CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-992

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

DEC 04 1998

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	**20-992**
Compound:	Synthetic Conjugated Estrogens (Cenestin™)
Sponsor:	Duramed Pharmaceuticals, Inc.
Type of Submission:	New Drug Product
Date of Submission:	March 27, 1998
Reviewers:	S.W. Johnny Lau, R.Ph., Ph.D., Ameeta Parekh, Ph.D.

Background:

Duramed has submitted this NDA for oral synthetic conjugated estrogens (Cenestin™) as a 505 (b)(2) application for the treatment of postmenopausal vasomotor symptoms. The sponsor claimed that Cenestin™ has three primary estrogenic substances (sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate) and six minor estrogens. Five Cenestin™ tablet strengths (0.3, 0.625, 0.9, 1.25, and 2.5 mg) were proposed for approval in this NDA.

A clinical efficacy trial was conducted as a double-blind, 4-center, placebo-controlled study with 12 weeks treatment in 120 menopausal women (72 patients on active treatment, 48 on placebo). Efficacy assessment was based on reduction of moderate to severe vasomotor symptoms. All patients were started at 0.625 mg or placebo tablet and after 7 days of treatment, the active arm was titrated up to 2x0.625 tablet or down to 0.3 mg tablet. The number of patients studied at different doses were 2 at 0.3 mg, 7 at 0.625 mg and 54 at 2x0.625 mg daily doses. Five subjects were titrated back from 2x0.625 mg dose to 0.625 mg dose based on clinical response. The majority of the clinical data (54 patients i.e. 75% of patients on active treatment or 45% of the patients enrolled) is from the 2x0.625 mg regimen. The clinically tested 0.3 and 0.625 mg tablets are identical to the tablets proposed for marketing, except for the color change for the 0.3 mg tablet.

Summary:

The pharmacokinetics/biopharmaceutics section of this NDA includes 5 in vivo studies, namely, CN054, BN038, 930125, BN037 and 941817, addressing the single-dose pharmacokinetics and food-effect on the 2x0.625 mg and 1x1.25 mg tablets (ATTACHMENT-1). Total (conjugated + unconjugated) and free (unconjugated) estrone and equilin were measured in all studies. All studies are conducted in healthy postmenopausal nonsmoking women assay has been used for all in vivo studies. In vitro dissolution has been conducted for all strengths. The following comments highlight the clinical pharmacology and biopharmaceutics information:

Approval is being sought by the firm for all 5 strengths. The 0.3 and 0.625 strengths were tested clinically while the 0.9, 1.25 and 2.5 mg strengths were not included in the clinical trial.

1. The lower strength tablets, 0.3, 0.625 and 0.9 mg, are compositionally similar (total tablet weight 154.6 mg). The higher strength tablets, 1.25 and 2.5 mg, are also compositionally similar to each other (total weight 214.28 mg) but they are different from the lower strengths. Formulation details are in ATTACHMENT 2. For both the low and high strengths, the differences in active ingredients are made up by

2. The sponsor has conducted separate bioavailability studies on the 0.625 mg and 1.25 mg Cenestin tablet strengths. Studies BN038 and BN037 provide data for 2x0.625 mg and 1x1.25 mg tablets under fasted conditions, respectively, while Studies 930125 and 941817 provide data for corresponding strengths under fed conditions. The daily dose of 2x0.625 mg tablets has been studied clinically, but the 1.25 mg tablet strength was not included in the clinical trial.

   Given that i) the 0.625 mg and 1.25 mg tablets are not compositionally similar (see Comment #1 above), and ii) the clinical efficacy and safety data were based on only 0.625 mg tablets, of concern is the bioavailability of the 1.25 mg tablet strength relative to the 0.625 mg tablet strength that has been used in the clinical trial to document the efficacy and safety of Cenestin. To support approval of the 1.25 mg tablet, therefore, a bioavailability or bioequivalence study comparing the sponsor's 0.625 mg and 1.25 mg tablets is warranted.

