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RESEARCH**

APPLICATION NUMBER:
20-992/S-016

MEDICAL REVIEW

NDA 20-992/S-016

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Medical Officer's Review
(Original Review)

Sponsor: Duramed Pharmaceuticals, Inc.,
a Subsidiary of Barr Laboratories, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213

Drug Name:
Generic: Synthetic conjugated estrogens, A
Trade: Cenestin®
Chemistry: Estrogens:
Estrone: 3-Hydroxyestra-1,3,5(10)-tien-17-one
Equilin: 3-Hydroxyestra-1,3,5(10),7-tetraen-17-one
17 α -Dihydroequilin: (17 α)-estra-1,3,5(10),7-tetraene-3,17-diol
17 α -estradiol: (17 α)-estra-1.3.5(10)-triene-3,17-diol
17 β -Dihydroequilin: (17 β)-estra-1,3,5(10),7-tetraene-3,17diol
17 α -Dihydroequilenin: (17 α)-estra-1,3,5,7,9-pentaen-3,17-diol
17 β -Dihydroequilenin: (17 β)-estra-1,3,5,7,9-pentaen-3,17-diol
Equilenin: 3-hydroxyestra-1.3.5.7.9-pentaen-17-one
17 β -estradiol: (17 β)-estra-1,3,5(10)-triene-3,17-diol

Pharmacologic category: Estrogen

Dosage Form: Oral tablet

Strength: 0.3 mg

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

Related Submission: IND 53,731
NDA 20-992/S-000 dated 3/27/98

Related Documents: NDA 20-992/S-016 Amendments dated 11/1/01, 5/16/02, 6/3/02, 6/6/02

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The Executive Summary of the Primary Clinical Review

1. RECOMMENDATION

1.1. Recommendations on Approvability

From a clinical perspective, the reviewer recommends approval of 0.3 mg Cenestin® (synthetic conjugated estrogens, A). The data presented in this supplemental new drug application provides sufficient evidence from one controlled clinical trial (Study DPI00-005) to support the safety and efficacy of 0.3 mg synthetic conjugated estrogens, A, taken orally each day, for the treatment of vulvar and vaginal atrophy associated with the menopause.

1.2. Recommendations on Postmarketing Studies and/or Risk Management Steps Where Appropriate

No postmarketing studies and/or risk management steps are recommended.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief Overview of the Clinical Program

Cenestin® (synthetic conjugated estrogens, A) is an approved oral drug product that contains the following nine estrogenic substances: 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 currently approved. Cenestin® 0.625 mg, 0.9 mg, and 1.25 mg Tablets are administered orally in a continuous daily regimen for the treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause.

The Sponsor's proposed indication in this submission is the treatment of vulvar and vaginal atrophy (VVA) associated with the menopause for the 0.3 mg Cenestin® (synthetic conjugated estrogens, A) dosage strength.

NDA 20-992/S-016 was submitted on August 16, 2001. One primary Phase 3 study was submitted for review. Study DPI00-005 was a Phase 3, 16-week, randomized (ratio of 1:1, active drug to placebo), double-blind, placebo-controlled, multicenter (5 US centers) study of 71 healthy postmenopausal women meeting the inclusion and exclusion criteria. Subjects between 30 and 80 years of age who had undergone spontaneous amenorrhea at least 12 months prior to screening or were surgically menopausal (hysterectomy with or without bilateral oophorectomy) received either placebo or 0.3 mg synthetic conjugated estrogens, A tablets daily for 16 weeks.

Safety data submitted in the 4-Month Safety Update (dated May 16, 2002) and in the Second Safety Update (dated May 16, 2002) were reviewed upon receipt.

2.2. Efficacy

From the data presented in the Phase 3 Study DPI00-005, 0.3 mg synthetic conjugated estrogens, A taken daily is effective in relieving vulvar and vaginal atrophy associated with the menopause in healthy postmenopausal women.

Seventy-two postmenopausal women, between 30 and 80 years of age, were enrolled at five participating centers in the US. One subject who did not meet the study inclusion criteria was enrolled in error and did not receive study medication. Seventy-one (71) subjects were randomized to receive study medication. Thirty-seven (37) subjects were randomized to the 0.3 mg synthetic conjugated estrogens, A treatment group, and 34 subjects were randomized to the placebo treatment group. Sixty-one percent (61%) of the study population was white, 18% of the study population was black, and 17 % of the study population was Hispanic.

Study DPI00-005, the single, primary Phase 3 study conducted, was a 16-week double-blind, randomized, placebo-controlled clinical trial in healthy postmenopausal women. Placebo and 0.3 mg synthetic conjugated estrogens, A tablets (identical in size and appearance) were administered orally once daily for the 16-week treatment duration.

Right and left lateral wall vaginal cytology specimens for Maturation Index were collected pretreatment (week-2) and at weeks 4, 8, 12, and 16. The Maturation Index represents the proportion of vaginal superficial cells relative to the number of parabasal and intermediate cells. Vaginal Maturation Index results in Study DPI00-005 demonstrate a statistically significant estrogenic effect on vulvar and vaginal tissue for the 0.3 mg synthetic conjugated estrogens, A tablet. The percentage of vaginal superficial cells increased significantly from pretreatment values by week 12 and this increase was maintained through week 16 ($p < 0.0001$ at each time point). In addition, vaginal pH decreased significantly ($p < 0.0001$) from pretreatment (week -2) to week 16 in the 0.3 mg synthetic conjugated estrogens, A treatment group (mean decrease of 0.97) compared to placebo (mean increase of 0.10).

2.3. Safety

Conjugated estrogens, estradiol, and esterified estrogens have been used clinically for hormone replacement therapy, given alone or in combination with a progestin, for up to 60 years. Numerous formulations of estrogens for oral, transdermal, and vaginal administration are approved for the indications of treatment of moderate-to-severe vasomotor symptoms, vulvar and vaginal atrophy, hypoestrogenism due to hypogonadism, castration or primary ovarian failure, the palliative treatment of metastatic breast cancer and androgen-dependent carcinoma of the prostate, and for the prevention of postmenopausal osteoporosis. The risks of estrogen use are well known.

Synthetic conjugated estrogens have been approved for use since March 24, 1999. There is currently no evidence that the use of "natural" estrogens results in a different risk profile than synthetic estrogens of equivalent estrogen dose.

Seventy-one healthy postmenopausal women were treated in Study DPI00-005. There were no deaths or serious adverse events reported during the 16-week treatment duration. Safety evaluations and monitoring were adequate and complete for the 70 subjects in the safety population.

Leukorrhea (24%, 17 of 70 subjects), vaginitis (20%, 14 of 70 subjects), headaches (16%, 11 of 70 subjects), and infection (11%, 8 of 70 subjects) were some of the more common treatment-emergent adverse events reported in Study DPI00-005. These reported treatment-emergent adverse events may be considered expected, and are generally similar to adverse events known to occur during treatment with estrogens.

A total of 2 subjects discontinued study medication due to an adverse event (3%, 2 of 70 treated subjects, one in each treatment group). This rate of discontinuation due to adverse events does not suggest a safety risk.

2.4.

Dosing, Regimen, and Administration

Conjugated estrogens, estradiol, and esterified estrogens, given alone, are approved for use in a variety of delivery systems for the treatment of vulvar and vaginal atrophy associated with the menopause. These delivery systems include oral tablets (Premarin®, Estrace®, Menest™ and Estratab®), vaginal cream (Premarin® Vaginal Cream and Estrace® Cream), vaginal ring (Estring® IVR), vaginal tablet (Vagifem®), and transdermal patch systems (Estraderm®, Vivelle®, Vivelle-Dot®, Climara®, Alora® and Esclim®). Because the use of unopposed estrogen in women with a uterus is known to increase the incidence of endometrial hyperplasia (endometrial hyperplasia may be a precursor to endometrial cancer), several combination estrogen/progestin drug product formulations are also approved for the treatment of vulvar and vaginal atrophy (Prempro®, Premphase®, Activella™, femhrt™, Ortho-Prefest™ and Combipatch™).

