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RESEARCH**

APPLICATION NUMBER:

20-992/S-016

ADMINISTRATIVE DOCUMENTS

NDA 20-992/S-016

EXCLUSIVITY SUMMARY for NDA # 20-992 SUPPL # 16
Trade Name Cenestin Generic Name synthetic conjugated
estrogen
Applicant Name Duramed Pharmaceuticals, Inc
HFD- 580
Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

- a) Is it an original NDA? YES/___/ NO /X/
- b) Is it an effectiveness supplement? YES /X/ NO /___/

If yes, what type(SE1, SE2, etc.)? SE1

- c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / / NO / /

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-992 Cenestin

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA 20-992/S-016

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / X / NO / ___ /

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or

2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / X / NO / ___ /

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES / ___ / NO / X /

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES / ___ / NO / ___ /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO / X /

If yes, explain:

(c) If the answers to (b) (1) and (b) (2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # "A Double-Blind, Randomized, Parallel, Placebo-Controlled Clinical study to Compare the Effects of 0.3 mg, once daily, Synthetic conjugated Estrogens, A (Cenestin® vs. Placebo Tablets on Vulvovaginal Atrophy in Healthy Postmenopausal Women)""DPI00-005

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO / X /

Investigation #2 YES /___/ NO /___/

sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- (a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # 53,731 YES / X / ! NO / ___ / Explain:
!
!
!
!

Investigation #2 !
!
IND # _____ YES / ___ / ! NO / ___ / Explain:
!
!
!
!

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES / ___ / Explain _____ ! NO / ___ / Explain _____
!

!

!

Investigation #2	!	
	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
	!	
_____	!	_____
	!	
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

 Signature of Preparer
 Title:

Date

Signature of Office or Division Director

Date

cc:

NDA 20-992/S-016

Archival NDA 20-992

HFD-580/Division File

HFD-580/Spell-leSane

HFD-093/Mary Ann Holovac

HFD-104/PEDS/T.Crescenzi

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Dornette Spell-LeSane
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Cenestin®
Addendum to Team Leader Secondary Review

NDA: 20-992/S-016

Drug: Cenestin® (Synthetic conjugated estrogens, A)

Indication: Treatment of vulvar and vaginal atrophy associated with the menopause.

Dosage/Form/ Route: 0.3 mg synthetic conjugated estrogens, A, oral tablet

Applicant: Duramed Subsidiary of Barr Laboratories, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213

Original Submission Date: August 16, 2001

Primary Review Completed: June 10, 2002

Secondary Review Completed: June 12, 2002

Date of Memorandum: June 20, 2002

The _____ facility in _____ was inspected June 17-19, 2002. Based on the inspection of all of the manufacturing sites cited in the NDA, including the _____ facility in _____, the Office of Compliance has issued an overall Acceptable recommendation. All of the Chemistry, Manufacturing and Controls requirements have now been satisfactorily addressed and the NDA may be approved. The recommendation of the clinical reviewer was that the NDA could be approved. I recommend that this NDA now be approved.

Shelley R. Slaughter, M.D., Ph.D.
Reproductive Medical Team Leader

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/s/

Shelley Slaughter
6/20/02 04:19:53 PM
MEDICAL OFFICER

Daniel A. Shames
6/20/02 04:39:15 PM
MEDICAL OFFICER

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**Cenestin®
Team Leader Secondary Review**

NDA: 20-992/S-016

Drug: Cenestin® (Synthetic conjugated estrogens, A)

Indication: Treatment of vulvar and vaginal atrophy associated with the menopause.

Dosage/Form/Route: 0.3 mg synthetic conjugated estrogens, oral tablet.

Applicant: Duramed Subsidiary of Barr Laboratories, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213

Original Submission Date: August 16, 2001

Review Completed: June 10, 2002

Date of Memorandum: June 12, 2002

Background

Cenestin® (synthetic conjugated estrogens, A) was approved on March 24, 1999 for the treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause. It is an oral drug product, administered in tablet form, that contains the following nine estrogenic substances in combination: sodium estrone sulfate, sodium equilin sulfate and sodium 17 α -dihydroequilin sulfate, sodium 17 α -estradiol sulfate, sodium 17 β -dihydroequilin sulfate, sodium 17 α -dihydroequilenin sulfate, 17 β -dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17 β -estradiol sulfate. Three dosage strengths of Cenestin® are approved, 0.625 mg, 0.9 mg, and 1.25 mg.

With this supplemental application, the Sponsor is seeking an indication for the treatment of vulvar and vaginal atrophy for the 0.3 mg Cenestin® dosage strength.

Regulatory History:

NDA 20-992 for Cenestin® 0.625 mg, 0.9 mg and 2 x 0.625 mg tablets was approved on March 24, 1999 for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause. Protocol #366, submitted with NDA 20,992/S-000, presented data from a randomized, double-blind, placebo-controlled dose titration study conducted over a 12-week period. One hundred and twenty subjects (120) were randomized to a single 0.625 mg Cenestin® tablet (72 subjects) or placebo (48 subjects). After seven days of treatment, if adequate clinical response was not achieved (defined as a 50% reduction in the baseline number of moderate-to-severe vasomotor symptoms), the daily dose of Cenestin® or placebo could be increased to two tablets of Cenestin® or two tablets of placebo. No additional increase in dose was allowed during the 12-week study duration. However, at any time during the 12 weeks of treatment, the dose could be lowered to a minimum daily dose of a single 0.3 mg tablet of synthetic conjugated estrogens, A or placebo if subjects exhibited signs of study drug intolerance such as breast tenderness, bloating/water retention or persistent headache and/or nausea.

