Minutes of Telecon

Date: September 21, 1998 **Time:** 2:30 PM - 2:45 PM **Place:** Parklawn; Dr. Rhee's Office

NDA: 20-992 **Drug Name:** Cenestin® (synthetic conjugated estrogens)

Type of Meeting: Pre-NDA

External Participant: Duramed Pharmaceuticals, Inc.

FDA Lead: Dr. Moo-Jhong Rhee **External Participant Lead:** Mr. John Rapoza

Meeting Recorder: Ms. Diane Moore

FDA Participants:

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (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)

External Constituents:

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

Meeting Objective:

To discuss the established name for Cenestin®.

Background: The established name has been discussed by the FDA Working Group.

Discussion Items:

- the FDA Center Conjugated Estrogens Working Group is proposing the name, "Synthetic Conjugated Estrogens Mixture A" for the established name for Cenestin®
- other synthetic conjugated estrogens are considered to be subsets of Premarin conjugated estrogens
- the sponsor objected to the term "mixture" because it appears awkward and suggests that the drug product is unplanned
- the broad term, "formulation," involves excipients and is therefore not a viable alternative
- the Working Group determined that "A" or "B" was a more descriptive term than alpha or beta

Decisions:

- Duramed will discuss the proposed name internally and respond to the Agency with an amendment or concerns

- when an agreeable name is determined, the sponsor will submit the name to USAN

To-do items

Item :	Responsible Person :	Due Date:
• respond to FDA proposal	Duramed	1- 2 days

10/7/98 — 10/7/98

Signature, minutes preparer Signature, Chair

drafted: dm/09.25.98/n20992tc92298.doc

Concurrences:
TRumble, DLin, MRhee 10.02.98

cc:
HFD-580
HFD-580/LRarick/Mann/Tvan der Vlugt/MRhee/DLin/AJordan/KRaheja/VJarugula/AParekh
HFD-580/KMeaker/LKammerman/JMercier/DMoore

Moore

Minutes of Telecon

Date: October 30, 1998 **Time:** 12:25 - 12:40 PM **Place:** Parklawn; Ms. Moore's Office

NDA: 20-992 **Drug Name:** Cenestin™ (synthetic conjugated estrogens)

Indication: Relief of Vasomotor Symptoms (VMS) in postmenopausal and perimenopausal women

Type of Meeting: Clinical Pharmacology Guidance

External Participant: Duramed Pharmaceuticals, Inc.

FDA Lead: Dr. Ameeta Parekh **External Participant Lead:** Mr. Ken Phelps

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

External Constituents:
Mr. Ken Phelps - Vice President, Corporate Projects, Duramed

Meeting Objective:
To request additional Biopharmaceutics data for NDA review.

Discussion Items:
- the clinical trial formulation is the same as the to-be-marketed tablets (0.3 mg, 0.625 mg doses); the only difference is that the 0.3 mg tablet in the clinical trial had a red color coating to match the 0.625 mg tablet in the clinical trial
- *in vitro* dissolution comparisons have been supplied to the chemist
- in order to compare the 0.625 mg and the 1.25 mg tablet doses in cross-study PK comparison tests, the assay must be the same for both tablets

Decisions Reached:
- the following Biopharmaceutical information should be submitted for review:
  - dissolution profiles for the 0.3 mg, 0.625 mg and 0.9 mg tablets
  - F_2 comparison tests for every tablet strength in the NDA; the reference tablet strength is the 0.625 mg tablet (0.625 mg tablet strength compared to the 0.3 mg, 0.9 mg, 1.25 mg, and the 2.5 mg tablet strengths)
  - summary of the media used in the comparison tests
  - summary of the dissolution for record completion
  - assay methodology used for the pharmacokinetic (PK) studies to compare the two 0.625 mg dose tablets with the 1.25 mg tablet dose

- summary of the assays used to compare the 0.625 mg and 1.25 mg tablets in the two separate studies
- cross-study comparison PK data on the 0.625 mg and 1.25 mg tablets (study data using two 0.625 mg tablets and data using one 1.25 mg tablet)
- summary of the fasting and fed studies performed on the 0.625 mg and 1.25 mg doses and the laboratory methods used including the different sites
- summary of PK data for 0.625 mg and 1.25 mg tmax, AUC (0-72), 0-(for each individual raw data point, AUC (not plasma level numbers), C_{max}, raw data for each individual data point
- individual linear profiles and non-linear profiles, if available
- analyses should be baseline-uncorrected

To-do items

Item :	**Responsible Person:**	**Due Date:**
• send telefacsimile of AUC and C_{max} data	Duramed	one day
• submit summary of assay methods for PK comparison study	Duramed	one week
• submit F_2 comparison test results	Duramed	one week

12/28/98

Signature, minutes preparer

Signature, Chair 1/4/99

drafted: dm/11.23.98/N20992tc103098.doc

Concurrences:
JLau 11.30.98/TRumble 12.01.98/AParekh 12.14.98

cc:
HFD-580
HFD-580/LRarick/Mann/Tvan der Vlugt/MRhee/DLin/AJordan/KRaheja/JLau/AParekh
HFD-580/KMeaker/LKammerman/DMoore

Minutes of Telecon

Date: December 4, 1998 **Time:** 11:00 - 11:20 AM **Place:** Parklawn; 18B37

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

Indication: Relief of Vasomotor Symptoms in menopausal women

Type of Meeting: Guidance

External Participant: Duramed Pharmaceuticals, Inc.