The literature supports the use of low dosage strengths of estrogens to relieve vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, and the prevention of postmenopausal osteoporosis. To date, oral estrogen dosage strengths approved for the treatment of vulvar and vaginal atrophy range from 0.3 mg/day to 2 mg/day and transdermal patch systems dosage strengths range from 0.025 mg/day to 0.1 mg/day.

The 0.3 mg synthetic conjugated estrogens, A dosage strength proposed in this submission poses no dose-toxicity or dose-response concerns when provided in a continuous daily regimen, as recommended. Attempts to discontinue medication should be made at 3 to 6 month intervals.

2.5. Drug-Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (*Hypericum perforatum*), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects. This information will be provided in labeling

2.6. Special Populations

Cenestin® is only indicated for use in postmenopausal women. There were insufficient numbers of geriatric subjects in Study DPI00-005 to determine if those over 65 years of age differ from younger subjects in their response to 0.3 mg synthetic conjugated estrogens, A. Although 45% (32 of 71 subjects) of the intent-to-treat study population were 60 years of age and older, only 13 study subject were over 65 years of age (18%, 13 of 71 subjects). Three of these 13 subjects over 65 years of age received active drug, ten received placebo.

Cenestin® has not been studied in women with liver disease or renal impairment. Cenestin® should not be used in pregnant women.

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Clinical Review

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication (s), Dose, Regimen, Age Groups

Cenestin® (synthetic conjugated estrogens, A) is an approved oral drug product 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 currently approved. Cenestin® 0.625 mg, 0.9 mg, and 1.25 mg Tablets are administered orally in a continuous daily regimen for the treatment of moderate-to-severe vasomotor symptoms (VMS) associated with the menopause.

The Sponsor's proposed indication in this submission is the treatment of vulvar and vaginal atrophy (VVA) associated with the menopause for the 0.3 mg Cenestin® (synthetic conjugated estrogens, A) dosage strength.

1.2. State of Armamentarium for Indication(s)

For products intended to treat vulvar and vaginal atrophy (VVA), prestudy and end-of-study (12 week treatment duration) vaginal cytology smears are collected to determine the percentages of parabasal, intermediate and superficial cells (Maturation Index). In 1999, the Division incorporated the assessment of vaginal pH (along with other physician assessment of signs) and the patient self-assessment of symptoms at baseline and at end-of-study. The physician assessment of signs includes the following categories: vaginal pH, color of the vaginal epithelium, and vaginal mucosal integrity (friability and petechiae). The subject's self-assessment of vaginal symptoms includes the following categories: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity. Three primary efficacy variables are considered for a treatment of vulvar and vaginal atrophy indication:

- The change in the Maturation Index between baseline and week 12 (statistically significant increase in superficial vaginal cells and decrease of parabasal vaginal cells).
- The change in vaginal pH between baseline and week 12 (statistically significant lowering of vaginal pH).
- The change in the subject self-assessment of symptoms between baseline and week 12. The primary efficacy analysis should show statistically significant improvement in the moderate-to-severe symptom identified by the subject as the most bothersome.

1.3. Important Milestones in Product Development

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 No. 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 No. 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.

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

1.4. Other Relevant Information

Cenestin® is only approved for marketing in the US.

1.5. Important Issues with Pharmacologically Related Agents

Cenestin® (0.625 mg, 0.9 mg, and 1.25 mg tablets) is currently the only synthetic conjugated estrogens, A formulation approved for use in the US. Premarin® (conjugated equine estrogens) 0.3 mg, 0.625 mg, 0.9 mg 1.25 mg, and 2.5 mg is approved for the treatment of VMS (0.625 mg /day), VVA (0.3 mg to 1.25 mg /day), prevention of postmenopausal osteoporosis (0.625 mg/day), treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure (0.3 mg or 0.625 mg/day), treatment of breast cancer (for palliation only) in appropriately selected women and men with metastatic disease (total dose of 30 mg/day for 3 months), and the treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only, 1.25 mg or 2.5 mg three times daily).

2. SIGNIFICANT FINDINGS FROM CHEMISTRY, ANIMAL PHARMACOLOGY AND TOXICOLOGY, AND/OR MICROBIOLOGY

2.1. Chemistry, Manufacturing and Controls

Cenestin® contains the following estrogenic substances: 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. Synthetic conjugated estrogens, A are water soluble. Duramed Pharmaceuticals, Inc. is currently the manufacturer for all strengths of synthetic conjugated estrogens, A tablets.

2.2. Animal Pharmacology and Toxicology

No clinical pharmacology or toxicology studies have been conducted. On October 26, 1998, in conjunction with the original NDA submission, the Pharmacology Team Leader, Division of Reproductive and Urologic Drug Products, concluded in a memorandum that any difference in toxicity between Premarin® and Cenestin® would be expected to be small and subtle. Since no current animal toxicology studies have the power to detect such differences, if they exist, the applicability of any small measured differences from such preclinical testing would be questionable. It was concluded that additional toxicology studies were neither needed nor appropriate to support the safety of Cenestin®.

2.3. Microbiology

No Microbiology Review was conducted for this oral drug product.

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

Please refer to the Clinical Pharmacology and Biopharmaceutics Review.

No pharmacokinetic and bioavailability data is presented from Study DPI00-005.

3.2. Pharmacodynamics

No pharmacodynamic data is presented from Study DPI00-005.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Source of Clinical Data

Duramed Pharmaceuticals, Inc. is the original sponsor of this single, Phase 3, primary Study DPI00-005 conducted to compare the effects of 0.3 mg synthetic conjugated estrogens, A with placebo on vulvar and vaginal atrophy after 16 weeks of treatment in 71 healthy postmenopausal women. NDA 20-992/S-016 was submitted on August 16, 2001. On October 26, 2001, the Agency was notified that Duramed Pharmaceuticals, Inc. was now a subsidiary of Barr Laboratories, Inc.

Protocol DPI00-005 was submitted to IND 53,731 on October 12, 2000.

4.2. Overview of Clinical Trials

Study DPI00-005 was a Phase 3, 16-week, randomized (ratio of 1:1, active drug to placebo), double-blind, placebo-controlled, multicenter (5 US centers) study of 71 healthy postmenopausal women meeting the inclusion and exclusion criteria. Subjects between 30 and 80 years of age who had undergone spontaneous amenorrhea at least 12 months prior to screening or were surgically menopausal (hysterectomy with or without bilateral oophorectomy) received either oral placebo or 0.3 mg Cenestin® tablets daily for 16 weeks.

4.3. Postmarketing Experience

The 0.625 mg, 0.9 mg, and 1.25 mg Cenestin® dosage strengths have been approved since March 1999 for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause. The sponsor has submitted regular Quarterly Adverse Experience Reports and Annual Reports to the NDA file.

4.4. Literature Review

References are provided in the submission that pertains, generally, to the overall risks and benefits of both estrogen-alone therapy and estrogen/progestin therapy. Additional references are provided that pertain, specifically, to postmenopausal vulvar and vaginal atrophy and the assessment of dosage strengths of both estrogen-alone and estrogen/progestin combination drug products and treatment durations. No additional FDA literature review was conducted.

5. CLINICAL REVIEW METHODS

5.1. Describe How Review was Conducted

NDA 20-992/S-016, Study DPI00-005, was submitted electronically on August 18, 2001. Study DPI00-005, the single Phase 3 study submitted for review, was reviewed in its entirety. The safety data submitted in the 4-Month Safety Update (dated May 16, 2002) and the Second Safety Update (dated May 16, 2002) were reviewed upon receipt.