3. From the studies submitted by the sponsor, only cross-study comparisons can be made between 0.625 mg and 1.25 mg tablets. Specifically, a cross-study comparison of fasted studies BN038 and BN037 showed that, on average, the 1.25 mg tablet may have up to 25% lower bioavailability (AUC and Cmax) than 2x0.625 mg tablets with respect to total or free equilin. A cross-study comparison of studies BN038 and 941817 (fasted arm) revealed that the 1.25 mg tablet had up to 46% and 38% higher AUC and Cmax, respectively, for free estrone while the pharmacokinetic parameter ratios for other measured estrogen moieties were within 20%. In contrast, the parameter ratios (details are in ATTACHMENT 3) were closer to unity for all parameters from the fed cross-study comparisons. The results of the two fasted cross-study comparisons do not seem to be consistent, and it is uncertain how reliable and predictable these comparisons might be for assessment of bioavailability for the 1.25 mg tablet strength compared to the 0.625 mg strength.

4. Study 941817, conducted as a 4-period crossover study, provides the food-effect information on the 1.25 mg tablet. While there was less than 10% change in AUCs, the study showed a higher Cmax with food (21% for total estrone, 29.5% for total equilin,

18.6% for free equilin). Study 930125 provides information on the bioavailability of 0.625 mg tablet of Cenestin taken with food, but a fasted arm was not included in this study. A cross-study comparison with Study BN038 revealed that, on average, both Cmax and AUC were higher with food (Cmax - 29% for total equilin, 36% for free estrone and 53% for free equilin; AUC - 50% for free estrone and 31% for free equilin). Pharmacokinetic measures and ratios for these fed/fasted comparisons are in ATTACHMENT 4. The clinical relevance of the observed differences due to the effect of food is unknown. It is noted however that in the pivotal clinical study Cenestin tablets were given without regards to meals.

5. The 2.5 mg dose/tablet has not been studied in any clinical setting for this NDA.

6. Waiver of bioavailability requirements for 0.3 and 0.9 mg strengths may be based on formulation composition proportionality and in vitro dissolution comparisons to the 0.625 mg strength that has been tested clinically.

   Only in vitro dissolution data for sodium estrone sulfate were provided in the NDA (see Item 7 below for method). These data demonstrated similar dissolution profiles between the 0.3, 0.625 and 0.9 mg tablet strengths ($f2 > 50$ when compared to the reference 0.625 mg tablet). The dissolution data are in ATTACHMENT 5. However, in addition to providing comparative dissolution data on sodium estrone sulfate for the 0.3, 0.625, and 0.9 mg tablet strengths, comparative dissolution profile data are also needed for sodium equilin sulfate for these tablet strengths in order to satisfy the bioavailability waiver requirements.

7. The proposed dissolution procedure is

   The sponsor has proposed the following specifications:

Time (hours)	Sponsor Proposed Limits for 0.3, 0.625, 0.9 mg Tablets	Sponsor Proposed Limits for 1.25 and 2.5 mg Tablets
2		
5		
8		
10		

   The proposed dissolution method and specifications for sodium estrone sulfate are acceptable.

8. It is noted that a multiple-dose study is currently ongoing to assess the pharmacokinetics and pharmacodynamics of Cenestin after daily dose of 0.625 mg for 3 months.

9. The to-be-marketed 0.3 mg tablet is identical to the clinically tested tablet except for the color. The sponsor has provided acceptable comparative dissolution data on sodium estrone sulfate (i.e., clinically tested tablet versus to-be-marketed tablet) but dissolution profile data are also needed for sodium equilin sulfate in order to assess the acceptability of the proposed tablet color change.

Labeling Comments:

The comments below pertain to the package insert.

ABSORPTION

The statement "The Cenestin formulation is designed to slowly release the synthetic conjugated estrogens over a period of several hours" should be deleted.

The next sentence starting with "Maximum plasma concentrations...." should be modified to "Cenestin maximum plasma concentrations...."

