (HFD-580)
- Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
- Robert Seevers, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
- John Hunt - Deputy Director, Office of Clinical Pharmacology and Biopharmaceutics II (OCPB; HFD-870)
- Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, OCPB @ DRUDP (HFD-580)
- Sam Haidar, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
- Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
- Christine F. Rogers, J.D. - Regulatory Counsel @ DRUDP (HFD-580)

**External Constituents:**

Mr. John R. Rapoza, M.S., R.Ph. - Vice President, Regulatory Affairs
Mr. Kenneth V. Phelps - Vice President
James A. Simon, M.D. - Medical Consultant
Dr. George J. Wright, Bioavailability Consultant
Mr. David Adams, Esq. (Olsson, Frank & Weeda)

**Meeting Objectives:**

To discuss the filability of the NDA proposed by Duramed for their synthetic conjugated estrogens product as a 505(b)(2).

**Discussion Points:**

- Clinical
  - this product was modeled after the DESI guidance for conjugated estrogens
  - Duramed is seeking class labeling for the treatment of vasomotor symptoms (VMS) indication; the sponsor's goal was to match their product with the existing major product profile
  - several bioavailability studies were performed using the 0.625 mg and 1.25 mg dose tablets; estrone and equilin levels were determined under both fasting and nonfasting conditions; the existing modified-release product was tested
  - the sponsor maintained that different estrogens are effective for VMS; a wide range of doses are effective; and variable routes of administration are effective
  - the sponsor also maintained that doses of estrogen should be titrated for each patient and no single concentration of active ingredient (estradiol, estrone, equilin) is universally effective in all patients
  - sponsor also maintained that the different estrogen compounds are effective for VMS; estrone, sodium equilin and estrone combined with equilin are all effective for VMS
  - the sponsor does not believe there is a safety issue with their product; they seek to use the DESI reviews and published literature as a data base for a 505(b)(2) submission
- Chemistry
  - Cenestin is the chosen trade name for the Duramed product; this name appears acceptable but will be reviewed by the Nomenclature committee
  - the proposed established name, "synthetic equine estrogens" is problematic because the product is made from plant material, not equine material; estrone is a human estrogen; "synthetic conjugated estrogens" would be a preferable established name
  - a five-component product would contain active and concomitant components; a two-component mixture could be called by the component names
  - the chemistry data presented is from the previous ANDA
  - the 36-month stability data on 3 batches of the drug product meet stability requirements
  - bracketing doses is permittable; the highest and lowest strength data are required for bracketing with less data required for middle doses
  - USP is in the process of implementing a new dissolution procedure for Conjugated Estrogens (see March-April 1997 issue of Pharmaceutical Forum)
  - a different dissolution method could be used with data from study
  - as of the last review, the DMFs from are acceptable; the DMFs will need to be re-reviewed when the NDA is submitted again
  - inspections of manufacturing sites will be submitted to compliance staff; those visited within the last two years may not need to be reinspected, but new sites would need to be inspected

- Logistics of filing NDA
  - items not found in the generic submission may be requested directly from the sponsor
  - ANDA specifications and ranges are broader than in new drug applications; ratios and ranges in both drug substance and product may be tighter than in the previous review
  - impurity and dissolution specifications are included in new drug reviews that may have been omitted from previous submissions to the ANDA
  - a 505(b)(2) application must link the proposed drug product to pertinent published literature references or referenced clinical data; in order to link the Duramed product to the literature, it would require data on VMS with a product similar to the Duramed product
  - bridging study data to a new NDA is both a scientific and policy decision; safety and efficacy must be demonstrated scientifically; the Agency works under a "substantial evidence standard" i.e., data should be presented to reasonably conclude that a product is safe and effective; the identity of the drug formulation and bioavailability of a product are required; a 505(b)(2) is not the same as an ANDA
  - the referenced 1992 study by the Upjohn company using the Duramed product would not be considered an adequate trial on which to base a 505(b)(2) filing for this product; the IND product is a faster release product, the study had no placebo control or estrogen alone arm, and the required VMS standards were not met (less hot flushes than requirement)
  - the Clinical database for new drugs usually requires two 12-week trials in women with moderate-to- severe vasomotor symptoms (7-8 VMS/day or 56 VMS /week); clinical trial design issues can be discussed with the Division to support a standard NDA submission instead of the proposed 505(b)(2)
  - two adequate and well-controlled trials have always been required for an NDA for their type of product; the Division is willing to consider one trial for estrogens; FDA cannot change standards for one company over another, but must treat each sponsor equitably; all estrogens should be treated the same; there must be substantial evidence of efficacy for an approval
  - the sponsor should submit a protocol for a clinical study for VMS; premenopausal women rendered menopausal would not be equal to true menopausal women; the sponsor plans to study the 0.625 and 1.25 mg doses against placebo in a study with 30 completers per arm; hot flushes would be tracked through patient diaries; blood levels and estradiol levels would be taken; an 80% power is targeted to show a difference between drug and placebo
  - questions that arise prior to submitting the IND (i.e., study design or the statistical analysis plan questions) can go through the CSO
  - if the sponsor plans to market the 0.3 mg dose, information on the efficacy of the 0.3 mg dose should be submitted; this dose should be studied
  - the sponsor is seeking to submit the chemistry data for review as a presubmission with an NDA number prior to submitting the rest of the NDA; they also desire to perform a clinical study concurrently with the review process for the Chemistry and Biopharmaceutics Disciplines
  - the sponsor requests a waiver from user fee applications
  - filing an NDA before a clinical trial has been started is risky for the sponsor; a time line would be needed for the clinical trial as this risks non-filing for the NDA if the clinical data is critical to the fileability of the NDA