5.2. Overview of Materials Consulted in Review

Study DPI00-005 was a double-blind, placebo-controlled clinical trial conducted in 5 US centers that enrolled 72 postmenopausal women. One subject who did not meet the study inclusion was enrolled in error and did not receive study medication (Subject 066). Subject 066 was excluded from the ITT, PP, and safety analyses. Seventy-one (71) subjects were randomized to receive study medication. Thirty-seven (37) subjects were randomized to the 0.3 mg synthetic conjugated estrogens, A treatment group, and 34 subjects were randomized to the placebo treatment group.

5.3. Overview of Methods Used to Evaluate Data Quality and Integrity

The 0.625 mg, 0.9 mg, and 1.26 mg dosage strengths of Cenestin® were approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause in 1999. Two Division of Scientific Investigations (DSI) audits were completed during the review of the original NDA 20-992/S-000. Both centers did adhere to all federal regulations and/or good clinical investigational practices governing the conduct of clinical investigations and the protection of human subjects.

A review of the five US centers participating in Study DPI00-005 showed consistency in outcomes (adverse events, non-compliance with study protocol, subject withdrawals). Two exceptions were noted. First, subject enrollment was not evenly distributed across the five participating centers. Centers # 1, 2, and 4 (Chicago Center for Clinical Research, Phoenix Center for Clinical Research, and the San Antonio Center for Clinical Research, respectively) enrolled 86% of the subjects (61 of 71 treated subjects) while Centers # 3 and 5 (Pharmacology Research Clinic, Las Vegas and the Southeast Research Associates in Marietta, GA, respectively) enrolled 14% of the subjects (10 of 71 treated subjects). However, per the submission and the Statistical Review, in the final model of the analysis of variance the site and the treatment-by-site effects were not statistically significant. Second, Center # 4 (San Antonio) had the largest number of missing or inadequate vaginal Maturation Index samples (41%, 7 of 17 inadequate samples, 7 placebo subjects). Per the protocol study design, each subject had 5 vaginal Maturation Index samples taken: week -2, weeks 4, 8, 12, and 16. The 7 inadequate samples that were reported for Center # 4 were attributed to inadequate samples obtained by the study coordinator trained in the sampling techniques after the center investigator broke his arm. However, because the primary analysis, per the protocol, included the vaginal Maturation Index results from baseline (week -2) and week 16 (weeks 4, 8 and 12 were considered secondary analyses) using the last observation carried forward (LOCF) approach after week 4, and did not include the clinic visits where these inadequate samples were taken (primarily weeks 4 and 8, only one week 12 smear was found inadequate at Center #4), these subjects were retained in both the intent-to-treat (ITT) and per protocol (PP) analyses.

Initially, Centers # 2 (Phoenix Center for Clinical Research) and Center # 4 (San Antonio Center for Clinical Research) were selected for DSI (The Division of Scientific Investigation) audits. However, at The Division of Reproductive and Urologic Drug Products (DRUDP) filing meeting on October 9, 2001, DRUDP determined that the DSI inspection could be waived for this efficacy supplement based on the data available. No subjects were excluded from the intent-to-treat analysis at either center.

5.4. Were Trials Conducted in Accordance with Accepted Ethical Standards

The informed consent document proposed for use in Study DPI00-005 was appropriate. Appropriate standards of patient care were administered during the conduct of the clinical trial in accordance with regulations pertaining to Good Clinical Practice (GCP).

5.5. Evaluation of Financial Disclosure

Financial disclosure information was received from the eleven (11) principal investigators and subinvestigators at the five participating centers for Study DPI00-005. None of the investigator or subinvestigator had any disclosable information.

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6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

The data presented in NDA 20-992/S-016 for Study DPI00-005 provides sufficient evidence from one placebo-controlled clinical trial to support the safety and efficacy of the 0.3 mg Cenestin® tablet, taken daily, for the treatment of vulvar and vaginal atrophy associated with the menopause. Per the proposed revision of the Agency's 1995 HRT Guidance for Industry, only a single placebo-controlled clinical trial is required to demonstrate the safety and efficacy of an estrogen-alone drug product.

6.2. General Approach to Review of the Efficacy of the Drug

A single Phase 3, double-blind, placebo-controlled study (Study DPI00-005) is included in the submission. No other studies are included in the efficacy analysis.

6.3. Detailed Review of Trials by Indication

Study DPI00-005, the single primary Phase 3 study submitted, was a 16-week double-blind, randomized, placebo-controlled clinical trial in healthy postmenopausal women to evaluate the safety and efficacy of 0.3 mg synthetic conjugated estrogens, A versus placebo for the treatment of vulvar and vaginal atrophy associated with the menopause. Five investigational centers in the US initially randomized 72 subjects. One subject (Subject 066 at Center # 3 randomized to placebo) who did not receive study medication was excluded from all analyses. The number of randomized subjects at a center ranged from three (3) at Center # 5 (Marietta, GA) to twenty-two (22) at Center # 2 (Phoenix). All participating centers were considered as individual study sites.

Randomization into Study DPI00-005 began on November 22, 2000. Protocol DPI00-005 was submitted for review to IND 53,731 on October 12, 2000. Therefore, per the Sponsor, approximately 60 subjects had been randomized upon receipt of the Division's letter, dated January 18, 2001, containing comments and recommendations on Protocol DPI00-005. Nonetheless, most of the study inclusion and exclusion criteria meet the standards used for other VVA clinical trials with a few exceptions:

- The Sponsor felt that an overall 6-week washout period from any prior hormonal drug product use would be adequate to revert to an atrophic vagina; rather than the Agency's proposed washout periods based on the type of prior hormone use (such as vaginal creams, tablets, or transdermal systems).

Reviewer's Comments

Per the proposed revision of the 1995 HRT Guidance, the following washout periods are recommended before baseline assessments are made in studies on menopausal symptoms:

- 1) At least a 1-week washout period for prior vaginal hormonal products (rings, creams, gels).
- 2) At least a 4-week washout period for prior transdermal estrogen or estrogen/progestational products.
- 3) At least an 8-week washout period for prior oral estrogen and/or progestational product.
- 4) At least 3 months for prior progestational implants, estrogen or estrogen/progestational injectable drug therapy.
- 5) At least 6 months for prior estrogen pellet therapy or progestational injectable drug therapy.

In the submission, all subjects in both treatment groups said no to the exclusion criteria – “use of any oral or transdermal estrogen or progestin-containing product, or any topical medication within 6 weeks of the screening visit (week –2).” Therefore, the 6 weeks pre-screening washout period exceeded the recommended washout period for prior vaginal hormonal product use (6 weeks versus 1 week) and for prior transdermal hormonal product use (6 weeks versus 4 weeks). However, an 8-week washout period for prior oral hormonal product use was not met. Also, the prior use of progestational implants, estrogen or estrogen/progestational injectable drug therapy, estrogen pellet therapy or progestational injectable drug therapy was not mentioned in the exclusion criteria.

In the data submitted however, at screening, the mean Maturation Index score was similar for both treatment groups (39.51 for synthetic conjugated estrogens, A treatment group and 40.72 for the placebo treatment group) and both mean values were significantly below the upper limit of the screening inclusion criteria of a vaginal Maturation Index score of ≤ 55 . Therefore, it is unlikely that an overall 6-week washout period from any prior hormonal drug product use would have influenced the primary outcome variable - the difference between the 0.3 mg synthetic conjugated estrogens, A and placebo groups in the change in the Maturation Index between pretreatment (week -2) and the end-of-treatment (week 16).

- No pre-treatment or end-of-study subject self-assessment of symptoms was conducted. In response to this recommendation, the sponsor indicated that the use of a subject self-assessment of symptoms might "lead" the subject.