The data submitted in NDA 20-992/S-000 confirmed the safety and efficacy of a single 0.625 mg per day tablet and the 2 x 0.625 mg per day tablets for the treatment of moderate-to-severe vasomotor symptoms. There was insufficient data submitted to assess the safety and efficacy of the 0.3 mg per day dosage strength. Because the 0.9 mg per day Cenestin® dosage strength, not included in Study 366, was bracketed by the approved 0.625 mg and 2 x 0.625 mg dosage strengths, approval of 0.9 mg Cenestin® dosage strength was also granted.

On January 28, 2000, a single 1.25 mg dosage strength tablet was approved based on the results of a bioequivalence study showing that the reformulated single 1.25 mg Cenestin® tablet was bioequivalent to 2 x 0.625 mg Cenestin® tablets.

Protocol DPI00-005 was submitted for review to IND 53,731 on October 12, 2000. The Division sent comments on the protocol to Duramed on January 18, 2001. Included in the January 18, 2001 letter was the recommendation (in accord with proposed revisions to the 1995 Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women) that pretreatment and end-of-study subject self assessment of symptoms be evaluated and that the endpoint for efficacy include improvement in this self assessment. The Division also specified that baseline and endometrial biopsies should be performed to assess safety, instead of transvaginal ultrasounds which had been proposed by the Sponsor. The Sponsor indicated that 60 subjects had already been randomized and started in the study at the time of receipt of the Division's letter of January 18, 2001. As the study was well underway, the Division did not insist that subject-self assessment of symptoms be included in the efficacy analyses. The Sponsor did modify the protocol to incorporate an end-of-study endometrial biopsy into the study design when the end-of-study TVUS double-wall endometrial thickness was reported ≥ 4 mm.

On October 26, 2001, the Agency was notified that Duramed Pharmaceuticals, Inc. was now a subsidiary of Barr Laboratories, Inc.

NDA 20-992/S-016 was received August 17, 2001. It was filed on October 17, 2001.

Clinical Efficacy and Safety

Efficacy for Study DPI00-0005

Study DPI00-0005 was a randomized, double blind, placebo-controlled, multi-center (5 centers) study conducted in the U.S. Seventy-one (71) healthy postmenopausal women (12 months of spontaneous amenorrhea or surgically menopausal) between the ages of 30 and 80 were randomized to receive placebo or 0.3 mg Cenestin®. Treatment duration was 16 weeks.

Three of the five participating center (centers 1,2, and 4) enrolled 86% (61/71) of the treated subjects. Data from centers were not pooled. Per the sponsor, there was no center effect on treatment. One subject (Subject 066 at center # 3) did not receive any study medication and was excluded from the efficacy analysis

The primary outcome variable was the difference between the 0.3 mg synthetic conjugated estrogens, A and placebo groups in the change in the Maturation Index (MI) between pretreatment (week -2) and the end-of-treatment (week 16). Secondary outcome variables included change in the MI from pretreatment (week -2) to each interim week visit (4, 8, and 12)

and changes from week -2 to end-of-treatment (week 16) in vaginal pH, serum lipid profile, serum markers of cardiovascular disease risk and bone resorption.

The intent-to treat analysis for maturation index is presented in table 1

Table 1
Summary of Maturation Index Results for Study DPI00-005, Intent-to-Treat Population

Cell Type	Study Week	Cenestin® N = 37		Placebo N = 34		p-value
		Mean (SD)	Mean Change (SD)	Mean (SD)	Mean Change (SD)	
Parabasal (%)	-2	23.0 (22.2)		20.2	(20.7)	
	4	5.4 (13.5)	-18.8 (21.0)	18.9 (19.9)	-1.3 (17.5)	0.002
	8	1.4 (4.5)	-22.9 (22.0)	17.7 (19.2)	-5.7 (13.2)	0.0011
	12	1.3 (3.4)	-22.3 (21.9)	19.2 (20.8)	-2.1 (17.4)	0.0001
	16	1.6 (1.6)	-21.5 (22.9)	15.7 (19.6)	-4.5 (15.0)	0.0004
Intermediate (%)	-2	74.9 (21.6)		78.3 (20.0)		
	4	81.5 (14.2)	7.7 (18.7)	76.3 (18.2)	-2.1 (17.0)	0.0207
	8	85.5 (10.9)	11.7 (21.1)	77.4 (17.5)	1.3 (14.8)	0.0410
	12	84.9 (13.7)	10.5 (22.7)	75.6 (20.3)	-1.4 (19.5)	0.0248
	16	82.5 (13.8)	7.6 (23.7)	79.0 (17.3)	0.7 (15.13)	0.1166
Superficial (%)	-2	2.1 (2.52)		1.6 (2.8)		
	4	13.0 (11.87)	11.1 (11.3)	4.8 (8.0)	3.4 (7.6)	0.0019
	8	13.1 (11.04)	11.2 (10.3)	4.9 (5.7)	5.7 (9.1)	0.0053
	12	13.8 (14.05)	11.8 (12.9)	5.2 (8.5)	3.6 (7.9)	0.0116
	16	15.9 (13.94)	13.8 (13.4)	5.3 (7.3)	3.8 (7.4)	0.0002
Maturation Index Score	-2	39.5 (11.6)		40.7 (10.9)		
	4	53.8 (10.51)	14.6 (14.9)	42.9 (12.1)	2.3 (10.5)	<0.0001
	8	55.9 (6.41)	16.7 (13.6)	43.6 (11.2)	3.5 (8.3)	=0.0002
	12	55.6 (7.56)	17.0 (13.9)	42.98 (12.3)	2.8 (19.4)	<0.0001
	16	57.2 (7.4)	17.7 (14.5)	44.8 (11.9)	4.1 (9.1)	<0.0001