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)
Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)
Shelley Slaughter, M.D., Ph.D. – Acting Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Lana L. Pauls, M.P.H. - Acting Associate Director, DRUDP (HFD-580)
Terri Rumble – Acting Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Team leader, DPE II; (HFD-870)
Johnny Lau, Ph.D. - Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing and Communication (DDMAC; HFD-40)
Carol Drew - Regulatory Policy Staff

External Constituents:
Mr. John Rapoza, V. P. Regulatory Affairs, Duramed
Mr. Ken Phelps, V. P. Corporate Projects, Duramed
Ms. Annette Arlinghaus, Regulatory Affairs

Meeting Objective:
To inform Duramed that the 1.25 mg and 2.5 mg doses and possibly the 0.3 mg dose are not approvable with the clinical data presented and to request additional Biopharmaceutics data for NDA review.

Background:
After review of the data presented in the NDA, it was decided that some additional information from the sponsor would be necessary to approve several strengths of Cenestin as proposed in the NDA.

Discussion Items:
- most of the reviews have been completed for the NDA

- additional *in vitro* dissolution information is needed for the completion of the Biopharmaceutics review; the dissolution specifications should be specified for more than one active ingredient; *in vitro* dissolution data for equilin sulfate should be provided to set specifications
- the waivers for the 0.3 and 0.9 mg doses and the 0.625 mg dose dissolution specifications were based on estrone sulfate and equilin sulfate (*in vitro* dissolution) data; the same applies to the waiver for the color change to the 0.3 mg tablet
- no direct comparison of the 1.25 and 0.625 doses was made, only cross-study comparisons were done
- the 1.25 mg tablets and the 2.50 mg tablets differ from the lower strengths only because of the coatings used; the tablets could be reformulated for further consideration
- there is no clinical data to support the use of the 2.5 mg dose
- the proposed name, "synthetic conjugated estrogens, composition A" is being discussed and reviewed internally
- further labeling discussions may ensue later

Decisions Reached:

- the 0.625 mg dose, 0.9 mg dose and the 2 x 0.625 mg dose can be approved
- the clinical data does not support approval of the 0.3 mg dose; the issue of whether to include the 0.3 mg dose with the approval of other doses will be discussed at higher levels before making a final decision
- the 1.25 mg tablets and the 2.5 mg tablets are not bioequivalent to the 2 x 0.625 mg tablets and the 4 x 0.625 mg tablets, respectively and no data was submitted for 4 x 0.625 mg tablets; therefore, the 1.25 mg dose and the 2.5 mg dose will not be approved
- in order to grant a waiver for the low and high strengths and the color changes for the 0.3 mg dose, (from green to red), additional data on equilin sulfate is needed
- the blood levels were established based on equilin and estrone; in order to waive the other strengths, the dissolution characteristics of equilin are needed for the 0.3 mg, 0.625 mg, 0.9 mg and 2 x 0.625 mg doses
- the F_2 test should be performed for equilin using the same batches tested for estrone sulfate
- Duramed will respond with the time frame for submitting their proposal next week
- all references to the 1.25 and 2.50 mg doses will be removed from the labeling
- the label may include the 0.3 mg dose, but it may not be approved based on the lack of clinical data
- Chemistry and Biopharmaceutics deficiencies will be conveyed along with the labeling comments

To-do items

Item :	**Responsible Person:**	**Due Date:**
• submit Biopharmaceutics data for equilin sulfate	Duramed	two weeks
• send labeling comments	DRUDP	one week

Signature, minutes preparer 12/6/98

Signature, Chair 12/15/98

Post Meeting Addendum: In a telephone conversation on December 7, 1998, Duramed suggested that they would be submitting the requested Biopharmaceutics data by December 10, 1998.

drafted: dm/12.08.98/N20992tc120498.doc

Concurrence:

TRumble 12.07.98/LRarick, LPauls, AParekh, KMeaker, SSlaughter 12.14.98
CDrew 12.15.98/MMann 12.16.98/Tvan der Vlugt 12.17.98