Reviewer's Comments

The proposed revision of the 1995 HRT Guidance recommends that a subject self-assessment of symptoms be completed at baseline and end-of-study to include the following categories: vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, vaginal pain associated with sexual activity, and vaginal bleeding associated with sexual activity. This proposed self-assessment of symptoms would allow the individual subject to identify the symptom classified as "most bothersome" prior to treatment, and provide a subjective measure of the relief of the "most bothersome symptom" over the treatment duration.

- No pre-treatment endometrial biopsy was obtained as recommended. However, a pre-treatment transvaginal ultrasonography (TVUS) was obtained with the provision that an endometrial biopsy would be performed at screening if the double-wall endometrial thickness was > 4 mm (the TVUS decision point recommended by the Division). 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.

Reviewer's Comments

The proposed revision of the 1995 HRT Guidance recommends that pre-treatment endometrial biopsies be performed for subjects with uteri for safety assessments, and that subjects with a diagnosis of endometrial hyperplasia be excluded from study participation.

Protocol DPI00-005 did incorporate a physician assessment of signs that included obtaining a vaginal pH, and an assessment of vaginal pallor (color of the vaginal epithelium), dryness, and diminished rugosity of the vaginal mucosa during screening. In the submission, however, only the data collected for vaginal pH is presented.

Upon request, the Sponsor confirmed that an assessment of vaginal atrophy, pallor, and dryness was evaluated as part of the inclusion criteria but were not numerically rated, and that no similar assessment was conducted during any other scheduled clinic visits (weeks 4, 8, 12, and 16) (Amendment submitted to the Agency on June 3, 2002).

Seventy-two postmenopausal women were enrolled at five centers; 71 subjects were randomized to received study medication (37 received 0.3 mg synthetic conjugated estrogens, A and 34 subjects received placebo) identical in size and appearance. Placebo and 0.3 mg synthetic conjugated estrogens, A tablets were administered orally once daily for the 16-week treatment duration. Duramed Pharmaceuticals, Inc. prepared, packaged, labeled, and provided all study medication.

Right and left lateral wall vaginal cytology specimens for Maturation Index were collected pre-treatment (week-2), and at weeks 4, 8, 12, and 16. The Women's Pathology Services laboratory (one "experienced", blinded pathologist) assessed the specimens for the number of parabasal, intermediate, and superficial cells and the percentages of each cell type was calculated utilizing the following equation:

$(\% \text{ Parabasal Cells times } 0.0) + (\% \text{ Intermediate Cells times } 0.5) + \% \text{ Superficial Cells times } 1.0 = \text{Maturation Index Score.}$

A Maturation Index score of ≤ 55 at screening was required for study entry.

Vaginal pH was measured at pretreatment (week -2) and week 16.

Reviewer's Comments

The proposed revision of the 1995 HRT Guidance recommends that a maximum of 5% superficial cells in the Maturation Index be used as an inclusion criterion if a treatment of vulvar and vaginal atrophy indication is being sought. However, this recommendation was initiated after the submission of the IND protocol for Study DPI00-005. Nonetheless, a review of the findings of each subject's pre-treatment Maturation Index shows that 95% of the subjects in the synthetic conjugated estrogens, A treatment group met the inclusion criterion (35 of 37 subjects, 2 subjects exceeded 5% superficial cells at screening), as did 91% of subjects in the placebo treatment group (31 of 34 subjects, 3 subjects exceeded 5% superficial cells at screening).

Fasting blood samples (≥ 12 hours) were collected for:

- Serum chemistry (glucose, creatinine, uric acid, BUN, AST, ALT, GGT, LDH, CPK, alkaline phosphatase, potassium, sodium, chloride, CO₂, calcium, phosphorous, magnesium, total protein, albumin, and total bilirubin) and hematology (complete blood with an automated differential) at pre-treatment (week -2) and week 16.
- Serum lipid profiles (total cholesterol, HDL cholesterol, LDL cholesterol, total/HDL cholesterol ratio, LDL/HDL cholesterol ratio, and triglycerides) at pre-treatment (week -2), prior to the start of study medication (week 0), and weeks 12 and 16.
- Cardiovascular disease risk markers (lipoprotein (a)[Lp(a)] and high sensitivity c-reactive protein (hs-CRP) at pre-treatment (week -2), prior to the start of study medication (week 0), and weeks 12 and 16.
- Bone markers levels (serum carboxy teleopeptide cross-link [sCTX]) at pre-treatment (week -2), prior to the start of study medication (week 0), and weeks 12 and 16.

For Study DPI00-005, 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 between pre-treatment (week -2) and the end-of-treatment (week 16). The secondary outcome variables included the:

- Changes in the Maturation Index between pre-treatment (week -2) and each interim visit (weeks 4, 8, and 12);
- Changes from pretreatment (week -2) to end-of-treatment (week 16) in vaginal pH, serum lipid profile, serum markers of cardiovascular disease risk, and bone resorption. For the serum lipid profile, markers of cardiovascular disease risk, and bone resorption, pre-treatment was either week -2 or the average of week -2 and week 0. For the serum lipid profile, the end-of-treatment value was considered week 16, or the average of week 12 and week 16. Per the submission, the analyses of lipid profile results were completed using the average of weeks 12 and 16.

Analysis of the primary and secondary outcome variables were completed for the ITT population (considered primary) and the PP population. Missing values were imputed utilizing the method of last observation carried forward (LOCF).

All of the 71 randomized subjects received treatment. Sixty-three subjects completed to week 16 (89%, 63 of 71 subjects). Eight subjects discontinued the study (11%, 8 of 71 subjects). One of the 8 subjects who discontinued was lost to follow-up (Subject 013 on synthetic conjugated estrogens, A), 2 discontinued because of adverse events (Subject 093 on synthetic conjugated estrogens, A for nausea, and Subject 012 on placebo for multiple symptoms), 1 for non-compliance (Subject 001 on placebo), 1 withdrew consent (Subject 036 on placebo), and 3 classified as other (Subject 100 on synthetic conjugated estrogens, A lost the study medication, Subject 046 on placebo due to personal conflict, and Subject 047 on placebo due to lack of efficacy). Overall, there was no significant difference between treatment groups in the number of subjects who completed the study or in the reasons for discontinuations. The disposition of subject by treatment groups is presented in Table 1.

Table 1: Disposition of Subjects by Treatment for Study DPI00-005

Parameter	Treatment Group		Total N (%)
	Cenestin® N (%)	Placebo N (%)	
Randomized Subjects (%)	37 (52)	34 (48)	71 (100)
Completed Study (%)	34 (48)	29 (41)	63 (89)
Did Not Complete Study(%)	3 (4)	5 (7)	8 (11)
Adverse Event	1 (3)	1 (3)	2 (3)
Non-Compliant with Protocol	0 (0)	1 (3)	1 (1)
Withdrew Consent	0 (0)	1 (3)	1 (1)
Lost to Follow-up	1 (3)	0 (0)	1 (1)
Other	1 (3)	2 (6)	3 (4)

Source: Adapted from NDA 20-992/S-016, Section 16.2, Listing 16.2.1, Table 14.1.1.a-1.

Two subjects in Study DPI00-005 are listed with protocol violations. Subject 008 on placebo had a history of thrombophlebitis (approximately 30 years ago) and had use estrogens for 12 years with no complications. Duramed Pharmaceuticals, Inc. approved the protocol violation. Data for this subject was included in all analyses. Subject 066 on placebo had a screening FSH level of 39.4 mIU/ml and was not approved for study participation.

Overall, for Study DPI00-005 there were no major differences in the demographic and baseline characteristics between the two treatment groups. See Table 2.

