CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-788

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date:	September 12, 2008
From:	Shelley R. Slaughter, M.D., Ph.D.
NDA:	21-788
Applicant:	Duramed Pharmaceuticals, Inc, Subsidiary of Barr Pharmaceuticals, Inc.
Date of Submission:	March 13, 2008
PDUFA:	September 12, 2008
Requested Proprietary Name/	Bijuvia™ Vaginal Cream
Established (USAN) name:	synthetic conjugated estrogens, A vaginal cream
Dosage forms/Strength:	1 g synthetic conjugated estrogens, A vaginal cream
Proposed Indication:	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause
Recommendation:	Approval contingent upon agreement between the Sponsor and the Agency on the label. The Sponsor will be asked to agree to a Phase 4 commitment to study the lowest effective dose for each indication

Executive Summary:

1. Introduction

With this complete response, Duramed is seeking for synthetic conjugated estrogens, A vaginal cream an indication for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to the Menopause. A Not Approvable decision was taken on April 25, 2005 based on failure to demonstrate statistically significant improvement in any symptom of vulvar and vaginal atrophy even though appropriate changes to vaginal cytology (statistically significant increase in superficial cells and statistically significant decrease in parabasal cells relative to placebo) and vaginal pH (statistically significant decrease in pH) were demonstrated. At a meeting on July 18, 2005 the Agency indicated to Duramed that it would be necessary to conduct a well-controlled trial that demonstrated statistical significance for all co-primary endpoints [proportion of vaginal superficial and parabasal cells, vaginal pH, and the (individual) most bothersome moderate to severe symptom of vulvar and vaginal atrophy] as outlined in the 2003 Draft Guidance for Industry entitled, "ESTROGEN AND ESTROGEN/PROGESTIN DRUG PRODUCTS TO TREAT VASOMOTOR SYMPTOMS AND VULVAR AND VAGINAL ATROPHY SYMPTOMS – RECOMMENDATIONS FOR CLINICAL EVALUATION" (henceforth referred to in this review as the 2003 Draft HT Clinical Trial Guidance). In response, Duramed has submitted Study DR-CEN-302, a randomized, multicenter, double-blind, placebo controlled trial to compare the effects of 12 weeks of treatment with synthetic conjugated estrogens, A vaginal cream vs. placebo vaginal cream on vulvar and vaginal atrophy in healthy postmenopausal women.

2. Background

In 1972, the Federal Register Drug Efficacy Study Implementation Notice (DESI 1533.37 FR 14826 dated July 31, 1972) which was based on the National Academy of Sciences-National Research Council Drug Efficacy Study Group (NAS-NRC) review of published literature found non-contraceptive estrogen drugs to be effective for several "DESI Indications". This 1972 notice and two additional notices (DESI 1543, 41 FR$#114 dated September 29, 1976 and 51 FR 12568 dated April 11, 1986) defined these "DESI Indications" as follows:

1. moderate-to-severe vasomotor symptoms (MSVS) associated with the menopause;
2. senile vaginitis;
3 kraurosis vulvae;

4. pruritis vulvae;
5. abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology;
6. female hypogonadism;
7. amenorrhea;
8. female castration;
9. primary ovarian failure;
10. prevention of postpartum breast engorgement;
11. palliation of selected cases of inoperable progressing mammary and prostatic carcinoma; and
12. postmenopausal osteoporosis.

On September 29, 1976, Federal Register notice 41 FR 43108 instituted "class labeling" for estrogen products. The purpose was to introduce uniform labeling with respect to benefits and risks of these products. Prior to 1999, the indication of treatment of vulvar and vaginal atrophy was granted to drug products as part of non-contraceptive estrogen class labeling for products that demonstrated efficacy for the treatment of moderate to severe vasomotor symptoms. On September 22, 1999, draft revision of the LABELING GUIDANCE FOR NON-CONTRACEPTIVE ESTROGEN DRUG PRODUCTS-PRESCRIBING INFORMATION FOR HEALTH CARE PROVIDERS AND PATIENT LABELING was noticed in 64 FR number 186. This Labeling Guidance specified that indications for estrogen and estrogen/progestin drug products would not be granted based on class labeling and would be granted based on clinical trial demonstration of efficacy for the requested indication. Subsequent to this notice, the indication for treatment of vulvar and vaginal atrophy was granted based on demonstration of statistically significant improvement in the maturation index (vaginal superficial, intermediate and parabasal cells) from baseline to study end for the drug product when compared to placebo. On October 18, 1999, the Advisory Committee on Reproductive Drugs recommended that the Division evaluate drug product efficacy based on demonstration of symptomatic relief in addition to changes in the signs of vulvar and vaginal atrophy. Keeping this sound advice in-mind, when the Division drafted an updated and revised Guidance for Industry for products intended to treat vasomotor symptoms and vulvar and vaginal atrophy associated with the menopause, the 2003 Draft HT Clinical Trial Guidance, we recommended that to be considered efficacious for the indication, a drug product should be studied in a trial where subjects display at least one moderate to severe symptom of vulvar and vaginal atrophy at baseline that was self-identified by the subject as most bothersome to her, as well as physical findings consistent with vulvar and vaginal atrophy ($pH \geq 5.0$ and vaginal smear superficial cells $< 5\%$). To be considered efficacious, products when compared to placebo, should demonstrate statistically significant improvement in the subject's self-identified most bothersome symptom (reduction in severity), vaginal superficial (increase in percentage) and parabasal (reduction in percentage) cells and vaginal pH (reduction).