The table that contains the pharmacokinetic parameters should include total equilin and baseline-corrected total estrone for the 2x0.625 mg dose and be labelled as such. Also included should be concentration versus time profiles for unconjugated equilin and unconjugated estrone **not** corrected for baseline for the 2x0.625 mg dose and be labelled as such.

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

DISTRIBUTION

Rather than having a general range of t1/2 values, as proposed, specific half lives should be provided for the estrogen components of Cenestin.

Recommendations:

The Division of Pharmaceutical Evaluation II in the Office of Clinical Pharmacology and Biopharmaceutics has reviewed Section 6 of NDA 20-992. Based on the studies submitted, the Division has the following recommendations:

1. The clinically tested 0.625 mg tablet is identical to the to-be-marketed tablet and acceptable pharmacokinetic and biopharmaceutic information has been provided to meet the requirements outlined in 21 CFR 320.

2. The 0.3 and 0.9 mg tablets, which are compositionally similar to the 0.625 mg tablet strength (i.e., the differences in active ingredients are made up only by the small change in , 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.

3. 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 also need to be provided for sodium equilin sulfate.

4. The proposed to-be-marketed 1.25 mg and 2.5 mg Cenestin tablets are not compositionally similar to the 0.3, 0.625 or 0.9 mg Cenestin tablets. The 1.25 mg and 2.5 mg tablet strengths were not studied clinically. The provided information, or lack thereof, for the 1.25 mg and 2.5 mg tablets does not meet the requirements as outlined in 21 CFR 320 (see Comments #2 and 3 under Summary).

5. The sponsor's proposed in vitro dissolution method and specifications (see Comment #7 under Summary) for sodium estrone sulfate are acceptable.

Comments #2 and 3 together with Recommendations #2 and 3, and the labeling comments should be forwarded to the sponsor.

Johnny Lau 12/4/1998
S.W. Johnny Lau, R.Ph., Ph.D.

Ameeta Parekh 12/4/98
Ameeta Parekh, Ph.D.

Final Draft John Hunt 12/4/98

cc:
NDA 20992, HFD-870 (M. Chen, A.Parekh, S.W.J. Lau, Hunt), HFD-580 (S. Slaughters, T. van der Vlugt, D. Moore), CDR (B. Murphy for Drugs)

ATTACHMENT 1

F. Human Pharmacokinetics and Bioavailability Summary, Continued

Table 1

Study Information[1]	Studies				
	CN054	BN038	930125	BN037	941817
Study Type	Fasted- Pilot	Fasted	Effect-of-Food	Fasted	Effect-of-Food
Treatments	Cenestin™ 0.625 mg Premarin® 0.625 mg	Cenestin™ 0.625 mg Premarin® 0.625 mg	Cenestin™ 0.625 mg Premarin® 0.625 mg	Cenestin™ 1.25 mg Premarin® 1.25 mg	Cenestin™ 1.25 mg Premarin® 1.25 mg
Dose	2 x 0.625 mg	2 x 0.625 mg	2 x 0.625 mg	1 x 1.25 mg	1 x 1.25 mg
Cenestin™ Batch number	C-0005, C-0006	C-0005	C-0005	C-0015	C-0015
Study Design	3 treatment, 3 period, crossover, open, single dose, randomized, fasted overnight	2 treatment, 4 period, 4 sequence, crossover, open, single dose, randomized, fasted overnight	2 treatment, 2 period, crossover, open, single dose, randomized, fasted overnight, standard high-fat breakfast before dosing	2 treatment, 4 period, 4 sequence, crossover, open, single dose, randomized, fasted overnight	4 treatment, 4 period, 4 sequence, crossover, open, single dose, randomized, fasted overnight, fasting or standard high-fat breakfast before dosing
Number of Periods	3	4	2	4	4
Washout	1 week	2 weeks			
Number of Subjects	12 (all completed)	36 (34 completed)	18 (all completed)	36 (33 completed)	24 (22 completed)
Subject Population	Healthy, postmenopausal women, FSH ≥50mIU/mL, 17β-estradiol ≤20 pg/mL. Age ≥21 yr and ≤65 (60 for pilot) yr, non-smokers. Other inclusion/exclusion according to the Div. Of Bioequivalence Guidance for Conjugated Estrogens				
Confinement	84 hours per period				
Sampling Times	-48, -24, 0 (pre-dose), 1.5, 3, 4.5, 6, 7.5, 9, 10.5, 12, 14, 16, 24, 32, 40, 48, 60 and 72 hours				
Analytical Method					
Pharmacokinetic Parameters	C_{max}, T_{max}, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}72}$, ($AUC_{0\text{-}60}$ for pilot), k_{el}, and $t_{½}$, for total estrone (baseline corrected) and equilin. $AUC_{0\text{-}inf}$, k_{el}, and $t_{½}$ were not calculated for total estrone (as measured) and free estrone and equilin				
Statistical Methods	Descriptive statistics	ANOVA on bioequivalence parameters including an evaluation of error attributable to subjects, periods and treatments. Sequence effects were included as a between-subject error term			
ANDA Reference	Not filed	Submission date:9/26/94; Vol 7; page 1725		Submission date:10/9/96; Vol 2; page 67	