Source Statistical Review Table 6, Summary of Maturation Index Analyses, Intent to Treat Population

The results of Study DPI00-0005 demonstrates that treatment with Cenestin® 0.3 mg resulted in a statistically significant (p=0.0001) reduction from baseline in vaginal parabasal cells and a statistically significant (p=0.0116) increase from baseline in superficial vaginal cells when compared to placebo at week 12 (the specified endpoint assessment time period per the proposed revised HRT Guidance document). These statistically significant changes are maintained to study end at week 16.

Vaginal pH decreased significantly (p=0.0001) from week -2 to week 16 in the synthetic conjugated estrogens treatment group compared to the placebo treatment group (mean change - 0.97 ± 1.00 and 0.10 ± 0.57, respectively). Vaginal pH was only assessed at week 16. See Table 2.

Table 2: Mean (\pm SD) Vaginal pH Assessments Evaluated at Baseline and Week 16, Intent-to-Treat Population

Study Week	Treatment Group		p-Value
	Cenestin®	Placebo	
	N = 37	N = 34	
Week -2 (Pretreatment)	6.20 \pm 0.86	6.03 \pm 0.82	0.4023*
	N = 36	N = 31	
Week 16 (End-of-Study)	5.19 \pm 0.75	6.13 \pm 0.81	0.0001**
Change***	0.97 \pm 1.00	0.10 \pm 0.57	

The proposed revisions to the HRT Guidance Document specifies that in the evaluation of efficacy for the treatment of vulvar and vaginal atrophy drug products should demonstrate a statistically significant improvement vs. placebo for maturation index, vaginal pH and the symptom that the subject identifies as most bothersome to them. As stated above, the Sponsor was not informed of the need to perform subject-self symptom analysis until enrollment into the study was 85% complete. Therefore, the Sponsor was not required to demonstrate that treatment with the drug product resulted in improvement in self-reported symptoms. A statistically significant difference vs. placebo was demonstrated for both vaginal Maturation Index and vaginal pH.

Safety for Study DPI00-0005

Seventy-one subjects are included in the safety database in Study DP100-005. Thirty-seven (37) subjects received 0.3 mg synthetic conjugated estrogens, A (52%, 37 of 71 subjects), and 34 subjects received placebo (48%, 34 of 71 subjects). The mean duration of exposure to study medication (calculated by the Statistical Reviewer) was 131 days for synthetic conjugated estrogens, A and 127 days for placebo.

There were no deaths and no serious adverse events reported during the study. Eight subjects (11%, 8 of 71 subjects) discontinued Study DPI00-005 (3 subjects in the synthetic conjugated estrogens, A group and 5 subjects in the placebo group). Two of the eight subjects (one on 0.3mg Cenestin® and one on placebo) who discontinued did so because of an adverse event.

Eighty-three percent (83%, 59 of 71 subjects) of subjects reported treatment emergent adverse events (TEAE). In subjects treated with 0.3 mg Cenestin® 86.5% (32 of 37 subjects) reported at least one adverse event. Twenty-seven (27) of 34 subjects on placebo (79.4%) reported TEAEs. The only significant difference in the incidence of TEAEs between placebo and Cenestin® groups was an increase in urinary tract infection in the placebo treatment group (18% placebo vs. 0% Cenestin®). The most commonly reported TEAEs were leukorrhea (32% in 0.3 mg Cenestin® vs. 15% placebo), vaginitis (24% 0.3 mg Cenestin® vs. 5% placebo) and headache (11% in 0.3mg Cenestin® vs. 21% in placebo). Three instances each of thickened endometrium (> 4mm) on transvaginal ultrasound were noted in the 0.3 mg Cenestin® and the placebo treatment group. Endometrial biopsy was attempted on each of these six subjects. Two of the subjects (both on 0.3 mg Cenestin®) had a tissue diagnosis of proliferative endometrium. One subject on 0.3 mg Cenestin® had a tissue diagnosis of “strips of benign superficial epithelium suggestive of an atrophic endometrium”. One placebo subject had a tissue diagnosis of atrophic endometrium. The remaining two subjects with endometrial thickness > 4 could not be sampled because of

cervical stenosis. These two subjects had both received placebo treatment. The NDA did not present information regarding referral or additional endometrial evaluations of these two subjects. Prometrium 300 mg/day was to be dispensed to all subjects with a uterus.