Following a Not Approvable action on April 25, 2005, Duramed has submitted a complete response with Study DR-CEN-302, a randomized, multicenter, double-blind, placebo controlled 12 weeks study comparing treatment with synthetic conjugated estrogens, A vaginal cream vs. placebo vaginal cream on vulvar and vaginal atrophy in healthy postmenopausal women. The study has coprimary endpoints analyses of change from baseline in vaginal superficial and parabasal cells, vaginal pH and the patient self-assessed most bothersome symptom. Because the study protocol did not pre-specify the symptoms to be considered in the primary analysis (choices were vaginal dryness, pain with intercourse, vaginal irritation/itching and vaginal soreness) a statistical adjustment for multiple comparisons was applied.

Currently five dosage strengths of oral Cenestin® (synthetic conjugated estrogens, A) tablets, 0.3 mg, 0.45 mg, 0625 mg, 0.9 mg and 1.25 mg are marketed in the U.S. Cenestin®, synthetic

conjugated estrogens, A oral tablets, doses 0.625 mg/day, 0.9 mg/day and 2 x 0.625 mg/day, received approval on March 24, 1999 for the treatment of moderate to severe vasomotor symptoms associated with the menopause. On March 24, 2000, a single 1.25 mg dosage strength table was approved based on the results of bioequivalence of the 1.25 mg Cenestin® tablet to 2 x 0.625 mg Cenestin® tablets. On June 21, 2002 Cenestin® 0.3 mg strength oral tablet received approval for the treatment of vulvar and vaginal atrophy associated with the menopause based on a 16-week study assessing the change in the maturation index from baseline to week 16 relative to placebo as the primary efficacy evaluation. On February 5, 2004, a 0.45 mg Cenestin® tablet was approved for the treatment of moderate to severe vasomotor symptoms associated with the menopause based on the data presented in a single randomized, double-blind, placebo-controlled 12-week clinical trial.

Synthetic conjugated estrogens, A vaginal cream is not marketed in any country.

3. CMC/Devise

Synthetic conjugated estrogens A, vaginal cream contains 0.625 mg of synthetic conjugated estrogens, A in a non-liquefying base containing benzyl alcohol, cetyl alcohol, cetyl esters wax, glycerin, glyceryl monostearate, light mineral oil, methyl stearate, propylene glycol monostearate, sodium hydroxide, sodium lauryl sulfate, sodium phosphate dibasic anhydrous and white wax. Synthetic conjugated estrogens, A, is a blend of nine (9) synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17-dihydroequilin sulfate, sodium 17-estradiol sulfate, sodium 17-dihydroequilin sulfate, sodium 17-dihydroequilenin sulfate, sodium 17-dihydroequilenin sulfate, sodium equilenin sulfate and sodium 17-estradiol sulfate.

The major CMC issue of this review cycle centered on the change in the analytical method for "Free Steroids" from the USP procedure based on gas chromatography (GC) to a high pressure liquid chromatography (HPLC) method. The new method was noted to yield results —times lower than the previous method. The Sponsor was asked to provide additional data to support the validation report findings. The Sponsor responded with information that demonstrated that "Free Steroids" are not lost during the extraction step in the new method. The "Free Steroids" specification limit was lowered by a factor of —rom 3% to —%. b(4)