01 - 105

ATTACHMENT 2

D. Chemistry, Manufacturing, and Controls Summary

1. Drug Substance

a. Description

Synthetic Conjugated Estrogens Solution drug substance contains the major synthetic estrogenic ingredients and minor synthetic estrogenic substances identified in pregnant mare's urine. The major (primary) estrogenic substances include sodium estrone sulfate, sodium equilin sulfate and sodium 17α-dihydroequilin sulfate with estrone and equilin being considered the active drug ingredients. The 17α-dihydroequilin estrogenic substance is the third most abundant estrogen and is included in order to establish a 100% label claim for synthetic conjugated estrogens solution. The other minor estrogenic substances are sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17β-estradiol sulfate.

Active Ingredients (primary estrogens)
Sodium estrone sulfate
Sodium equilin sulfate
Sodium 17α-dihydroequilin sulfate

Excipients
Sodium 17α-estradiol sulfate
Sodium 17β-dihydroequilin sulfate
Sodium 17β-estradiol sulfate

Degradation Products
Sodium equilenin sulfate
Sodium 17α-dihydroequilenin sulfate
Sodium 17β-dihydroequilenin sulfate

1) Names

Active Ingredients (Primary Estrogens):

Estrone: 3-Hydroxyestra-1,3,5(10)-trien-17-one

Equilin: 3-Hydroxyestra-1,3,5(10),7-tetraen-17-one

17 α-Dihydroequilin: Estra-1,3,5(10),7-tetraene-3,17-diol

Continued on next page

1. Drug Substance, Continued

a. Description - continued

2) Physical and Chemical Characteristics

Synthetic Conjugated Estrogens are water soluble and

The molecular formulas and molecular weights are summarized below for the primary estrogens. The structural formulas for all estrogenic substances are also included on the next page.

Primary Estrogens: Molecular Formula and Weight

Estrogen	Molecular Formula	Molecular Weight Steroid	Molecular Weight Sulfate Ester
Estrone	$C_{18}H_{22}O_2$	270.37	371.42
Equilin	$C_{18}H_{20}O_2$	268.36	369.41
17 α-Dihydroequilin	$C_{18}H_{22}O_2$	270.37	371.42

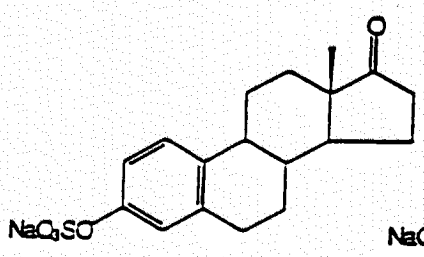
Continued on next page

1. Drug Substance, Continued

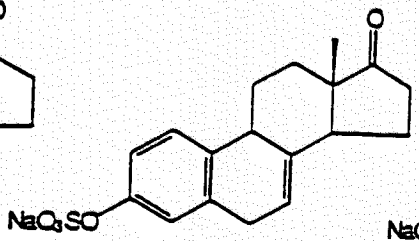
a. Description - continued

2) Physical and Chemical Characteristics - continued

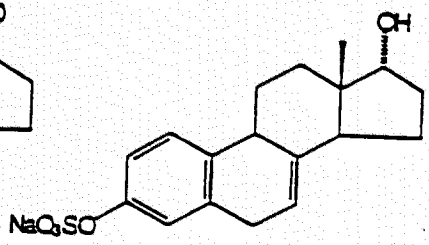
Synthetic Conjugated Estrogens Structural Formulas