The Sponsor submitted the 4-Month Safety Update on May 16, 2002 and the Second Safety Update on May 16, 2002. No additional studies with 0.3 mg Cenestin® had been initiated, and no additional safety data had been collected since the NDA submission. No further information was provided on the two placebo subjects with cervical stenosis who had exhibited an increased endometrial thickness (> 4mm) on transvaginal ultrasound. Overall, however, the safety program for 0.3 mg Cenestin® was appropriate and the safety profile is acceptable.

Dosing, Regimen, and Administration

The 0.3 mg dosage strength of Cenestin® is the only dose sought for the treatment of vulvar and vaginal atrophy. It is expected that this would be the lowest effective dose. The 0.625 mg, 0.9 mg, and 1.25 mg dosage strengths of Cenestin® are currently approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause. In the original NDA 20-991/S-000, no information was presented for the treatment of vulvar and vaginal atrophy.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

In compliance with DSI recommendations (regarding clinical inspections to support efficacy supplements) at the time of filing of this NDA, no DSI inspections of clinical sites were requested by Medical Officer for this efficacy supplement

Clinical Pharmacology and Biopharmaceutics

The pharmacokinetic and biopharmaceutics requirements for the 0.3 mg dose of Cenestin® were reviewed in NDA 20-992/S-000 and found to be acceptable. No new pharmacokinetic or bioavailability data was presented from Study DPI00-005

From the Office of Clinical Pharmacology and Biopharmaceutics perspective, the NDA is acceptable for approval.

Chemistry Manufacturing and Controls (CMC)

The only change made in this efficacy supplement concerning the drug substance is the revision of the drug substance organic volatile impurity acceptance criteria. The proposed revisions were acceptable. There are no proposed changes in the raw materials used, raw materials specifications, manufacturing process, in-process controls and tests, or packaging components affecting the drug product for this efficacy supplement. The only new information with respect to the drug product includes revision of the drug product specification, a summary of the production history to date, updated stability data and proposed drug product expiration date based on the updated stability data. This information was all deemed satisfactory.

A categorical exclusion for the Environmental Assessment was submitted under 21 CFR § 25.31. The Sponsor states that no extraordinary circumstances exist as per 21 CFR § 25.21 which would require the inclusion of an Environmental Assessment despite qualification for a categorical exclusion. This was deemed satisfactory. The method validation and the labeling were all deemed satisfactory.

An EER was submitted on December 28, 2001 for the sites except for the additional Barr packaging site, which was submitted on May 17, 2002. The overall recommendation from the Office of Compliance is pending inspection of the ~~facility in~~ facility in

From Chemistry, Manufacturing and Controls point of view the application can be approved pending final acceptable c GMP inspection of all manufacturing facilities.

Product Name

Cenestin® is the registered tradename.

Pre-clinical Pharmacology and Toxicology

Cenestin® is approved at dosage strengths (0.625 mg, 0.9 mg and 1.25 mg) higher than the 0.3 mg dosage strength sought in this application, therefore a Pre-clinical Pharmacology and Toxicology review was not required

Discussion and Conclusions

The data collected in Study DPI00-005, confirm the efficacy and safety of Cenestin® 0.3 mg in the treatment of vulvar and vaginal. It is recommended that this application be approved pending a final acceptable cGMP inspection of all manufacturing sites.

At the time of this memorandum the Sponsor is reviewing the labeling with recommendations from the Division. Labeling changes suggested by the Division would make this label consistent with other approved estrogen replacement products. The final agreed upon label will be included with the Action Package.

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

cc: Division File NDA 21-239
D. Shames, MD
T. van der Vlugt, MD
K. Meaker.
D. Spell-Lesane
S. Slaughter, M.D., Ph.D.

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Internal Meeting Minutes

Date: June 4, 2002 Time: 2:00 - 2:20 PM Place: Parklawn; Room 17B-43

NDA: 20-992/S-016 Drug Name: Cenestin® (synthetic conjugated estrogens, A)
Tablets 0.3 mg

Type of Meeting: 10 month Status meeting

Indication: relief of vulvar and vaginal atrophy associated with the menopause.

Sponsor: Duramed (a subsidiary of Barr Laboratories, Inc.)

FDA Lead: Dr. Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Participants:

Shelley Slaughter, M.D., Ph.D., Team Leader, Division of Reproductive and Urologic Drug Products DRUDP (HFD-580)

Theresa van der Vlugt, M.D., M.P.H., Medical Officer, DRUDP (HFD-580)

Dornette Spell-LeSane, NP-C, Project Manager, (DRUDP; HFD-580)

David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Moh-Jee Ng, M.S., Statistician, Division of Biometrics II (DBII; HFD-715)

Meeting Objective:

To discuss the status of the reviews for the 0.3 mg strength of Cenestin for the relief of vulvar and vaginal atrophy associated with the menopause.

Background:

Supplement 16 was submitted on August 16, 2001, received on August 17, 2001. The 10-month User Fee Goal date is June 17, 2002.