Table 2: Demographic Information for Study DPI00-005, Intent-to-Treat Population

Characteristic	Treatment Group						Total		
	Cenestin®			Placebo			N	Mean	SD
Parameter	n	Mean	SD	N	Mean	SD	N	Mean	SD
Age (years)	37	57.1	8.4	34	60.7	8.8	71	58.8	8.7
Last Menstrual Period (months)	37	194.2	110.5	34	185.2	141.0	71	189.9	125.2
Weight (pounds)	37	156.9	24.9	34	150.2	21.6	71	153.7	23.4
Height (inches)	37	64.8	2.5	33	63.4	2.5	70	64.1	2.5
Body Mass Index (kg/m ²)	37	26.3	3.8	33	26.3	4.3	70	26.3	4.0
Race		N (%)			N (%)			N (%)	
White		20 (54)			23 (67)			43 (61)	
Black		8 (21)			5 (15)			13 (18)	
Hispanic		7 (19)			5 (15)			12 (17)	
Asian		1 (3)			1 (3)			2 (3)	
Other		1 (3)			0			1 (1)	

Source: Adapted from NDA 20-992/S-016, Section 14, Tables 14.1.2-1 and 14.3.4.

Reviewer's Comments

As noted in Table 2, the mean age for subjects in Study DPI00-005 was 58.8 (SD 8.7). In this reviewer's experience, a mean age of 58.8 years is higher than normally reported for most HRT clinical trials (mean age range of 50 to 53 years of age). In Study DPI00-005, 10 % of the study population was < 50 years of age (7 of 71 subjects), 45% of the study population was 50 to 59 years of age (32 of 71 subjects), and 45 % of the study population was 60 years of age and above (32 of 71 subjects). However, this is not unexpected for a clinical trial investigating symptomatic postmenopausal women with vulvar and vaginal atrophy. Postmenopausal women with longer periods of hypoestrogenism are more likely to present with vulvar and vaginal itching, burning and dryness.

Per Table 2, the racial distribution within treatment groups in Study DPI00-005 is more equal than observed in other HRT clinical trials. Overall, in Study DPI00-005, sixty-one percent (61%) of subjects in Study DPI00-005 were white (43 of 71 subjects), 18% were black (13 of 71 subjects), 17% were Hispanic, (12 of 71 subjects) and 4% were Asian/Other (3 of 71 subjects). In other HRT clinical trials, more than 80% of the study population is white. The Sponsor is to be commended for achieving the racial distribution within treatment groups in Study DPI00-005.

Treatment compliance was measured by monitoring weekly drug accountability records. Non-compliance was defined as < 80% of the scheduled intakes of study medication taken. Three subjects reported < 80% compliance with study medication. Two of the 3 subjects were in the placebo treatment group (Subject Nos. 046 and 093), both were excluded from the PP analysis. The third subject, Subject No. 066, randomized in error to the placebo treatment group (FSH of 39.4 mIU/ml) was excluded from PP, ITT, and safety analyses.

Overall, 97% of the subjects in Study DPI00-005 were 80% compliant or better in both treatment groups. In the ITT population, the mean (standard deviation) for the synthetic conjugated estrogens, A group was 98.4% (5.8) and 98.7% (3.9) for the placebo group.

For Study DPI00-005, the primary efficacy parameter was the change in the Maturation Index between pre-treatment (week -2) and the end-of-treatment (week 16) for the 0.3 mg synthetic conjugated estrogens, A and placebo treatment groups. In the submission, the Sponsor presented the median change in the Maturation Index between pre-treatment (week -2) and week 16. In the proposed revision of the Agency's 1995 HRT Guidance, a 12 week treatment period of the mean difference in the Maturation Index between baseline and week 12 is recommended for the treatment of vulvar and vaginal atrophy indication. Upon request, the Sponsor presented data for parabasal, intermediate and superficial cells: means, standard deviations and coefficient of variation at week -2, week 12, and the change from week -2 to week 12, and provided the SAS data sets.

To better demonstrate the data presented by the Sponsor, the Agency's Statistical Reviewer prepared a summary of the Maturation Index analyses for the ITT population showing the mean difference in the Maturation Index between pre-treatment (week -2), and weeks 4, 8, 12, and 16. As shown in Table 3, the mean Maturation Index score was similar at baseline for the two treatment groups (39.5 for the synthetic conjugated estrogens, A group and 40.7 for the placebo treatment group). By week 4 the synthetic conjugated estrogens, A treatment group exhibited a statistically significant reduction in the mean Maturation Index (p-value < 0.0001) which continued through week 12 and week 16 (p-value < 0.0001 for both weeks). Superficial cells increased by a mean of 11.8% for the synthetic conjugated estrogens, A treatment group compared to 3.6% for the placebo treatment group at week 12, and 13.8% for the synthetic conjugated estrogens, A treatment group compared to 3.8% for the placebo treatment group at week 16. Corresponding decreases in parabasal and intermediate cells are shown in Table 3.

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Table 3: 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: Adapted from NDA 20-992/S-016, Section 16.4 (listing 9.b), Amendment dated November 1, 2001, and Statistical Review.

SD = Standard Deviation

In the submission, an analysis of median change in the vaginal pH from week -2 to week 16 was also performed. On November 1, 2001, upon request, the Sponsor provided the mean change in the vaginal pH from week -2 to week 16 for both treatment groups. Vaginal pH decreased significantly ($p=0.0001$) from week -2 to week 16 in the synthetic conjugated estrogens, A treatment group compared to the placebo treatment group (mean change -0.97 ± 1.00 and 0.10 ± 0.57 , respectively). See Table 4.

Table 4: 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	

Source: NDA 20-992/S-016, Table 14.2.4.a-1 and requested information provided by the Sponsor on November 1, 2001.

* P-values were derived by a one-way analysis of variance.

** Mean difference was derived through natural log-transformation. P-value derived from ANOVA of the ranked values to test for between treatment differences.

*** Change = Week 16 - Week -2.

Reviewer's Comments

In the submission, data was presented for the change in Maturation Index and vaginal pH between baseline and weeks 12 and 16, two of the three primary efficacy variables felt to be appropriate for a treatment of vulvar and vaginal atrophy indication (per the proposed revision of the Agency's 1995 HRT Guidance for Industry). However, since approximately 60 subjects had been enrolled in Study DPI00-005 upon receipt of the Agency's letter dated January 18, 2000, no data supporting the change in the subject's self-assessment of symptoms is presented in the submission.

6.4. Efficacy Conclusions

Data from a total of 71 healthy postmenopausal women in Study DPI00-005 was presented in the submission for the treatment of vulvar and vaginal atrophy associated with the menopause. From the data presented in Study DPI00-005, 0.3 mg synthetic conjugated estrogens, A taken daily, shows a statistically significant improvement in the Maturation Index score versus placebo that was detected at week 4 and maintained through weeks 8, 12, and 16. A statistically significant improvement in the vaginal pH between baseline and week 16 for 0.3 mg synthetic conjugated estrogens, A versus placebo was also evident.

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Conclusions

The safety data for Study DPI00-00 presented in the submission shows that the overall safety profile of 0.3 mg synthetic conjugated estrogens, A is acceptable. No deaths occurred during the conduct of Study DPI00-005. No serious adverse events were reported during the 16-week clinical trial duration. Two subjects discontinued due to treatment-emergent adverse events.

7.2. Materials Utilized in the Review

Study DPI00-005 was reviewed for safety outcomes. The safety population included all subjects who received at least one dose of study medication and had at least one follow-up safety evaluation.

7.3. Description of Patient Exposure

Seventy-one (71) subjects were randomized in Study DPI00-005 and are included in the safety database. 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. Baseline demographics were similar between placebo and 0.3 mg synthetic conjugated estrogens, A treatment groups (see Table 2, page 14 of this review).

7.4. Safety Findings from Clinical Studies

There were no deaths and no serious adverse events reported during Study DPI00-005. Sixty-three (63) subjects completed the study to week 16 (34 in the 0.3 mg synthetic conjugated estrogens, A treatment group and 29 in the placebo treatment group). 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.

