This large placebo effect, which this reviewer anticipated, may have occurred due to perimenopausal women being included in the eligible study population.

To assess the impact of each individual dose regimen used in the study on the efficacy results (0.3 mg, 0.625 mg, and 2 x 0.625 mg Cenestin™ or placebo), the Division Statistician performed an analysis by actual dose level. Descriptive statistics for the actual dose received prior to each primary efficacy timepoint (4, 8, and 12 weeks) were performed for exploratory purposes only and are shown in Table 6.

Table 6: Descriptive Statistics by Actual Dose; Intent-to-Treat Population; Study # 366

		Actual Dose					
Hot Flushes Per Week		0.3 mg/day		0.625 mg/day		2 x 0.625 mg/day (total 1.25 mg/day)	
		Cenestin	Placebo	Cenestin	Placebo	Cenestin	Placebo
Week 4 (dose level received at Week 2 visit)	N Mean SD Range	0	1 -87.0	13 -69.7 29 -127, -40	10 -65.6 40 -126. –15	57 -67.7 47 -239, 15	36 -42.5 47 -239, 14
Week 8 (dose level received at Week 6 visit)	N Mean SD Range	1 -67.5	0	13 -83.6 26 -127, -44	12 -70.0 35 -134, -15	56 -77.2 53 -317, 7	35 -48.9 53 -247, 34
Week 12 (dose level received at Week 10 visit)	N Mean SD Range	4 -89.5 23 -123, -75	0	11 -86.2 35 -161, -47	13 -73.2 35 -133, -15	55 -78.4 54 -326, 7	34 -49.8 51 -246, 22

Source: Statistical Review and Evaluation (Patient Listings in Appendix 16.2.5.3.1 and SAS data sets)

From this statistical analysis we see that no data are available for the 0.3 mg/day Cenestin™ dose at four weeks and no comparative placebo data is available, at this dose level, for Weeks 8 and 12. Thus, there is insufficient data to assess the efficacy of the 0.3 mg Cenestin™ dose for relief of MSVS.

For the 1 x 0.625 mg/day dose, the reduction in mean number of MSVS per week for the Cenestin™ group is similar to placebo at Week 4 (-69.7 for Cenestin™ and –65.6 for placebo; a difference of only –4.1), but higher at Week 8 (a difference of –13.6 favoring Cenestin™) and at Week 12 (a difference of –13 favoring Cenestin™).

For the 2 x 0.625 mg/day Cenestin™ group, the results show a larger reduction in the mean number of MSVS per week over placebo by Week 4 that continued through Week 12. These results meet the clinically meaningful difference (-25.2 at Week 4, -28.3 at Week 8, and –28.2 at Week 12) proposed by the sponsor (28 per week) at Weeks 8 and 12.

Reviewer's comments

The greatest difference in MSVS was shown with the 2 x 0.625 mg Cenestin™ dose. However, a single 1.25 mg dose tablet was not included in the clinical trial and the 2 x 0.625 mg dose has not been demonstrated to be bioequivalent to the 1.25 mg Cenestin™ tablet (see the Clinical Pharmacology and Biopharmaceutics Review). Approval of the 0.625 mg Cenestin™ dose is recommended. Labeling should include the 0.625 mg dose but should reveal that the majority of patients in the clinical trial required 2 x 0.625 mg for relief of vasomotor symptoms.

The 0.9 mg Cenestin™dose, not included in the clinical trial, is compositionally similar to the 0.625 mg tablet. Because this 0.9 mg dose is bracketed by the clinically effective 1 x 0.625 mg and 2 x 0.625 mg doses, approval for this dose level is recommended.

There is insufficient date to recommend approval of the 0.3 mg Cenestin™ dose.

Four centers participated in the study submitted. The enrollment of subjects was not evenly distributed across the centers with Center 4 (Cincinnati, OH) enrolling 57% (n = 68 of 120) of the patients compared to 15% for Center 1 (Lincoln, NE; n = 18/120), 16% for Center 2 (Omaha, NS; 19/120), and 13% for Center 3 (Phoenix, AZ; N = 15) (see Table 7).