Discussion:

Clinical

- draft review with Team Leader
- final labeling comments have been incorporated into the clinical review
- recommend approval

Chemistry, Manufacturing and Quality Control

- chemistry review is in draft
- the efficacy supplement may be approved pending final acceptable cGMP inspection of all manufacturing facilities cited; specifically, decision on the drug substance manufacturer is pending
- inspections scheduled for June 13, 2002

Pharmacology

- no review is required for this supplement

Clinical Pharmacology and Biopharmaceutics

- the pharmacokinetic information has been reviewed in the original NDA ; the sponsor provided appropriate information to satisfy bioavailability requirements for 0.3 mg, 0.625 mg and 2 x 0.625 mg; no additional pharmacokinetic data was submitted to this efficacy supplement for review

Biometrics

- biometrics review is completed
- the primary and secondary endpoints were met with a statistical difference

Action items:

- PM to draft Action Letter
- PM to send draft labeling comments to sponsor by June 10, 2002

Signature, minutes preparer

Signature, Chair

HFD-580:NDA 20992/S016

Drafted: 6.5.02

Concurrence:

Lin, Slaughter, Van der Vlugt, 6.5.02

Final: 6.17.02

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/s/

Shelley Slaughter
6/17/02 03:43:54 PM
I concur.

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Meeting Minutes

Date: February 19, 2002 **Time:** 2:00 - 2:10 PM **Place:** Parklawn; Room 17B-43

NDA: 20-992/S-016 **Drug Name:** Cenestin® (synthetic conjugated estrogens, A) Tablets
0.3 mg

Type of Meeting: 6 month Status meeting

Indication: relief of vulvar and vaginal atrophy associated with the menopause.

Sponsor: Duramed

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:

Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)

Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)

David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Division of Pharmaceutical Evaluation II (DPBII)
@ DRUDP (HFD-580)

Moh-Jee Ng, M.S. – Statistician, Division of Biometrics II (DBII; HFD-715)

Meeting Objective:

To discuss the status of the reviews for the 0.3 mg strength of Cenestin for the relief of vulvar and vaginal atrophy associated with the menopause.

Background:

Supplement 16 was submitted on August 16, 2001, received on August 17, 2001. The 10-month User Fee Goal date is June 17, 2002.

Decisions:

- Clinical
 - review pending
- on October 17, 2001, the following were requested from the sponsor:
 - a table showing the mean percentages of parabasal, intermediate, and superficial cells at baseline and Week 12, and the mean change from Baseline to Week 12
 - a table showing the mean vaginal pH assessment at Baseline and at Week 12 and Week 16 was requested from the sponsor; no vaginal pH assessment was performed at Week 16
 - a proposed annotated label
 - a benefit/risk relationship discussion for the supplement
- the information was submitted on November 1, 2001
- DSI inspection waived
- Chemistry, Manufacturing and Quality Control

- review pending
- EES inspection pending
- Pharmacology
 - review pending
- Clinical Pharmacology and Biopharmaceutics
 - review pending
- Statistics
 - review pending; SAS data sets for up to Week 12 were received from the sponsor
- Regulatory
 - final reviews are due to the Medical Team Leader by June 3, 2002

Action items:

Item:	Responsible Person:	Due Date:
• submit consult to DDMAC and DSRCS for labeling reviews	Mrs. Moore	1-2 months

Signature, minutes preparer

Signature, Chair

drafted: dm/2.27.02/N20992SM21902.doc

Concurrence:

A.Parekh, T.van der Vlugt 3.4.02/D.Lin, S.Slaughter 3.5.02/M.Ng 3.6.02

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/s/

Diane V. Moore
3/6/02 08:41:46 AM

Shelley Slaughter
3/11/02 11:29:14 AM
I concur.

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Meeting Minutes

Date: October 9, 2001 **Time:** 2:00 - 2:40 AM **Place:** Parklawn; Room 17B-43

NDA: 20-992/S-016 **Drug Name:** Cenestin® (synthetic conjugated estrogens, A) Tablets

Type of Meeting: Filing

Indication: relief of vulvar and vaginal atrophy associated with the menopause.

Sponsor: Duramed

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:

Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)

Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)

Diane Moore - Project Manager, Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)

Eric Duffy, Ph.D. – Director, Division of New Drug Chemistry II (DNDC II; HFD-820)

David Lin, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Division of Pharmaceutical Evaluation II (DPBII)
@ DRUDP (HFD-580)

Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Moh-Jee Ng, M.S. – Statistician, Division of Biometrics II (DBII; HFD-715)

Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing, Advertising and
Communications (DDMAC; HFD-42)

Meeting Objective:

To discuss the fileability of Duramed's Supplemental NDA to add a 0.3 mg strength of Cenestin for the relief of vulvar and vaginal atrophy associated with the menopause.

Background:

Supplement 16 was submitted on August 16, 2001, received on August 17, 2001. The 10-month User Fee Goal date is June 17, 2002.