Concurrence not received from JLau/LStockbridge

cc:
HFD-580
HFD-580/LRarick/Mann/SSlaughter/Tvan der Vlugt/MRhee/DLin/AJordan/KRaheja/AJordan
HFD-580/KMeaker/LKammerman/JMercier/DMoore/TRumble/LPauls/JLau/AParekh
HFD-40/LStockbridge
HFD-005/CDrew

Minutes of Telecon

Date: January 22, 1999 **Time:** 9:00 - 9:25 AM **Place:** Parklawn; Room 17B-43

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

Type of Meeting: Labeling

External Participant: Duramed

FDA Lead: Dr. Lisa Rarick **External 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)
Marianne Mann, M.D.- Deputy, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. – Medical Officer, DRUDP (HFD-580)
Terri Rumble – Acting Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Dornette Spell-LeSane – 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)
David Lin, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) DPE II; (HFD-870) @ DRUDP (HFD-580)

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

Meeting Objective:
To discuss the 0.3 mg dose of Cenestin in the NDA.

Background: The sponsor submitted a telefacsimile on January 20, 1999, requesting a Teleconference to discuss the 0.3 mg dose of Cenestin and the release characteristics to be included in the product labeling (see attached).

Discussion Items:
- Regarding the 0.3 mg dose
  - the NDA is based on one clinical trial which used the 0.625 mg dose as the starting dose and titrated the subjects to higher (2 X 0.625 mg) or lower (0.3 mg) dosages, as needed; not enough data was generated to support the efficacy of the 0.3 mg dose
  - from a Biopharmaceutics aspect, the 0.3 mg dosage could be waived based on proportionality with other studied doses; however, the current issue is that the limited clinical data with 0.3 mg does not support the efficacy of this dose

- this NDA is not being reviewed as a DESI ruling and the application is not a bioequivalence application; a comparison to Estratab is not relevant; this NDA must stand on its own merits, i.e., all doses must be supported with clinical data
- a new protocol to explore the 0.3 mg dose could be submitted, if desired
- the 0.9 mg dose can be approved based on data generated using doses higher and lower than the 0.9 mg dose
- the 1.25 mg dose was clinically studied as 2 X 0.625 mg tablets, but if the formula of the 1.25 mg tablet is similar to the 0.625 mg tablet, the sponsor may request a waiver of the bioequivalence demonstration
- the 2.5 mg dose is a higher dose than that studied in the clinical trial
- the sponsor plans to file a supplement for a single 1.25 mg tablet to replace the two 0.625 mg tablet dose; the 1.25 mg formulation would be identical to the 0.625 mg tablet formulation

- Regarding the food-effect study
  - currently, the labeling states that there is no information on food-effect for Cenestin
  - the sponsor claims to have studied the 0.625 mg dose in a food-effect study, however, because the results were from two separate studies, these do not qualify as a standard food-effect study that can be included in the labeling

Decisions:

- a food-effect study could be performed using the 1.25 mg dose; a labeling change could be proposed using that data in a subsequent submission
- discussion regarding the slow-release characteristics of the product in the labeling will be discussed at a later Telecon with representatives from the Office of Clinical Pharmacology and Biopharmaceutics
- the 0.3 mg dose will not receive approval at this time

To-do items

	Item :	**Responsible Person** :	**Due Date:**
•	schedule Teleconference with Duramed	Ms. Moore	one week

2/17/99
Signature, minutes preparer

2/19/99
Signature, Chair

drafted: dm/01.26.98/n20992tc12299.doc

Concurrence:
TRumble 02.01.99/LRarick, MMann, Tvan der Vlugt, DLin, AParekh 02.05.99/MRhee 02.08.99
Concurrence not received from DSpell-LeSane

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/MRhee/DLin/AJordan/KRaheja/JLau
HFD-580/AParekh/KMeaker/LKammerman/DMoore

Meeting Minutes

Date: February 1, 1999 **Time:** 1:45 - 2:00 PM **Place:** Parklawn; Room 17B-43

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

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

Type of Meeting: Labeling

Sponsor: Duramed

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D. - Deputy Director, DRUDP (HFD-580)
Shelley Slaughter - Team Leader, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Dornette Spell-LeSane - Project Manager, DRUPD (HFD-580)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing and Communication (DDMAC; HFD-40)

Meeting Objective:
To discuss the labeling submitted on February 2, 1999 by Duramed.

Background: The labeling was submitted in response to the discussion between representatives of the FDA and Duramed in the Teleconference dated January 29, 1999.