Table 7: Enrollment by Center (All Randomized); Study # 366

	Cenestin™ (n = 72)		Placebo (n = 48)		Total (n = 120)	
Site #; Location	N	%	N	%	N	%
1 Lincoln, NE	11	15%	7	15%	18	15%
2 Omaha, NE	13	18%	6	13%	19	16%
3 Phoenix, AZ	8	11%	7	15%	15	13%
4 Cincinnati, OH	40	56%	28	58%	68	57%

Source: Statistical Review and Evaluation; Volume 4.2, Section 10.1; Data listings

Per the submission, the mean MSVS per week at baseline in Center 4 was much higher than in the other three centers, which were similar to each other (see Table 8). Per the Division's Statistical Review and Evaluation, patients in Center 4 with the higher baseline MSVS values correspond to larger reductions in MSVS on treatment. To determine the impact of Center 4 results on the overall analyses, the Statistical Reviewer reran the ANOVA analyses performed by the sponsor excluding Center 4. However, the results were inconclusive due to the small sample size (n = 52).

Table 8: Baseline Number of MSVS per Week by Center (ITT; n=117): Study # 366

	Center # 1		Center # 2		Center # 3		Center # 4	
	Cenestin	Placebo	Cenestin	Placebo	Cenestin	Placebo	Cenestin	Placebo
N	11	7	13	6	8	7	38	27
Mean	84.8	99.0	76.0	86.6	83.5	99.0	110.2	93.2
SD	19	14	12	26	20	21	52	42
Min	61.5	77.6	62.5	60.5	62.0	63.0	63.0	64.0
Max	125.5	119.0	95.2	137.5	122.5	133.5	325.8	254.0

Source: Statistical Review and Evaluation; SAS datasets

The discrepancy in baseline MSVS per center was further explored. Review showed that thirteen patients from Center 4 (10 in the Cenestin™ group and 3 in the placebo group) had MSVS mean baseline values which were higher (140 or above) than the largest mean baseline MSVS value (137 per week) for the other 3 centers. Three of these thirteen patients had MSVS baseline values above 200. Dropping these three patients, who could be considered outliers, and rerunning the ANOVA model produced results that continue to support the sponsor's conclusion that there is a statistically significant difference in the reduction of mean number of MSVS between the two treatment groups at 4, 8, and 12 weeks (all p-values $\leq .01$) (see Statistical Review and Evaluation, Appendix; Table 1 and Figure 1).

Reviewer's comments

These exploratory analyses suggest that by dropping the three subjects with the most extreme baseline values, Center 4 essentially represents the same patient population at baseline as the other 3 centers.

In addition, the dropout rate across centers was not consistent. Center 4 had the highest dropout rate. Ten of the eleven patients who discontinued the study (see **4.9 Withdrawals and compliance**) were patients at Center 4. See the next section, **4.12 Safety analysis**, for additional information on these patients.

4.12 Safety analysis

In Study 366, treatment emergent adverse events were reported by 111 (93%) of the 120 patients enrolled in the study. No deaths or serious adverse events were reported during the 12-week study. Sixty-eight (94%) patients receiving synthetic conjugated estrogen tablets reported at least one adverse event compared to 43 (90%) of the placebo patients. Table 9 summarizes all adverse events that occurred at a rate ≥ 5% by body system and treatment group.