Decisions:

- Clinical
 - Fileable
- DSI
 - the DSI inspection can be waived for this efficacy supplement at this time; if future review of the supplement indicates a need for a DSI audit, the request will be made at that time
- Chemistry, Manufacturing and Quality Control
 - Fileable; the 0.3 mg strength tablet was acceptable in the review of the original NDA; additional stability data were submitted in this application

- the sponsor has requested a waiver for the environmental assessment; the Drug Master Files will be reviewed
- Pharmacology
 - Fileable per pharmacology reviewer
- Clinical Pharmacology and Biopharmaceutics
 - Fileable
 - the lots of 0.3 mg strength used for the trial submitted in this application are the same as were used in the original approved NDA submission
 - the dissolution specifications need to be reviewed for acceptance criteria
- Statistics
 - Fileable; SAS data sets for up to Week 12 should be requested from the sponsor
- Regulatory
 - Fileable
 - final reviews are due to the Medical Team Leader by June 3, 2002

Action items:

Item:	Responsible Person:	Due Date:
• request a table showing the mean percentages of parabasal, intermediate, and superficial cells at baseline and Week 12, and the mean change from Baseline to Week 12	Ms. Moore	1 week
• request a table showing the mean vaginal pH assessment at Baseline and at Week 12 and Week 16	Ms. Moore	1 week
• request SAS data sets for up to Week 12	Ms. Moore	1 week

Signature, minutes preparer

Signature, Chair

Post meeting addendum: On October 17, 2001, the sponsor was requested to submit the following to the supplemental application:

- a table of percentages of parabasal, intermediate and superficial cells at baseline and Week 12 and the mean change from Baseline to Week 12
- a table showing the mean vaginal pH assessment at Baseline and at Weeks 12 and 16
- SAS data sets for up to Week 12
- a proposed annotated label
- a benefit/risk relationship discussion for the supplement

drafted: dm/10.15.01/N20992FM10901.doc

Concurrence:

T.Rumble, D.Lin, M.Ng, T.van der Vlugt 10.16.01/A.Parekh 10.17.01/S.Slaughter 10.18.01

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/s/

Diane V. Moore
10/18/01 12:07:26 PM

Shelley Slaughter
10/18/01 12:16:23 PM

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Division of Reproductive and Urologic Drug Products

ADMINISTRATIVE REVIEW OF APPLICATION

Application Number: 20-992/S-016

Name of Drug: Cenestin® (synthetic conjugated estrogens, A) tablets

Sponsor: Duramed Pharmaceuticals, Inc.

Material Reviewed

Submission Date: August 16, 2001

Receipt Date: August 17, 2001

Filing Date: October 17, 2001

User-fee Goal Date: June 17, 2001

Proposed indication: Vulvar and Vaginal Atrophy associated with the menopause

Other Background Information:

Review

PART I: OVERALL FORMATTING^a

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		
2. Form FDA 356h (original signature)	X		
a. Reference to DMF(s) & Other Applications	X		
3. Patent information & certification	X		
4. Debarment certification (note: must have a definitive statement)	X		
5. Financial disclosure	X		
6. Comprehensive Index	X		
7. Pagination	X		
8. Summary Volume		X	
9. Review Volumes	X		CMC and CLINSTAT sections submitted
10. Labeling (PI, container, & carton labels)	X		
a. unannotated PI	X		
b. annotated PI		X	Annotated labeling has been requested from the sponsor
c. immediate container	X		

d. carton	X		
e. foreign labeling (English translation)			N/A
11. Foreign marketing History			N/A
12. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		
13. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		

Y=Yes (Present), N=No (Absent)

PART II: SUMMARY^b

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		
2. Summary of Each Technical Section	X		
a. Chemistry, Manufacturing, & Controls (CMC)	X		
b. Nonclinical Pharmacology/Toxicology		X	No section submitted
c. Human Pharmacokinetic & Bioavailability		X	No section submitted
d. Microbiology		X	No section submitted
e. Clinical Data & Results of Statistical Analysis	X		
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies		X	Comments provided in the final report
4. Summary of Safety		X	See Final report
5. Summary of Efficacy		X	See Final report

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS^c

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		
2. Controlled Clinical Studies	X		
a. Table of all studies	X		
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		

c. Optional overall summary & evaluation of data from controlled clinical studies		X	
3. Integrated Summary of Efficacy (ISE)	X		Only one study submitted
4. Integrated Summary of Safety (ISS)	X		Only one study submitted
5. Drug Abuse & Overdosage Information		X	N/A this drug is not a potential drug abuse problem
6. Integrated Summary of Benefits & Risks of the Drug	X		Only one study submitted
7. Gender/Race/Age Safety & Efficacy Analysis Studies	X		Table 11.2-1

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population	X		Requested a waiver of pediatric study
2. Diskettes	X		
a. Proposed unannotated labeling in MS WORD 8.0	X		
b. Stability data in SAS data set format	X		August 29, 2001 submission
c. Efficacy data in SAS data set format	X		August 29, 2001 submission
d. Biopharmacological information & study summaries in MS WORD 8.0		X	N/A no biopharmacological studies submitted
e. Animal tumorigenicity study data in SAS data set format		X	N/A Higher doses previously approved
3. User-fee payment receipt		X	User fee waived; the dose and indication were previously requested in the original NDA submission and not approved.

Y=Yes (Present), N=No (Absent)

a"GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

b"GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS" (FEBRUARY 1987).

c"GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS" (JULY 1988).

Additional Comments:

Conclusions

Fileable from a regulatory perspective.