Decisions:

- **DESCRIPTION** section
  - the phrase, "pregnant mare's urine" should be deleted from the first sentence
- **ADVERSE REACTIONS** section
  - the numbers associated with the bolded section heads, e.g., **Body as a Whole** . . . 60 (83), 39 (81) and 99 (83), should be deleted so that only the composite numbers remain in the table
  - the items in the table that have greater than 5% levels for the placebo, and less than 5% in the active arm should be deleted
  - the items with less than 5% frequency in the active arm could be placed in the less frequent events section or moved to the text
- the Black Box **WARNING** at the beginning of the label should also appear in a Black Box in the patient package insert

To-do items

Item :	Responsible Person :	Due Date:
• convey comments to sponsor	Ms. Moore	1-2 days

3/5/99
Signature, minutes preparer

3/11/99
Signature, Chair

drafted: dm/02.10.98/n20992tc2199.doc

Concurrence:
TRumble 02.26.99/DSpell-LeSane 03.01.99/LRarick, MMann 03.02.99
SSlaughter, LStockbridge 03.03.99

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/MRhee/DLin/AJordan/KRaheja/VJarugula
HFD-580/AParekh/KMeaker/LKammerman

Minutes of Telecon

Date: February 4, 1999 **Time:** 1:00 - 1:30 PM **Place:** Parklawn: Rm. 17B-43

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

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

External Constituent: Duramed

Type of Meeting: Labeling

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Dornette Spell-LeSane - Project Manager, DRUDP (HFD-580)
Mei-Ling Chen, Ph.D. - Director, Division of Pharmaceutical Evaluation II (DPE II), Office of Clinical Pharmacology and Biopharmaceutics (OCPB; HFD-870)
John Hunt - Deputy Director, Division of Pharmaceutical Evaluation II (DPE II; HFD-870)
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 changes submitted in the Labeling amendment dated February 2, 1999.

Discussion Items:
- the Cenestin tablet is designed to slowly release the synthetic conjugated estrogens over a period of several hours
- the unique characteristics of the formulation should be described in the labeling
- only apparent terminal elimination half-life values for the conjugated estrone and equilin were provided in the **Excretion** section of the label, but apparent terminal elimination half-life values for unconjugated estrone and equilin were not provided; the sponsor indicated that the unconjugated estrogens are lower in concentration in the body because they interconvert with the conjugated estrogens
- when the original ANDA was submitted to the FDA, an agreement was reached with OGD to not measure AUC to infinity because errors would be too great; AUC_{0-72} was calculated instead

Decisions Reached:

- the second and third sentences of the **Absorption** section of the label, should be revised as follows: "The Cenestin tablet releases the synthetic conjugated estrogens slowly over a period of several hours. Maximum plasma concentrations of conjugated and unconjugated estrogens are attained within 4 to 16 hours after oral administration."

Action Items:

• **Item**	**Responsible Party**	**Due Date:**
• submit revised label	Duramed	ASAP

Signature, recorder 3/10/99

Signature, Chair 3/11/99

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

Concurrences:

TRumble 02.26.99/JHunt 02.27.99/DSpell-LeSane 03.01.99
LRarick 03.02.99/MChen, JLau, AParekh 03.03.99

Minutes of Telecon

Date: February 4, 1999 **Time:** 1:35 - 1:55 PM **Place:** Parklawn: Rm. 17B-43

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

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

External Constituents: Duramed

Type of Meeting: Guidance

FDA Lead: Dr. David Lin

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Diane Moore - Project Manager, DRUDP (HFD-580)
Dornette Spell-LeSane - Project Manager, DRUDP
David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

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

Meeting Objective: To discuss the methods validation package for Cenestin.

Discussion Items:
- the specifications for content uniformity have been revised to include 17α-dihydroequilin; therefore, the validation package should be updated to match
- the dissolution methods validation should include equilin
- discrepancies in the package
  - the assay chromatogram for the test method for the conjugated estrogens solution on page 43 of the validation package and the assay chromatogram for the test method for tablets on page 153 appear to be the same; the assay from both the solution and tablet should be included in the methods validation package when the package is updated
- there is a discrepancy between the dissolution test solutions for the conjugated estrogens tablet, and the validation of the dissolution Mobil phase chromatogram for monobasic potassium phosphate (see pages 159 and 115 of validation package)

Decisions Reached:
- the name proposed by the Conjugated Estrogens Working Group, "synthetic conjugated estrogens A" is acceptable to the sponsor
- the proper conditions should be clarified for monobasic potassium phosphate
- the new validation report for solubility should be included in the update to the specifications
- content uniformity data is nearing completion and will be submitted for review when available

Action Items:

• **Item**	**Responsible Party**	**Due Date:**
• update methods validation package with chromatograms for GC test method for the conjugated estrogens and test method for tablets	Duramed	with updated package
• correct conditions for dissolution solutions	Duramed	ASAP
• submit content uniformity specifications	Duramed	ASAP

Signature, recorder 3/9/99

3/10/99
Signature, Chair

drafted: dm/2.15.99/n20992TCB2499.doc
cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/MRhee/DLin/DMoore/DSpelllesane

Concurrences:
TRumble 02.26.99/DLin 02.27.99/DSpell-LeSane 03.01.99