Table 9: Number (%) of Patients with Adverse Events With a Greater than 5% Occurrence Rate by Body System and Treatment Group

Body System **Adverse Event**	**Synthetic Conjugated Estrogens A N (%)**	**Placebo N (%)**	**Total N (%)**
Number of Patients Who Received Medication	72 (100)	48 (100)	120 (100)
Number of Patients With Adverse Events	68 (94)	43 (90)	111 (93)
Number of Patients Without Any Adverse Events	4 (6)	5 (10)	9 (8)
Body As A Whole	**60 (83)**	**39 (81)**	**99 (83)**
Abdominal Pain	20 (28)	11 (23)	31 (26)
Asthenia	24 (33)	20 (42)	44 (37)
Back Pain	10 (14)	6 (13)	16 (13)
Fever	1 (1)	3 (6)	4 (3)
Headache	49 (68)	32 (67)	81 (68)
Infection	10 (14)	5 (10)	15 (13)
Pain	8 (11)	9 (19)	17 (14
Cardiovascular System	**16 (22)**	**15 (31)**	**31 (26)**
Palpation	15 (21)	13 (27)	28 (23)
Digestive System	**30 (42)**	**25 (52)**	**55 (46)**
Constipation	4 (6)	2 (4)	6 (5)
Diarrhea	4 (6)	0 (0)	4 (3)
Dyspepsia	7 (10)	3 (6)	10 (8)
Flatulence	21 (29)	14 (29)	35 (29)
Nausea	13 (18)	9 (19)	22 (18)
Vomiting	5 (7)	1 (2)	6 (5)
Metabolic and Nutritional	**11 (15)**	**9 (19)**	**20 (17)**
Peripheral Edema	7 (10)	6 (13)	13 (11)
Musculoskeletal System	**24 (33)**	**16 (33)**	**40 (33)**
Arthralgia	18 (25)	13 (27)	31 (26)
Myalgia	20 (28)	15 (31)	35 (29)
Nervous System	**55 (76)**	**35 (73)**	**90 (75)**
Depression	20 (28)	18 (38)	38 (32)
Dizziness	8 (11)	5 (10)	13 (11)
Hypertonia	4 (6)	0 (0)	4 (3)
Insomnia	30 (42)	23 (48)	53 (44)
Leg Cramps	7 (10)	3 (6)	10 (80
Nervousness	20 (28)	20 (42)	40 (33)
Paresthesia	24 (33)	15 (31)	39 (33)
Vertigo	12 (17)	12 (25)	24 (20)
Respiratory System	**18 (25)**	**11 (23)**	**29 (24)**
Cough Increased	4 (6)	1 (2)	5 (40
Pharyngitis	6 (8)	4 (8)	10 (8)

Rhinitis	6 (8)	7 (15)	13 (11)
Skin and Appendages	**9 (13)**	**5 (10)**	**14 (12)**
Rash	3 (4)	3 (6)	6 (5)
Special Senses	**3 (4)**	**6 (13)**	**9 (8)**
Urogenital System	**30 (42)**	**11 (23)**	**41 (34)**
Breast Pain	21 (29)	7 (15)	28 (23)
Dysmenorrhea	4 (6)	3 (6)	7 (6)
Metrorrhagia	10 (14)	3 (6)	13 (11)

Source: NDA 20-992, Amendment 1, Volume 2, Pages 02-73 – 02-75

Per the sponsor, the statistical significance of any difference in occurrence rates between treatment groups was not determined. From the above table, the frequency of adverse events was similar for both the Cenestin™ and placebo treatment groups.

Adverse events reported by greater than 30% are compared overall and by treatment in Table 10.

Table 10: Adverse Events Reported by > 30% of all patients

	% (n) of All Patients		
Adverse Event	Cenestin™ (n=72)	Placebo (n=48)	Overall (n-120)
Headache	68 (49)	67 (32)	81 (68)
Insomnia	42 (30)	48 (23)	44 (53)
Asthenia	33 (24)	42 (20)	37 (44)
Nervousness	28 (20)	42 (20)	33 (40)
Paresthesia	33 (24)	31 (15)	33 (39)
Depression	28 (20)	38 (18)	32 (38)
Myalgia	28 (20)	31 (15)	29 (35)

Source: NDA 20-992, Amendment 1, Volume 2, Page 02-074.