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). The number of subjects who withdrew due to an adverse event was equal in both treatment groups (one in each group). Two of the eight subjects who discontinued did so because of an adverse event:

- Subject No. 093 (synthetic conjugated estrogens, A): Subject discontinued due to an adverse event, nausea.
- Subject No. 012 (placebo): Subject discontinued due to an adverse event, multiple vaginal symptoms

Two of the remaining 6 subjects were assigned to the synthetic conjugated estrogens, A treatment group:

- Subject No. 013 (synthetic conjugated estrogens, A): Subject was lost to follow-up.
- Subject No. 100 (synthetic conjugated estrogens, A): The Sponsor discontinued subject because she lost the study medication (classified as other).

The remaining 4 subjects assigned to the placebo treatment group:

- Subject No. 001 (placebo): Principal investigator discontinued subject due to noncompliance with the protocol.
- Subject No. 036 (placebo): Subject withdrew consent.
- Subject No. 046 (placebo): Subject discontinued due to personal conflict (classified as other).
- Subject No. 047 (placebo): Subject discontinued due to lack of efficacy (classified as other).

See Table 1, "Disposition of Subjects by Treatment for Study DPI00-005" on page 14 of this review for a summary of subject disposition by treatment group for Study DPI00-005.

Reviewer's Comments

A high percentage of subjects (89%, 62 of 71 subjects) completed the primary Phase 3 Study DPI00-005.

A total of 59 subjects in the safety database (83%, 59 of 71 subjects) reported treatment-emergent adverse events (TEAE). Of the subjects who received 0.3 mg synthetic conjugated estrogens, A, 32 (86.5%, 32 of 37 subjects) reported at least one adverse event. Twenty-seven (27) subjects who received placebo (79.4%, 27 of 34 subjects) reported at least one adverse event. There were no significant differences between treatment groups in the overall incidence of treatment-emergent adverse events with the exception of an increased incidence of urinary tract infection in the placebo treatment group (18%, 6 of 34 subjects) compared with the 0.3 mg synthetic conjugated estrogens, A treatment group (0%). Leukorrhea (32%, 12 of 36 subjects in the synthetic conjugated estrogens, A group, and 15%, 5 of 34 subjects in the placebo group), vaginitis (24%, 9 of 36 subjects in the synthetic conjugated estrogens, A group, and 15%, 5 of 34 subjects in the placebo group), and headache (11%, 4 of 36 subjects in the synthetic conjugated estrogens, A group, and 21%, 7 of 34 subjects in the placebo group) were the most commonly reported treatment-emergent adverse events.

See Table 5 for the number and percent of subjects reporting treatment-emergent adverse events that occurred at a rate of $\geq 2\%$ in Study DPI00-005.

Table 5: All Treatment Emergent Adverse Events Regardless of Drug Relationship Reported at a Frequency $\geq 2\%$ for Study DPI00-005

Body System/Preferred Term	Cenestin® N (%)	Placebo N (%)
Selected Safety Population	36 (97)	34 (100)
Subjects with Adverse Events	32 (87)	27 (79)
Body as a Whole		
Headache	4 (11)	7 (21)
Infection	4 (11)	4 (12)
Allergic Reaction	3 (8)	1 (3)
Flu Syndrome	3 (8)	1 (3)
Injury Accident	2 (5)	1 (3)
Abdominal Pain	1(3)	2 (6)
Back Pain	2 (5)	1 (3)
Cyst	2 (5)	0 (0)
Neoplasm	0 (0)	1 (3)
Chest Pain	0 (0)	1 (3)
Asthenia	3 (8)	2 (6)
Cardiovascular		
Vasodilatation	1 (3)	0 (0)

Hypertension	0 (0)	1 (3)
Hypotension	1 (3)	0 (0)
Palpitations	0 (0)	1 (3)
Digestive		
Nausea	4 (11)	2 (6)
Dyspepsia	2 (5)	1 (3)
Vomiting	3 (8)	0 (0)
Increased Appetite	2 (5)	0 (0)
Constipation	0 (0)	2 (6)
Anorexia	0 (0)	1 (3)
Dysphagia	1 (3)	0 (0)
Enteritis	0 (0)	1 (3)
Gastroenteritis	1 (3)	0 (0)
Stomach Ulcer	1 (3)	0 (0)
Musculoskeletal		
Arthralgia	1 (3)	2 (6)
Arthritis	1 (3)	0 (0)
Rheumatoid Arthritis	1 (3)	0 (0)
Bone Disorder	0 (0)	1 (3)
Myalgia	1 (3)	0 (0)
Neurological		
Emotional Labile	2 (5)	2 (6)
Hypertonia	1 (3)	3 (9)
Insomnia	1 (3)	3 (9)
Dizziness	3 (8)	0 (0)
Anxiety	0 (0)	1 (3)
Confusion	1 (3)	0 (0)
Depression	1 (3)	0 (0)
Dry Mouth	0 (0)	1 (3)
Nervousness	1 (3)	0 (0)
Vertigo	1 (3)	0 (0)
Respiratory		
Sinusitis	3 (8)	3 (9)
Rhinitis	2 (5)	2 (6)
Dyspnea	0 (0)	1 (3)
Pharyngitis	1 (3)	0 (0)
Skin		
Rash	2 (5)	4 (12)
Dry Skin	1 (3)	1 (3)
Acne	1 (3)	0 (0)
Hirsutism	1 (3)	0 (0)
Pruritis	1 (3)	0 (0)
Sweat	1 (3)	0 (0)

Urogenital		
Leukorrhea	12 (32)	5 (15)
Vaginitis	9 (24)	5 (15)
Endometrial Thickening*	3 (8)	3 (9)
Urinary Tract Infection	0 (0)	6 (18)
Breast Pain	2 (5)	4 (12)
Urinary Incontinence	3 (8)	1 (3)
Abnormal Urine	1 (3)	2 (6)
Dysuria	0 (0)	2 (6)
Metrorrhagia	2 (5)	0 (0)
Urinary Frequency	2 (5)	0 (0)
Breast Enlargement	1 (3)	0 (0)
Cystitis	0 (0)	1 (3)
Vaginal Hemorrhage	0 (0)	1 (3)
Hematuria	1 (3)	0 (0)

Source: NDA 20-992/S-016, Table 12.2.1-1, Section 14 (Table 14.3.5.a), Section 16.4 (Listing 19).

* Coding corrected per amendment dated June 3, 2002.

One blinded pathologist reviewed the endometrial biopsy slides as safety assessments for this 16-week study. In the initial submission, three cases of endometrial hyperplasia were listed for the synthetic conjugated estrogens, A treatment group and three cases of endometrial hyperplasia were listed for the placebo treatment group under the urogenital body system. On June 3, 2002, the Sponsor submitted an amendment to the NDA stating that a coding error had occurred. Per the amendment, "all six women had an increase in their endometrial thickness with no endometrial hyperplasia present." Therefore, "the correct term should be endometrial *thickening*." The reviewer has incorporated this coding correction in Table 5.

Reviewer's Comments

In Study DPI00-005, if a TVUS performed at week 16 was reported to be > 4 mm, an endometrial biopsy was performed. Three subjects in the synthetic conjugated estrogens, A treatment group had a TVUS double-wall endometrial thickness > 4 mm at week 16 (Subjects 002, 007, and 068), as did 3 subjects in the placebo treatment group (Subjects 094, 096, and 102). All 6 of these subjects had endometrial biopsies attempted/performed at week 16. The outcomes are as follows:

Synthetic conjugated estrogens, A treatment group:

- Subject 002, week 16 TVUS = 6.8 mm, endometrial biopsy result = proliferative endometrium consistent with mild estrogen stimulation; end-of-study Prometrium® dispensed;
- Subject 007, week 16 TVUS = 7.5 mm, endometrial biopsy result = strips of benign superficial epithelium suggestive of atrophic endometrium; end-of-study Prometrium® dispensed;
- Subject 068, week 16 TVUS = 9 mm, endometrial biopsy result = proliferative endometrium consistent with mild estrogen stimulation; end-of-study Prometrium® dispensed.