Name
Regulatory Health Project Manager

cc:

Original NDA

HFD-580/Div. Files

HFD-580/CSO/D.Moore

HFD-580/SAllen/MMann/SSlaughter/MRhee/AJordan/AParekh/LKammerman

draft:

r/d initials

final:

ADMINISTRATIVE REVIEW

Revised 3/22/00

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/s/

Diane V. Moore
10/17/01 04:39:30 PM
CSO

Terri F. Rumble
10/17/01 04:47:59 PM
CSO
I concur.

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Filing Memorandum
Division of Reproductive and Urologic Drug Products

NDA 20-992/S-016

Trade Name:	Cenestin® Tablets
Generic Name:	Synthetic conjugated estrogens, A
Sponsor:	Duramed Pharmaceuticals, Inc. 5040 Duramed Drive Cincinnati, Ohio 45213
Classification:	3S
Submission Date:	August 16, 2001
Date Received:	August 17, 2001
Indication:	Treatment of vulvar and vaginal atrophy associated with the menopause.
Related Submission:	IND 53,731
User Fee Goal Date:	June 17, 2002
Division Goal Date:	May 17, 2002
Team Leader Goal Date:	April 30, 2002
Filing Meeting date:	October 9, 2001
Medical Reviewer:	Theresa H. van der Vlugt, M.D., M.P.H.

Submission Resume

NDA 20-992/S-000 for Cenestin® was approved on March 24, 1999 for the treatment of moderate-to-severe vasomotor symptoms (MSVS) in a postmenopausal population. The approved dosing regimen allowed for a range of doses including the 0.625 mg tablet, the 0.9 mg tablet, and 2 x 0.625 mg tablets. The original NDA submission included the 0.3 mg synthetic conjugated estrogens, A dosage strength for the treatment of moderate-to-severe vasomotor symptoms (MSVS). Insufficient efficacy data was provided for consideration of approval. On March 10, 2000, Duramed Pharmaceuticals was advised that their supplemental new drug application (S-006) was approved, providing for the addition of a single 1.25 mg tablet strength for the treatment of MSVS in a postmenopausal population.

Synthetic conjugated estrogens, A 0.3 mg tablet is the subject of this efficacy supplement (NDA 20-992/S-016). The results of a double-blind, placebo-controlled, multi-center clinical trial in which 72 healthy postmenopausal women (71 treated) were randomized to 0.3 mg synthetic conjugated estrogens, A or placebo tablets for a 16 weeks treatment duration to determine efficacy in the treatment of vulvar and vaginal atrophy.

Per the submission, the lot of synthetic conjugated estrogens, A used in this clinical trial (C-0034) was also used in the original NDA clinical trial. Updated stability information on the referenced clinical lot and additional validation lots is provided in the submission.

Fileability of NDA 20-992/S-016

NDA 20-992/S-016 is fileable.

Review Issues

1. The primary efficacy outcome variable presented in the submission is the median change in the Maturation Index score between baseline and week 16. This is unacceptable. The Sponsor has included, however, as a secondary outcome variable, descriptive and inferential statistics for the mean number of parabasal, intermediate and superficial cells for week -2, week 16 and the mean change from week -2 to week 16. Per the proposed, revised 1995 Hormone Replacement Therapy (HRT)

Guidance, a 12-week treatment period is recommended for the treatment of vulvar and vaginal atrophy indication. An analysis of the mean difference in the Maturation Index (parabasal, intermediate and superficial cells) between baseline and week 12 will be requested.

2. 14% (10 of 71) of subjects had an inadequate vaginal smears for Maturation Index at some time point (Center # 4 had 7 of 20 subjects with an inadequate MI at some time point).
2. In the Division letter dated January 18, 2001 we recommended that the Sponsor modify Study DPI00-005 to include a subject self-assessment of symptoms and an investigator assessment of signs. The Sponsor advised the Division on February 16, 2001 that the study had already begun and that the Maturation Index score would be the only objective finding as 60 subjects had already been enrolled.
3. The median change in vaginal pH assessment between baseline and week 16 is provided. An analysis of the mean vaginal pH assessment at baseline and week 16 will be requested.
4. A six weeks washout period prior to the start of study medication was utilized. We recommended in the January 18, 2001 letter to the Sponsor that the proposed washout period be modified per the proposed, revised 1995 HRT Guidance.
5. For the analyses of lipid profile measurements the statistical analysis plan indicated that the change from week -2 to week 16 would be presented. However, the Sponsor completed the analyses using the average of week 12 and week 16.

Request for Data

1. The Sponsor is requested to provide a table showing the mean percentage of parabasal, intermediate, and superficial cells at baseline and week 12, and the mean change from baseline to week 12.
2. The Sponsor is requested to submit a table showing the mean vaginal pH assessment at baseline and weeks 12 and 16.

Recommendations for a Division of Scientific Investigations Audit

1. Phoenix Center for Clinical Research (Center # 2), George Schade, M.D.
2. San Antonio Center for Clinical Research (Center # 4), Robert Nett, M.D.