- Biopharmaceutics
  - the sponsor is seeking approval for five tablet dosage strengths which have modified drug releasing characteristics; for immediate release oral products, waivers of bioavailability studies have been allowed for different strengths using dissolution data
  - historically, NDAs for oral products without immediate release characteristics have required single-dose studies for each strength plus a multiple-dose study, usually at the highest strength, and a food effect study
  - there is no apparent *in vitro* dissolution-*in vivo* correlation available, but approval is being requested for three tablet strengths (i.e., 0.3, 0.9 and 2.5 mg) with no *in vivo* bioavailability or clinical data
  - 
  - the standard requirements such as metabolism information, protein binding information and drug/drug interaction information can be obtained from literature reports
  - in vitro dissolution data should be submitted using the new method that is being proposed in the USP; if bio/clinical data on the tablet strengths is available, an alternative method could be product specific
  - the Division acknowledged that the PK requirements being covered for part of an NDA are what are normally required, but the final decision would be made by the Clinical Division

- Biometrics
  - blinding issues caused by using different sizes of the tablets should be addressed

- Pharmacology
  - there are no pharmacology or toxicology issues with this drug product

Decisions reached:

- Duramed has not adequately established a link between their product and the referenced literature; the data presented for this product and indication are inadequate for filing a 505(b)(2)
- a clinical study should be performed using the to-be-marketed product; the study should be a placebo-controlled, parallel study to confirm the dose(s) to be used
- the chemistry submission could be provided 4 months in advance of the NDA submission with an NDA number; the tablet formulation data must be submitted
- the sponsor must submit an IND with the Division and file the clinical study protocol under that IND; the ANDA can be referenced in the IND
- a request for a waiver of the 30 day safety review could be requested when the IND is submitted if the sponsor has already obtained feedback from the Division on the adequacy of the protocol

**Action Items:**

| Item: | Responsible Person: | Due Date: |
|---|---|---|
| ♦ submit the VMS study protocol for FDA review | Duramed | one month |

Signature, minutes preparer 8/4/97

Concurrence, Chair 8/5/97

drafted: dm/06.23.97/duramed.619

cc:
NDA Arch:
HFD-580
HFD-005/JAxelrad
HFD-102/JBilstad/LRipper
HFD-580/LRarick/HJolson/LPauls/DMoore/MRhee/RSeevers/ADorantes/SHaidar/LKammerman
HFD-870/JHunt
HFD-800/Yuan-Yuan Chiu
HFD-580/Christine F. Rogers

Concurrences:

TRumble 06.26.97/SHaidar, ADorantes, RSeevers, MRhee, HJolson, CRogers 06.27.97
LKammerman 06.30.97/LRarick, JHunt 07.01.97/LPauls 07.03.97/JAxelrad 07.14.97

Concurrences not received from:

JBilstad/LRipper

D Moore
8/4/97

# MINUTES of TELECON

**Date:** July 25, 1997 **Time:** 9:00 - 10:00 AM **Location:** Parklawn; Rm 17B-45

**IND:** **Drug Name:** Cenestin (Synthetic Conjugated Estrogens Tablets)

**External Participant:** Duramed

**Type of Meeting:** Guidance

**Meeting Chair:** Dr. Lisa Rarick **External Participant Lead:** Ken Phelps

**Meeting Recorder:** Mrs. Diane Moore

**FDA Attendees:**

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Julian Safran, M.D. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Consumer Safety Officer, DRUDP (HFD-580)
Tatiana Pavlova M.D., Ph.D. - Clinical Pharmacology Fellow
Angelica Dorantes, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

**External Constituents:**
Mr. Kenneth V. Phelps - Vice President
Annette Arlinghaus - Associate Director, Regulatory Affairs

**Meeting Objectives:**

To discuss the study design and protocol submitted for Cenestin (IND ) to be initiated in August, 1997.