Placebo treatment group

- Subject 094, week 16 TVUS = 5.2 mm, endometrial biopsy results = atrophic endometrium, end-of-study Prometrium® dispensed.
- Subject 096, week 16 TVUS = 8 mm, endometrial biopsy results = cervical stenosis, unable to obtain endometrial sample, end-of-study Prometrium® dispensed.
- Subject 102, week 16 TVUS = 7 mm, endometrial biopsy result = cervical stenosis, unable to obtain endometrial sample, end-of-study Prometrium® dispensed.

A diagnosis was presented for 4 of the 6 subject with TVUS double-wall endometrial thickness > 4 mm at week 16. Since Subjects 096 and 102 in the placebo treatment group presented with cervical stenosis, no endometrial samples for diagnosis were obtained for these two subjects. While it is not unexpected for subjects with a mean of 189.9 months (15.8 years) since last menstrual period to present with cervical stenosis, it is important for safety reasons to complete appropriate endometrial evaluations in clinical trials. In the submission, however, there is no information presented regarding referrals for Subjects 096 and 102 for additional endometrial evaluations (e.g., endometrial dilatation and curettage).

No adverse events are reported, however, in the 4-Month Safety Update or the Second Safety Update submitted to NDA 20-992/S-016.

Thirty-five subjects with uteri were provided 300 mg Prometrium® daily for 14 days at end-of-study or early withdrawal, per protocol. However, one subject with a uterus who early terminated was not provided Prometrium® (Subject 093 in the synthetic conjugated estrogens, A treatment group), and no report is available for one placebo subject with a uterus (Subject 046). In addition, there is no evidence in the submission of any post-study contact with those subjects with uteri provided Prometrium® to determine compliance with medication or to assess post-medication vaginal bleeding.

Reviewer's Comments

Prometrium® (micronized progesterone) 200 mg per day for 12 days, sequentially per 28-day cycle, is approved for the prevention of endometrial hyperplasia in postmenopausal women with a uterus who are receiving daily conjugated estrogens tablets. In Study DPI00-005, all subjects with uteri were provided 300 mg Prometrium® per day for 14 days at the end-of-study. Although the 300 mg Prometrium® dose is not the approved dose for protection of the endometrium, The American College of Obstetricians and Gynecologists (ACOG, Hormone Replacement Therapy Education Bulletin, Number 247, May 1989) states that 200-300 mg micronized progesterone per day for 12 days per month is sufficient to protect against endometrial hyperplasia. In addition, no post-treatment adverse events are reported in the 4-Month Safety Update.

One subject in the 0.3 mg synthetic conjugated estrogens, A treatment group (Subject 002) had a high calcium level at screening (10.4 mg/dL) and at week 16 (10.7 mg/dL). With this one exception, no serum chemistry, hematology, or urinalysis test results were deemed to be clinically significant for any subject during the conduct of Study DPI00-005. Changes in systolic and diastolic blood pressure during Study DPI00-005 were small in magnitude, less than 4 mm in both treatment groups. Body weight remained stable throughout the 16-week treatment duration. Mean changes in both treatment groups were less than two pounds.

The results of serum lipid profiles (total cholesterol, HDL cholesterol, LDL cholesterol, total/HDL cholesterol ratio, LDL/HDL cholesterol ratio, and triglycerides), cardiovascular disease risk markers (lipoprotein (a)[Lp(a)] and high sensitivity c-reactive protein (hs-CRP), and bone markers levels (serum carboxy teleopeptide cross-link [sCTX]) are presented in the submission as secondary efficacy endpoints.

A statistical summary for the change from the average of weeks -2 and 0 to week 16 was presented for Lp(a), hs-CRP and sCTX. No statistically significant changes in either the 0.3 mg synthetic conjugated estrogens, A or placebo treatment groups were found for lipoprotein (a). High-sensitivity CRP decreased significantly in the placebo treatment group, and no significant change was shown in the synthetic conjugated estrogens, A treatment group. However, a statistically significant decrease in serum CTX in the synthetic conjugated estrogens, A treatment group was shown (median of -0.1 ng/mL, p<0.0001). The clinical meaning of these results remains to be clarified.

In the submission, the results of serum lipid profile analyses are presented for the change from the average from weeks -2 and 0 to the average of weeks 12 and 16. Per the submission, there were no significant changes from baseline lipids in the placebo treatment group, whereas, all lipid variables were significantly affected in the synthetic conjugated estrogens, A treatment group with the exception of serum triglyceride.

Because averages from weeks -2 and 0 to weeks 12 and 16 were presented in the submission, the Statistical Reviewer performed an analysis of the change in the lipid profile from pretreatment week -2 (baseline) to week 16 (end-of-study).

These findings show that there were statistically significant differences between the 0.3 mg synthetic conjugated estrogens, A and placebo treatment groups in total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides, and total cholesterol/HDL cholesterol ratio. There was no statistically significant difference in the LDL/HDL cholesterol ratio. Please see Table 6.

Table 6: Serum Lipid Profile Summary for Study DPI00-005, Intent-to-Treat Population

Variable	Study Week	Cenestin® N = 34		Placebo N = 29	
		Mean (SD)	Mean Change From Baseline	Mean (SD)	Mean Change From Baseline
Total Cholesterol (mg/dL)	-2	226.4 (35.2)		228.1 (30.3)	
	16	211.3 (33.0)	-17.0	230.0 (30.3)	1.3 (24.8)
HDL Cholesterol (mg/dL)	-2	61.0 (14.2)		62.7 (13.8)	
	16	65.8 (17.9)	5.2 (9.1)	61.3 (13.2)	-1.9 (10.9)
LDL Cholesterol (mg/dL)	-2	140.0 (31.7)		140.7 (27.8)	
	16	119.8 (28.3)	-22.8 (26.5)	144 (29)	4.0 (22.1)
Triglycerides (mg/dL)	-2	127.3 (67.8)		129.4 (63.9)	
	16	128.8 (62.6)	3.4 (63)	127.4 (65)	-0.4 (53.8)
Total/HDL Cholesterol	-2	3.9 (0.9)		3.9 (1.0)	
	16	3.4 (0.8)	-0.6 (0.7)	3.9 (1.2)	0.2 (0.9)
LDL/HDL Cholesterol	-2	2.4 (0.7)		2.4 (0.8)	
	16	2.0 (0.6)	-0.5 (0.5)	2.4 (1.0)	0.2 (0.7)

Source: Adapted from the Statistical Review, SAS data.

SD = Standard Deviation

Reviewer's Comments

Overall, there was no significant difference between treatment groups in the incidence of treatment-emergent adverse events. In general, adverse events did not differ significantly between treatment groups with the exception of an increased incidence of urinary tract infection in the placebo group (18%, 6 of 34 subjects in the placebo group) compared with zero percent in the synthetic conjugated estrogens, A treatment group. This difference is unexplained.

Although, the reported incidence rates of leukorrhea (reported as white, yellow, or brown vaginal discharge/secretion) and vaginitis (reported as vaginal itching, dryness or burning, and vaginal infection [yeast and trichomonas]) appear to be high overall (24%, 17 of 71 subjects reported leukorrhea; and 20%, 14 of 71 subjects reported vaginitis), these rates are not significantly different from those reported in other similar HRT clinical trials. As shown in Table 5 on page 18 of this review, a higher number of subjects in the synthetic conjugated estrogens, A treatment group reported leukorrhea and vaginitis than in the placebo treatment group. This finding is not unexpected for estrogen drug products.

No abnormal endometrial histologic findings (simple, complex, or atypical hyperplasia or cancer) were reported for Study DPI00-005.