Although not reported by > 30% of patients, there appears to be a slightly higher incidence of breast pain and metrorrhagia adverse events in the Cenestin™ than in the placebo group. Twenty-nine percent (n=21) of the Cenestin™ patients reported breast pain compared to 15% (n=7) who received placebo. Likewise, 14% (n=10) of the Cenestin™ patients reported metrorrhagia compared to 6% (n=3) who received placebo. The highest incidence of vaginal bleeding was reported in patients who entered the study with < 6 months since last menses (n=7; 4 Cenestin™ patients and 3 placebo patients). Six additional Cenestin™ patients reported bleeding. Three of these patients reported 6-12 months since last menses upon study entry and 3 patients reported 13-36 months since last menses. No patient who entered the study at > 36 months since last menses reported vaginal bleeding. Per the sponsor, none of the patients reporting metrorrhagia required interventions (Fax transmission from sponsor dated November 13, 1998). In total, thirty (30) patients (19 Cenestin™ and 11 placebo patients) were referred to their personal physicians for possible progestin treatment at study end (Fax transmission from sponsor dated November 13, 1998).

Reviewer's comments

Breast tenderness/pain and metrorrhagia are commonly reported adverse events with estrogen replacement therapy and therefore are not a new or unexpected finding with this drug.

A total of 11 patients (5 Cenestin™, 6 placebo) discontinued the study. Two patients were dropped from the study for personal reasons and three for non-compliance reasons (see **Section 4.9 Withdrawals and compliance** in this review for additional information on these patients). The remaining six patients (3

Cenestin™ and 3 placebo) were dropped from the study for non-serious adverse events. Adverse events experienced in the three Cenestin™ patients included bilateral breast pain (Patient No. 092), abdominal cramps (Patient No. 076), and melancholia and persistent vasomotor symptoms (Patient No. 074). In the three placebo patients, adverse events included headache (Patient No. 031), breast soreness and left cystic mass (Patient No. 102), and nausea (Patient No. 061).

4.13 Summary of DSI audit

DSI audits were completed for Center 1 (Lincoln, NE) and Center 4 (Cincinnati, OH). Per the Division of Scientific Investigations, Clinical Investigations Branch, both centers did adhere to all federal regulations and/or good clinical investigational practices governing conduct of clinical investigations and the protection of human subjects.

5. Labeling review

Please see Attachment 2 for the final labeling.

6. Reviewer's assessment of safety and efficacy

This NDA 20-992 presents a pivotal clinical trial in support of the safety and efficacy of Cenestin™ (synthetic conjugated estrogens A) for the relief of vasomotor symptoms associated with menopause. In Study Number 366 (a randomized, double-blind, placebo-controlled, dose-titration study of 120 menopausal women), the primary efficacy endpoint was the reduction in the mean number of moderate to severe vasomotor symptoms during the fourth, eight, and twelfth weeks of treatment compared to placebo.

At menopause, because no ovulatory follicles are produced, the production of 17β-estradiol decreases dramatically (17β-estradiol is the principal estrogen produced by the functioning premenopausal ovary). This decrease results in symptoms of vasomotor instability including hot flashes, nausea, dizziness, headache, palpitations, diaphoresis, insomnia, and night sweats. Vasomotor symptoms are variable in frequency and severity and may persist for several months to a few years. Estrogen replacement therapy has been shown to be effective in the management and treatment of moderate to severe vasomotor symptoms associated with the menopause and has been available since 1942.

Study Number 366 is unique in that it was designed as a dose titration study, established minimal inclusion and exclusion criteria, and included both perimenopausal and postmenopausal women. All patients at randomization received a daily dose of 1 x 0.625 mg Cenestin™ or placebo. If the mean number of MSVS at Week 1 (day 7) was not 50% less than the mean number of MSVS at baseline, the daily dose was increased to 2 x 0.625 mg Cenestin™ or placebo daily. No additional increase in dose was allowed for the remaining 11 weeks of the study. However, the dose could be decreased at Week 1 to 0.3 mg Cenestin™ or placebo or decreased to a lower dose (either 0.625 mg or 0.3 mg) at any time after Week 1.