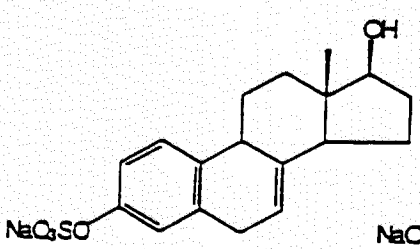
Estrone



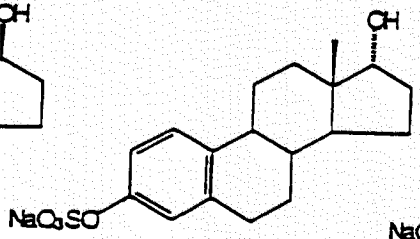
Equilin



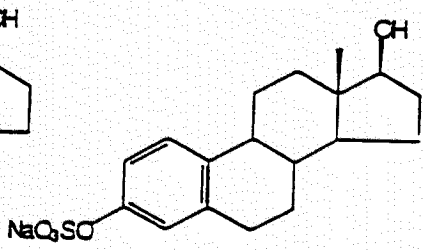
17α-Dihydroequilin



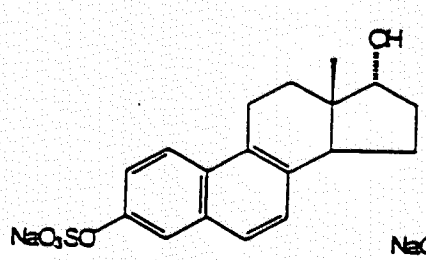
17β-Dihydroequilin



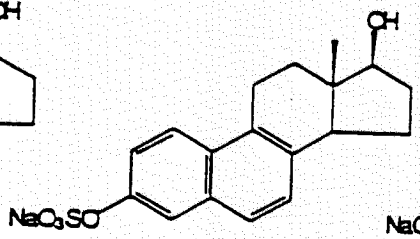
17α-Estradiol



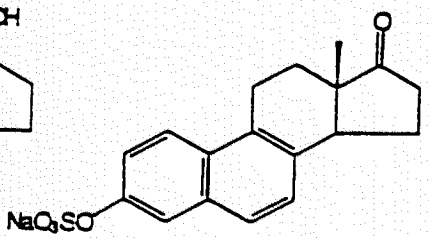
17β-Estradiol



17α-Dihydroequilenin



17β-Dihydroequilenin



Equilenin

Continued on next page

2. Drug Product

a. Composition and Dosage Form

Synthetic Conjugated Estrogens Tablets contain a blend of major synthetic estrogenic ingredients and minor synthetic estrogenic substances identified in pregnant mare's urine. The major (primary) estrogenic substances include sodium estrone sulfate, sodium equilin sulfate and sodium 17α-dihydroequilin sulfate. The other minor estrogenic substances are 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 proprietary name for the Synthetic Conjugated Estrogens Tablets is Cenestin™. This product is available in the following strengths with the corresponding identification characteristics:

Strength	Tablet Appearance
0.3 mg	Medium green, film-coated, round tablet debossed with 'dp' and '41'
0.625 mg	Red, film-coated, round tablet debossed with 'dp' and '42'
0.9 mg	White, film-coated, round tablet debossed with 'dp' and '43'
1.25 mg	Blue, film-coated, round tablets debossed with 'dp' and '44'
2.5 mg	Light blue, film-coated, round tablets debossed with 'dp' and '45'

Continued on next page

2. Drug Product, Continued

a. Composition and Dosage Form - continued

Proportionally similar composition of ingredients is demonstrated in the following list, which compares the ingredient levels of the 0.3 mg, 0.625 mg and the 0.9 mg tablets.