The Statistical Reviewer's analyses of serum lipid profile results were generally consistent with the results presented in the submission except for triglycerides (statistically significant difference from placebo found by the Statistical Reviewer) and the LDL/HDL ratio (no statistically significant difference from placebo). Overall, the serum lipid profile findings show that women treated with 0.3 mg synthetic conjugated estrogens, A have a more favorable increase in HDL cholesterol and a more favorable decrease in total cholesterol and LDL cholesterol.

7.5. Miscellaneous Studies

One primary, Phase 3 study constitutes the database for the information provided in the application. No additional studies were conducted that contribute to either the historical information regarding the product development or actual safety and efficacy data.

7.6. Literature Review for Safety

No independent literature review was conducted.

7.7. Postmarketing Surveillance – If Applicable

Cenestin® 0.625 mg, 0.9 mg, and 1.25 mg tablets are marketed in the US. Cenestin® is not marketed internationally.

7.8. Safety Update

4-Month Safety Update

On May 16, 2002, the sponsor submitted the 4-Month Safety Update. No additional studies with Cenestin® had been initiated, and no additional safety data had been collected since the NDA submission.

Second Safety Update

On May 16, 2002, the sponsor submitted the Second Safety Update. No additional studies with Cenestin® had been initiated, and no additional safety data had been collected since the NDA submission.

7.9. Drug Withdrawal, Abuse, and Overdose Experience

No serious adverse events were reported as a result of Cenestin® abuse or overdose during the clinical trial. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding in postmenopausal women with uteri.

7.10. Adequacy of Safety Testing

Physical examinations, including breast and pelvic/Pap smear examination, vital signs and body weight were completed at screening and week 16. Mammograms were performed at screening unless documented results of a previous normal mammogram (within the previous 36 weeks) were available. Endometrial biopsies were performed at end-of-study if the TVUS double-wall endometrial thickness was > 4 mm. All treated subjects with a uterus received a 14-day course of 300 mg Prometrium®/day at the end-of-study.

7.11. Labeling Safety Issues and Postmarketing Commitments

The proposed labeling for Cenestin® complies with the labeling guidance for estrogen drug products.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

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 these dosage strengths for the treatment of vulvar and vaginal atrophy.

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicant's Efficacy and Safety Analyses of Effects of Gender, Age, Race, or Ethnicity. Comment on Adequacy of Applicant's Analyses.

Cenestin® 0.3 mg/day should only be used in postmenopausal women for the relief of vulvar and vaginal atrophy.

In Study DPI00-005, 45% of the study population was 50 to 59 years of age (32 of 71 subjects), 45 % of the study population was 60 years of age and above (32 of 71 subjects), and 10 % of the study population was < 50 years of age (7 of 71 subjects). In the 60 years of age and above subgroup, 13 subjects (18%, 13 of 71 subjects) were over 65 years of age. Three of these subjects were assigned to the 0.3 mg synthetic conjugated estrogens, A treatment group and 10 were assigned to the placebo treatment group.

Reviewer's Comments

Eighteen percent (18%, 13 of 71 subjects) of the subjects in Study DPI00-005 were over 65 years of age. Having 18% of the study population over 65 years of age in an HRT clinical trial is commendable although not unexpected in a study solely designed to investigate the treatment of vulvar and vaginal atrophy. In other HRT clinical trial that combine VMS and VVA indications, the majority of women who meet the VMS inclusion criterion of at least 7 to 8 moderate-to-severe hot flushes per day are between 50 to 59 years of age.

Although the data obtained during the conduct of Study DPI00-005 provides equal information for the 50 to 59 and ≥ 60 years of age subgroups, there is an insufficient number of geriatric subjects over 65 years of age (a total of 13 subjects, 3 received synthetic conjugated estrogens, A and 10 received placebo) to support any conclusion regarding the use of 0.3 mg synthetic conjugated estrogens, A in a geriatric age population for inclusion in labeling.

9.2. Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

A request for a pediatric waiver was submitted with NDA 20-992/S-016 on August 16, 2001. Cenestin® is only recommended for use in postmenopausal women.

Reviewer's Comments

A pediatric waiver should be granted.

9.3. Data Available or Needed in Other Populations Such as Renal or Hepatic Compromised Patients, or Use in Pregnancy.

No data is available or needed for other special populations. Cenestin® should not be used during pregnancy.

10. CONCLUSIONS AND RECOMMENDATIONS, AND LABELING

10.1. Conclusions Regarding Safety and Efficacy

Cenestin® (0.625 mg, 0.9 mg, and 1.25 mg/ day) has been used clinically for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause since 1999. In this submission, results from a 16-week placebo-controlled clinical trial have demonstrated a statistically significant relief of vulvar and vaginal atrophy associated with the menopause in health postmenopausal women. Only a limited number of mild and moderate adverse events were reported with 0.3 mg synthetic conjugated estrogens in the Phase 3 clinical trial included in the submission.

10.2. Recommendations on Approvability

The data presented in this supplemental NDA provides sufficient evidence from one placebo-controlled clinical trial (Study DPI00-005) to support the safety and efficacy of 0.3 mg synthetic conjugated estrogens, A taken daily for the treatment of vulvar and vaginal atrophy associated with the menopause. From a clinical perspective, the 0.3 mg synthetic conjugated estrogens, A dosage strength can be approved.

10.3 Labeling

The proposed labeling submitted was modified in accordance with the proposed revisions to the "Labeling Guidance for Noncontraceptive Estrogen Drug Products – Prescribing Information for Healthcare Providers and Patient Labeling" as published in the **Federal Register**, Vol. 64, No. 186, September 27, 1999, Notices.

The **DESCRIPTION** section of the labeling has been modified to include the 0.3 mg Cenestin® dosage strength.

The **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, has been revised to include standard information found in other approved estrogen labels. The **Drug Interactions** subsection has been revised to include information on P450 3A4 inducers and inhibitors. A **Special Populations** subsection has been incorporated into labeling. In the **Clinical Studies** subsection, the Sponsor requested the addition of information regarding effects on vulvar and vaginal atrophy, and effects on lipids. Following discussion with the Sponsor on June 114, 2002, the information regarding the effects on vulvar and vaginal atrophy was modified to read,

In addition, Figure 2 entitled, "Summary of % Superficial Cells Results in Patients Following 16 Weeks of Treatment with Cenestin 0.3 mg" will be included under "*Effects on vulvar and vaginal atrophy*".

Under the **INDICATION AND USAGE** section, revised language has been recommended to include the dosage strengths approved for each indication.

Under the **WARNINGS** section, revised language has been recommended for the following subsections, **Induction of Malignant Neoplasms, Thromboembolic Disorders, Gallbladder Disease, and Hypercalcemia**. In the **PRECAUTIONS** section, revised language is recommended for the following subsections, **Addition of a progestin when a woman has not had a hysterectomy, Elevated blood pressure, and Familial hyperlipoproteinemia**. The following subsections have been included, **Hypothyroidism, Fluid retention, Exacerbation of endometriosis, and Hypocalcemia**.

In the **ADVERSE REACTIONS** section, the Sponsor is requested to replace Table 3 (renumbered Table 4) entitled, "Number (%) of Patients with Adverse Events With a Greater than Occurrence Rate By Body System and Treatment Group" with a table that shows adverse events with $\geq 2\%$ occurrence rate.

The **DOSAGE AND ADMINISTRATION** and **HOW SUPPLIED** sections have been appropriately modified to incorporate the addition of 0.3 mg Cenestin for the treatment of vulvar and vaginal atrophy associated with the menopause.

The **PATIENT INFORMATION** insert has been modified in compliance with the plain language initiative and recommendations from the Division of Drug Marketing, advertising and Communications (DDMAC), and the Division of Surveillance, Research & Communication Support (DSRCS).

See the attached labeling in Appendix 1 of this review.

APPENDIX 1

Revised Drug Label

**Appears This Way
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21 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

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/s/

Theresa Van Der Vlugt
6/17/02 12:50:41 PM
MEDICAL OFFICER

Shelley Slaughter
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I concur.

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