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NDA: 20-992/S-016

**45 Day Filing Meeting Checklist
CLINICAL**

ITEM	YES	NO	COMMENT
1) Is the clinical section of the NDA clearly organized?	X		
2) Is the clinical section of the NDA adequately indexed and paginated?	X		
3) Is the clinical section of the NDA legible?	X		
4) Is there an adequate rationale for selection of dose and dosing schedule?	X		
5) Are the requisite number of adequate and well controlled studies submitted in the application?	X		
6) Are the pivotal efficacy studies of appropriate design and duration to assess approvability of this product for its proposed indication?	X		
7) Are electronic data sets (with adequate documentation for their use) provided for pivotal efficacy studies?	X		
8) Has the applicant submitted line listings in a format to allow review of individual patient data?	X		
9) Has the applicant submitted a rationale for assuming the applicability of foreign trial results to the U.S. population?	NA		
10) Has the applicant submitted all required case report forms (i.e., deaths, drop-outs due to ADEs and any other CRFs previously requested by the Division)?	X		
11) If appropriate, have stratified analyses of primary safety and efficacy parameters been conducted for age, gender and race?	NA		
12) Has the applicant presented the safety data in a manner previously agreed to by the Division?	X		
13) If approved in other countries, have a summary and assessment of foreign post-marketing experience been provided?	NA		
14) Has draft labeling been submitted?	X		
15) Have all special studies/data requested by the Division during pre-submission discussions with the sponsor been submitted?	X		

16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	X		
17) Reasons for refusal to file:			

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/s/

Theresa Van Der Vlugt
10/9/01 03:23:41 PM
MEDICAL OFFICER

Shelley Slaughter
10/11/01 05:26:20 PM
MEDICAL OFFICER

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MEMORANDUMDEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: October 4, 2001

From: Jeanine Best, M.S.N., R.N.
Senior Regulatory Associate
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure Documents

To: NDA 20-992/S-016

I have reviewed the financial disclosure information submitted by Duramed Pharmaceuticals, Inc. in support of their Supplemental NDA 20-992/S-016 (SE-1).

One pivotal study was conducted to assess the safety and efficacy of Cenestin® (synthetic conjugated estrogens, A) 0.3.mg Tablets for the indication of vulvovaginal atrophy in postmenopausal women. The study number and the results of the review of financial disclosure documents are summarized below:

Study Number/Title	Study Status	Financial Disclosure Review
Study DP100-005/ "A Double-Blind, Randomized, Parallel, Placebo-Controlled, Clinical Study to Compare the Effects of 0.3 mg, Once Daily, Synthetic Conjugated Estrogens, A (Cenestin®) vs. Placebo Tablets on Vulvovaginal Atrophy in Healthy Postmenopausal Women"	Study Start: November 13, 2000 Study Complete: June 15, 2001	Appropriate documentation received, no financial disclosure submitted

Documents Reviewed:

- Form FDA 3454, "Certification: Financial Interests and Arrangements of Clinical Investigators" submitted August 16, 2001

Study DP100-005

There were 11 principal and subinvestigators (investigators) at 5 sites in this trial (72 patients). Financial disclosure information was received from all investigators; none had any disclosable information.

Conclusion:

Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of this trial.

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/s/

Jeanine Best
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CSO

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-992/S-016

CORRESPONDENCE



NDA 20-992\S-016

Barr Laboratories, Inc.
Attention: Christine Mundkur
Senior Vice President
Quality and Regulatory Counsel
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Dear Ms. Mundkur:

We acknowledge receipt of your October 3, 2002, submission containing final printed labeling in response to our June 21, 2002, letter approving your supplemental new drug application for Cenestin (synthetic conjugated estrogens, A) Tablets, 0.3 mg.

We have reviewed the labeling that you submitted in accordance with our June 21, 2002, letter and we find it acceptable.

If you have any questions, call Kassandra Sherrod, Regulatory Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-992/S-016

INFORMATION REQUEST LETTER

Barr Laboratories
Attention: John R. Rapoza
Senior Vice President, Regulatory Affairs
5040 Duramed Drive
Cincinnati Ohio, 45213

Dear Mr Rapoza:

Please refer to your supplemental new drug application (S-016) dated August 16, 2001, received August 17, 2001, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cenestin (synthetic conjugated estrogens, A) tablets.

We are reviewing the Physician Insert (PI) and the Patient Package Insert (PPI) section of your submission and have the following comments and information requests. Revisions have been incorporated directly into the enclosed physician insert and patient information insert. Additions have been noted with double underlining, deletions have been noted as ~~strikeouts~~. Additional comments requiring response are in **14-pt bold face type**.

Please submit your revised package insert (in hard copy and in electronic format) as soon as available so that we can continue the evaluation of your supplemental NDA.

If you have any questions, call Dornette Spell-LeSane, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Margaret Kober, R.Ph.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

19 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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/s/

Margaret Kober

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NDA 20-992

PRIOR APPROVAL SUPPLEMENT

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

Dear Mr. Rapoza:

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

Name of Drug Product:	Cenestin [®] synthetic conjugated estrogens, A) Tablets, 0.3 mg
NDA Number:	20-992
Supplement number:	S-016
Review Priority Classification:	Standard (S)
Date of supplement:	August 16, 2000
Date of receipt:	August 17, 2001

This supplement proposes the following changes: The addition of the 0.3 mg strength tablet for the relief of vulvar and vaginal atrophy associated with the menopause.

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 October 16, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be June 17, 2001, and the secondary user fee goal date will be August 17, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the

requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-992/S-016

Page 4

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jeanine Best
8/27/01 02:02:59 PM
signing for Terri Rumble

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