**Discussion Points:**

- Study duration
  - although hyperplasia is unlikely in a short term study, the sponsor chose 8 weeks for the study to avoid unnecessary exposure of the drug; the additional 4 weeks did not appear to enhance efficacy data in the study
  - the study should have a 2-week run-in period
  - the study should be lengthened to 12 weeks rather than 8 weeks so that safety issues can be studied
  - observations should be made at 4 and 8 weeks for efficacy

- General
  - because there are no endometrial biopsies performed at the end of the study, a progestin challenge should be offered to all patients at the end of the study to protect the women with uteri who received estrogen alone
  - the study could incorporate a stratification of the randomization scheme according to the amount of time it takes for a woman to qualify for the study on the hot flush criteria
  - the preclinical review of the protocol is pending
  -
  - the percentage reduction in the mean number of moderate-to-severe hot flushes should be the primary endpoint; severity is a secondary endpoint
  - currently, the escalation of the patient dose will be determined upon patient interview with each investigator making the determination independently; there should be a criteria or indication proposed for the investigators to determine which women will be dose-escalated
  - the sponsor should consider redesigning the study as a dose-titration design; the dose escalation study should utilize a titration of the five tablet doses; the dosing will start at the 0.625 mg dose and be titrated down to the 0.3 mg dose for women who have mild adverse events and titrate up to the 2.5 mg dose for those who do not respond to the 0.625 mg dose
  - the sponsor should consider making the 0.3 mg dose available
  - because the 2.5 mg tablet is a different size from the 0.625 and 0.3 mg tablets, placebos should be provided to match each dose for blinding in a two arm study
  - the placebo could be compared to the 1.25 mg treatment dose; women who were intolerant of the 1.25 mg dose could be changed to the 0.3 mg dose and compared to placebo
  - more than 90% of women are controlled by the 1.25 mg dose or less; the sponsor is willing to accept the risk that some women will not be affected; the goal is to show efficacy of the product, not which dose is effective for which women
  - the sponsor does not plan to pursue the 2.5 mg dose
- Study design
  - the screening period describes monitoring women until they have two consecutive weeks of 56-60 hot flushes per week for entrance into the study; this was designed to give more flexibility for the sponsor to enroll the patient or disqualify her from the study quickly
  - the sponsor should define the screening period to a set number of weeks
  - the randomization ratio is set at 3 active: 2 placebo; because the dropout rate may be larger in the placebo group, the placebo group could become too small
  - the ratio was chosen for recruitment purposes; it gives the woman a better chance of receiving the drug
  - the number of patients to be randomized should be stated at the beginning of the study
  - the sponsor plans on finishing the study with a minimum of 50 women
  - the assumption used to calculate the sample size estimate for the protocol should be defined

- the sponsor should perform an intent-to-treat analysis rather than analyzing evaluable patients
- the sponsor should consider powering the study to detect smaller differences that are clinically meaningful; the proposed study may be underpowered
- the sponsor performed a sensitivity analysis which indicated a placebo response of about 30% and an active group as low as around 70%; the results will be submitted to the IND

- Biopharmaceutics
  - there is a lack of data for the 0.3, 0.9 and 2.5 mg doses; although a decision has not been made to the acceptability of a waiver for these doses, data collected at this time could address possible phase 4 issues
  - if blood samples are collected in the proposed clinical study, estrone, equilin, total estrone and total equilin should be assayed

Decisions reached:

- Duramed understands the need for including the 0.3 mg dose in the study design; they will put a more objective number and severity in the protocol for changing dose escalation
- the sponsor will add a "not longer than . . " phrase to the inclusion criteria to indicate that the screening period will be a certain number of weeks
- the sponsor will discuss performing both intent-to-treat and evaluable patient analysis internally and with FDA statisticians at a to-be scheduled teleconference
- the sponsor agreed to amend the protocol by adding objective criteria for titrating patients in the study
- although the proposed clinical study would not be adequate to address the pharmacokinetic issues that are still pending, the sponsor agreed to

Action Items:

| Item: | Responsible Person: | Due Date: |
|---|---|---|
| set up statistical telecon to discuss power calculations | Mrs. Moore | one month |

Signature, minutes preparer 9/5/97

Concurrence, Chair

drafted: dm/07.28.97/i53731tc.725

cc:
NDA Arch:
HFD-580
HFD-580/LRarick & Attendees/AJordan/MRhee
HFD-715/ENevius

Concurrences:

LPauls 08.06.97/LRarick 08.10.97/Tvan der Vlugt, ADorantes 08.14.97/TPavlova 08.15.97
LKammerman 08.18.97/JSafran 08.20.97