Based on the results of the ANOVA model proposed in the analysis plan, there was a statistically significant larger reduction in the mean number of MSVS per week for the Cenestin™ group than the placebo group by Week 4 of treatment that continued through Week 12. Analyses of variance performed on the primary efficacy variable showed statistically significant differences between the active and placebo treatments at Week 4 ($p<0.022$), Week 8 ($p<0.010$), and Week 12 ($p< 0.010$). By Week 4 of treatment in the intent-to-treat population, a statistically significant decrease in moderate to severe hot flashes occurred despite a strong placebo effect.

Two concerns arose during the review, which required further investigation. First, there was a lack of balance noted between the 4 centers conducting the study. Centers 1, 2, and 3 were similar in the number of patients enrolled, the mean number of MSVS at baseline, and the number of dropouts. Center 4 (where 57% (n=68) of the patients were enrolled) included patients with higher baseline MSVS values (thirteen of the 68 patients enrolled had baseline MSVS values of 140 or above per week and 3 patients had baseline MSVS values above 200), and had 10 of the 11 dropouts. These findings raised concerns about Center 4 and its overall impact on the efficacy results reported. An exploratory analyses performed by the

Division's statistician, dropping the 3 subjects in Center 4 with the extremely high baseline MSVS values, confirmed sufficient evidence to support a difference in the reduction in mean number of MSVS per week between the two treatment groups.

A second concern was the amount of data available to support each dose for which the sponsor desired approval. Since most patients ended up on the highest dose of Cenestin™ (2 x 0.625 mg), the amount of data to support the lower doses was limited. To better understand how the actual dose received impacted the efficacy results, descriptive statistics for each time point of interest (4, 8, and 12 weeks) was developed for exploratory purposes only. Table 6 demonstrates the descriptive statistics by actual dose and suggests:

1) There is insufficient data to assess the efficacy of the 0.3 mg /day dose.
2) The reduction in mean number of MSVS per week for the 0.625 mg Cenestin™ group was similar to placebo at Week 4 but higher (13 units) at Weeks 8 and 12.
3) The reduction in mean number of MSVS per week for the 2 x 0.625 mg Cenestin™ group was higher than placebo at Weeks 4, 8, and 12 (25 to 28 units).

7. Recommended regulatory action

The 0.625 mg/day Cenestin™ dose, 0.9 mg/day Cenestin™ dose, and the 2 x 0.625 mg dose are recommended for approval. There is insufficient data to recommend approval of the 0.3 mg/day Cenestin™ dose.

2/17/99

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

agree -- 3/4/99

cc: NDA 20-992 Division File
HFD-580/MMann/DMoore/TvanderVlugt

Attachment 1. Regulatory History of INT NDA 20-992

Status Date: Dec. 14, 1998

IND

Name of Drug: Synthetic Conjugated Estrogens A Tablets, Cenestrin™
Name of Sponsor: Duramed

Regulatory History

June 19, 1997 Clinical Pharmacology and Biopharmaceutics Review; Issues: 1) lack of pharmacokinetic data for the 0.3, 0.9 and 2.5 mg strength tablets; 2) lack of multiple dose data; 3) waivers supported on comparative dissolution data; 4) pharmacokinetic section should be formatted according to internal guide; 5) ANDAs dissolution data are different than those used in the ANDA submission; 6) proposed labeling should be updated;
Recommendations: submission can be accepted for filing; OCPB/DPEII would prefer to review pharmacokinetics at steady state before approval, however these data may be collected in a Phase IV study; the requested bio-wavers for the 0.3 and 2.5 mg may not be granted and additional bio-studies would be needed due to the lack of clinical data to assure these doses are safe and effective.

Sept. 2, 1997 Meeting minutes of internal meeting held on July 23, 1997; Decisions reached: the sponsor should perform a dose titration study incorporating the 0.3 mg dose; the starting dose should be 0.625 mg; change clinical trial from 8 to 12 weeks; the criteria for escalation at day seven should be clarified; the sponsor should clarify 2-weeks of 60 or more hot flashes; the sponsor should state the exact number of patients to be randomized; the primary endpoint should be the absolute change from baseline of the mean number of reduction of hot flashes; in addition the sponsor should analyze the data as the percent change from baseline; reduction in severity should be considered a secondary endpoint; progestins could be given at the end of the study if needed.