Synthetic Conjugated Estrogens Tablets
Quantitative Formula for the 0.3 mg , 0.625 mg and 0.9 mg Strengths

Component	Amount per Tablet		
	0.3 mg	0.625 mg	0.9 mg
Core Tablet:			
Synthetic Conjugated Estrogens[1]	0.30 mg	0.625 mg	0.90 mg
Lactose Monohydrate, NF			
Hydroxypropyl Methylcellulose USP			
Pregelatinized Starch, NF			
Magnesium Stearate, NF			
Alcohol			
Purified Water, USP			
Subcoat Coat:			
Ethylcellulose Aqueous Dispersion, NF			
Triethyl Citrate, NF			
Purified Water, USP			
Color Coat:			
Red			
Green			
White			
Water,			
Clear Coat:			
Clear			
Purified Water, USP			
Total Theoretical Tablet Weight:	154.60 mg	154.60 mg	154.60 mg

[1] Contains a target 125 g of Synthetic Conjugated Estrogens per each
[2] Removed during the manufacturing process.
[3] Weights indicate theoretical amount of residue

Continued on next page

2. Drug Product, Continued

a. Composition and Dosage Form - continued

Proportionally similar composition of active and inactive ingredients is demonstrated in the following list that compares the ingredient levels of the 1.25 mg and the 2.5 mg tablets.

Synthetic Conjugated Estrogens Tablets
Quantitative Formula for the 1.25 mg and 2.5 mg Strengths

Component	Amount per Tablet	
	1.25 mg	2.5 mg
Core Tablet:		
Synthetic Conjugated Estrogens[1]	1.25 mg	2.5 mg
Alcohol		
Hydroxypropyl Methylcellulose SP		
Lactose Monohydrate, Crystalline, NF		
Magnesium Stearate, NF		
Pregelatinized Starch, NF		
Purified Water, USP		
Subcoat Coat:		
Ethylcellulose Aqueous Dispersion, NF		
Triethyl Citrate, NF		
Purified Water, USP		
Color Coat:		
Blue		
Light Blue		
Purified Water, USP		
Clear Coat:		
Clear		
Purified Water, USP		
Total Theoretical Tablet Weight:	214.28 mg	214.28 mg

[1] Contains a target 125 g of Synthetic Conjugated Estrogens per eac
[2] Removed during the manufacturing process.
[3] Weight indicates theoretical amount of residue

Continued on next page

5. Drug Formulation, Continued

Table 1

Comparison of Formulations for Each of the Five Strengths of Cenestin™ Tablets

Component	0.3 mg	0.625 mg	0.9 mg	1.25 mg	2.5 mg
Tablet Core:					
Synthetic Conjugated Estrogens	0.30 mg[1]	0.625 mg[1]	0.90 mg[1]	1.25 mg[1]	2.5 mg[1]
Lactose Monohydrate NF, Crystalline					
Hydroxypropyl Methylcellulose					
Pregelatinized Starch					
Magnesium Stearate					
Alcohol					
Purified Water					
Film Coat:					
Ethylcellulose Aqueous Dispersion					
Triethyl Citrate					
Purified Water					
Color Coat:					
Green					
Red					
White					
Blue					
Light Blue					
Purified Water					
Clear Coat:					
Clear					
Purified Water					
Total Theoretical Film Coated Tablet Weight	154.60 mg[2]	154.60 mg[2]	154.60 mg[2]	214.28 mg[2]	214.28 mg[2]

[1] Synthetic Conjugated Estrogens amount is calculated at 125 g (target) of Synthetic Conjugated Estrogens sulfate + sodium equilin sulfate assay results, the Based upon the sodium estrone to provide the theoretical amount of conjugated estrogens.

[2] Removed during the manufacturing process.

[3] Weights indicate theoretical amount of coating