Sept. 8, 1997 Minutes of internal meeting held on July 22, 1997; discussion will continue on July 23, 1997.

Sept. 8, 1997 Minutes of Teleconference on July 25, 1997; Decisions reached: Duramed will include the 0.3 mg dose in the study design; Duramed will put more objective criteria in the protocol for changing dose escalation; the sponsor will indicated that the screening period will be a certain number of weeks; a teleconference will be scheduled with the statistician; pharmacokinetics data will be collected from the bone study to begin in September; pharmacokinetics study protocol will be submitted to both DRUDP and DMEDP

Oct. 6, 1997 Medical Officer's Original Review: the study is reasonably safe to proceed; deficiencies:

- The sponsor should correct Protocol Amendment, Serial No. 001 to consistently include a limited screening period throughout the text of the protocol (as stated in the overview of changes found on page 8 of the submission).
- The sponsor should correct the MDS Harris Laboratories Informed Consent Form as follows:
- Under the section Clinic Visits, page 209 of the submission: sentence one should be modified to reflect the study extension to 12 weeks.
- Under the section Clinic Visits, Study Visits 3, 4, and 5, page 210 of the submission: change Study Visits 3, 4, and 5 to read Study Visits 3, 4, 5, and 6.
- Under the section Clinic Visits, Study Visit 6, page 210 of the submission: change Study Visit 6 to read Study Visit 8.
- Under the section Clinic Visits, page 210: add Study Visit 7 with the appropriate description of content.

•Under the section Drug Administration, page 210: correct the first sentence to read ---for the 12-week period (total 84 doses).
•The sponsor should provide the Phoenix International Life Sciences Informed Consent Form for review.
•The sponsor should add a pregnancy test to the screening/baseline laboratory determinations (per sponsor, a protocol amendment is being submitted).

Nov. 12, 1997 Minutes of Meeting on 9/4/97: Decisions Reached: the sponsor will submit an amendment to include above-mentioned editorial changes to the protocol; Unresolved Issues: a telecon will be set up to discuss sample size after further investigation into the effect on the placebo effect by the hormone replacement therapy status of women; Action items: Duramed will revisit the effect size calculation; biometrics will examine therapy status on effect size.

Nov. 20, 1997 Protocol Amendment Serial No. 002: submission revised to correct inconsistencies and editorial errors and to provide for a revised target enrollment of 120 patients.

Dec. 5, 1997 Division letter to sponsor following protocol review; comments and request for additional information: it should be clearly stated that the primary endpoint of interest is the absolute change from baseline in the number of moderate and severe vasomotor symptoms at Week 4, 8, and 12; all analysis other than intent-to-treat will be considered supportive; Protocol Amendment, Serial No. 001 should be corrected to consistently include a 4-week screening period; The sponsor should correct the MDS Harris Laboratories Informed Consent Form as follows:

•Under the section Clinic Visits, page 209 of the submission: sentence one should be modified to reflect the study extension to 12 weeks.
•Under the section Clinic Visits, Study Visits 3, 4, and 5, page 210 of the submission: change Study Visits 3, 4, and 5 to read Study Visits 3, 4, 5, and 6.
•Under the section Clinic Visits, Study Visit 6, page 210 of the submission: change Study Visit 6 to read Study Visit 8.
•Under the section Clinic Visits, page 210: add Study Visit 7 with the appropriate description of content.
•Under the section Drug Administration, page 210: correct the first sentence to read ---for the 12-week period (total 84 doses).

A copy of the Consent Form from Phoenix International Life Sciences should be provided for review; a pregnancy test should be added to the screening/baseline laboratory determinations; study may be underpowered because other NDA studies have had baseline values in the range of 9 to 12 hot flushes per day, whereas the assumption of 14 for this study is somewhat higher; in other studies the treatment differences between groups have ranged from 3 to 4 hot flushes per day, not the 5 to 6 for this study.

Jan. 7, 1998 Received from sponsor pre-NDA conference document.

Jan. 8, 1998 Serial No. 003: pre-NDA meeting package.

Jan. 20, 1998 Internal meeting minutes; discussed 8 action items sponsor submitted for pre-NDA meeting.

Jan.27, 1998 Minutes of meeting held with sponsor to discuss proposed NDA format; decisions reached: ANDA reference is acceptable; sponsor will contact chief mediator's office for info. on small business exemption; 3 year market exclusivity is acceptable; 0.625 mg will be starting dose; sponsor will provide more descriptive results by study center; sponsor will include data listings of the concomitant medications; data should be stratified and summarized by strength; intermediate dose waiver should be justified; sponsor will submit summaries of their four definitive clinical pharmacology studies; sponsor will provide SAS data sets and labeling disc; shape and color of tablet on carton should be changed; keep out of reach of children should be included on the label; use label format according to estrogen labeling guidance; primary variable is the absolute number of reduction of VMS at 4, 8, and 12 weeks, also percentage change;perfer the ITT to include patients with any data with LOCF; confidence intervals should be at the 95% level; recommend inclusion of Kaplan Meier chart of time to discontinuation.

March 11, 1998

Serial No. 004; CMC information: the 0.3 mg tablets used in the pivotal clinical trial (Protocol # 366) were made utilizing the same batch record and manufacturing conditions except that a different dye was used.

June 30, 1998

Oct. 12, 1998

Oct. 13, 1998

Nov. 4, 1998

Dec. 9, 1998

Serial No. 008; proposed proportional formulation of the 1.25 mg tablets; proposed to reformulate the 1.25 mg tablet so that it is identical to the 0.3, 0.625 and 0.9 mg tablets; refer to CMC for review and decision.

Status Date: Feb. 10, 1999

NDA 20-992

Name of Drug: Cenestin™ (Synthetic Conjugated Estrogens A) Tablets
Name of Sponsor: Duramed Pharmaceuticals, Inc.
Submission Date: March 27, 1998

Regulatory History

March 27, 1998	Original New Drug Application filing from sponsor.
April 6, 1998	Original Amendment: SAS programs for NDA submission.
May 1, 1998	Minutes of Meeting to discuss the filability of the NDA submitted; decisions reached: NDA does not qualify for priority review status, NDA filable; two DSI sites chosen; NDA should be considered for the usual class labeling indications including vasomotor symptoms published literature will be references for Pharmacology preclinical studies; additional biopharmaceutical studies may be needed on the release ratios of 0.3, 0.9 and 2.5 mg doses; the data should be recalculated using actual changes in vasomotor symptoms instead of absolute changes.
May 27, 1998	Clinical Efficacy Amendment submitted; the primary efficacy computations have been revised to remove the results based on calculation involving the absolute differences and replace these with the results based on actual differences.
May 29, 1998	Minutes of internal meeting to discuss the fileability and content of NDA 20-992 for Duramed; Decisions reached: there is sufficient amount of pharmacology and toxicology information for estrogen in the published literature to support a 505(b)(2); the safety data in the literature is acceptable for the product depending on the extent of the available information and look-alike products; clinical studies will be reviewed in addition to the literature; a unique identifying name for the product should be found; bio-waivers will be a review issue.
June 15, 1998	Internal meeting minutes: clinical decisions reached = the clinical effectiveness of the 0.3 mg dose should be determined, data has been submitted for review for the 1.25 and 0.625 mg doses, sponsor should clarify the patients in the "other" column, only two patients were titrated down; sponsor should recalculate the chemistry data; primary endpoint is 12 weeks; statistician will reconstruct the scenario for each patient; a bio-waiver of the 2.5 mg strength cannot be granted; OK for the 0.9 mg dose; Citizen's Petition should be resolved before action can be taken on the NDA.
June 16, 1998	Minutes of Telecon with sponsor; all components should be designated as active because it is a synthetic product; established specifications for each component; most viable established name is "synthetic conjugated estrogens α; Agency will discuss with USAN regarding the acceptability of the established name.
July 20, 1998	Internal meeting minutes: Decisions reached: 1

Cenestin dose should be determined by the sponsor; 5) dose justification should be provided by the sponsor, a drug-drug interaction study must be performed, dose proportionality should be shown, a food effect study should be performed for the combination product using the highest studied dose, a bioequivalence study should be performed the estrogen plasma levels of the combination product to the estrogen plasma levels of the estrogen-only product, estradiol, estrone, estrone sulfate and equilin sulfate should be studied; 6)a 95% CI is acceptable.

July 22, 1998	Minutes of meeting with sponsor: Discussion points: the sponsor proposed a PK study as a Phase 4 commitment to resolve outstanding steady state issue
Aug. 6, 1998	Minutes of Telecon; sponsor will submit revised calculations for the nine synthetic conjugated estrogens.
Sept. 2, 1998	Minutes of Telecon to discuss the methods validation for the NDA,
Sept. 21, 1998	Minutes of Telecon; FDA Conjugated Estrogens Working Group propose the name "synthetic conjugated estrogens mixture A"; sponsor will discuss and submit agreeable name to USAN.
Sept. 22, 1998	Amendment 001 from sponsor; Propose Synthetic Conjugated Estrogens Composition A as the established name for Cenestrin™.
Oct. 13, 1998	Letter to MDS Harris Labs from the Clinical Investigations Branch; inspection concluded that all federal regulations and/or good clinical investigation practices were observed.
Nov. 20, 1998	Labeling Amendment received from sponsor; under review.
Dec. 4, 1998	Minutes of Telecon to inform Duramed that the 1.25 mg/2.5 mg and possible the 0.3 mg doses are not approvable and to request additional biopharm. data for review.
Dec. 8, 1998	Human Pharmacokinetics Amendment; sponsor provides information requested in 12/4/98 telephone conference; dissolution data on equilin and F2 comparison test of the results between the 0.625 mg NDA bioavailability lot, the 0.3 mg and 0.9 mg NDA submission lots and the 0.3 and 0.625 mg lots used in the pivotal vasomotor clinical trial; sponsor concludes that the dissolution profile of equilin in each of the three dosage strengths is similar and that the two 0.3 mg batches have similar dissolution profiles.
Dec. 9, 1998	Amendment to withdraw the 1.25 mg and 2.5 mg dosage strengths; sponsor informed during 12/4/98 telephone conference that the 1.25 and 2.5 mg dosage strengths would not be approved since the 1.25 mg dosage strength was determined to be not bioequivalent to the 2 x 0.625 mg dosage used in the pivotal trial. Since the 2.5 mg dosage strength is dose proportional to the 1.25 mg, it too cannot be approved.
Dec. 15, 1998	Amendment to revise the drug substance and drug product specifications and the labeling; the proposed changes in the clinical studies section, warning section, adverse reaction section, and dosage and administration section have been made; patient package insert, use of estrogen section had been changed as

	recommended, sponsor request further discussion on recommended change to the discussion section.
Jan. 20, 1999	New correspondence outlining sponsor's views prior to scheduled teleconference regarding two issues: the approval of a 0.3 mg dosage strength and the wording to be used in the labeling to describe the delayed-release characteristics of Cenestin.
Feb. 2, 1999	Labeling Amendment
Feb. 4, 1999	Labeling Amendment

Attachment 2. Final Labeling

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

Safety Update Review

The sponsor stated in a submission dated March 4, 1999, that they have had no further contact with any of the patients in the pivotal clinical trial and they have not conducted any other clinical studies in humans since the filing of the NDA. Therefore, there were no adverse events of human experience to report in their safety update. No safety update memorandum will be prepared by the Medical Officer.