Additional minor deficiencies included: lack of ID test on release specifications; incorrect Total Yeast and Mold limit on specification; and use of a response factor in analytical method, instead of an official USP standard exists. These issues were all resolved. In the original complete response, the labeling did not list water among other inactive ingredients. This deficiency was adequately addressed in an amendment dated July 29, 2008. The original Drug Listing Data Elements (DLDE) table was deficient. It did not list water among the inactive ingredients and it was incorrectly split into two parts. The split was the result of the listing of the applicator in the table as part of the drug product. The Sponsor was informed about how the DLDE table should appear and the deficiency was successfully addressed in an amendment dated September 10, 2008.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/toxicology review was performed in the original review cycle for the drug product. Per agreement with the Division, the Sponsor did not conduct any non-clinical pharmacology or toxicology studies. The Sponsor requested and the Agency agreed that the Agency would refer to the referenced-listed conjugated estrogen cream products regarding the non-clinical pharmacology, ADME, and toxicology to satisfy NDA requirements for non-clinical assessment of Cenestin Vaginal Cream.

5. Clinical Pharmacology/Biopharmaceutics

The complete response included along with Study DR-CEN-302, a pharmacokinetic study, DR-CEN-10X, comparing two doses, 1 g (0.625 mg active ingredient) and 2 g (1.25 mg active ingredient), of synthetic conjugated estrogens, A vaginal cream (administered daily for 7 days, then twice weekly for a total of 27 days of administration of the product) to 0.3 mg Cenestin® oral tablet.. The PK results showed that steady-state systemic exposure (AUC0-24 and AUCweekly following Day 27 dose) from once daily for 7 days, then twice weekly administration of both doses, 1 g (0.625 mg) and 2 g (1.25 mg) synthetic conjugated estrogens, A vaginal cream was significantly lower than once daily administration of 0.3 mg Cenestin® oral tablet. See Clinical Pharmacology Review for complete discussion of systemic exposure and other pK parameters for synthetic conjugated estrogens, A vaginal cream.

The Sponsor did not conduct formal studies on age, gender race or any other special populations. Systemic drug interactions are expected to be lower than those demonstrated with oral synthetic conjugated estrogens, A products, nevertheless, the drug product will receive class labeling that inducers or inhibitors of cytochrome P450 3A4 may affect drug metabolism.

The Sponsor was asked to revise Table 2 title and Table 2 in the submitted labeling to remove Comparator data from both. The Sponsor was also requested to delete Figure 1 and replace it with a figure demonstrating the pharmacokinetic profile versus time for 1gram synthetic conjugated estrogens, A vaginal cream following the Day 27 dose demonstrating baseline-adjusted free estratiol, baseline-adjusted free estrone and free equilin. The Sponsor complied with an acceptable Figure 1 in an amendment dated September 11, 2008.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds the complete response to be acceptable from a clinical pharmacology perspective.

6. Clinical Microbiology:

The original NDA submission, dated June 25, 2004, included data for "Microbial Limits and Antimicrobial Effectiveness Testing" in the CMC section. These were all deemed to be satisfactory no new data was included in the resubmission.

7. Clinical /Statistical Efficacy

The Sponsor complied with the 2003 Draft HT Clinical Trial Guidance for co-primary endpoints. They evaluated a mITT population of subjects meeting all three Guidance recommended criteria for a VVA study, which was appropriate. The Statistical Reviewer and the Medical Officer agreed with this approach but noted that the Sponsor's ITT population was inappropriately defined as all subjects randomized who received at least one dose of study medication with a baseline assessment and at least one post randomization assessment of vaginal atrophy (this is best defined as a mITT) instead of as all subjects randomized who received at least one dose of study medication (traditional ITT group). As a result 54 subjects were inappropriately excluded from the ITT. However, there is doubt that inclusion of these subjects would have changed the outcome of the analyses. A total of 622 subjects were randomized on a 1:1:1:1 basis to the following treatment groups:

- 2 g synthetic conjugated estrogens, A vaginal cream – N=161
- matching placebo group to 2 g synthetic conjugated estrogens, A vaginal cream – N=156
- 1 g synthetic conjugated estrogens, A vaginal cream – N=150

- Matching placebo group to 1 g synthetic conjugated estrogens, A vaginal cream – N=155

Table 1 below is adapted from Statistical Review table 8 and was recommended for depiction of the symptom efficacy data in the label.

Table 1. Change from Baseline to Week 12 in the Severity of Vaginal Dryness and Pain During Intercourse, Symptoms That Were Self-Identified at Baseline by the Postmenopausal Study Patient as her Most Bothersome Symptom

Most Bothersome Symptom at Baseline	**Synthetic Conjugated Estrogens, A Vaginal Cream** 1 g administered twice weekly	**Placebo**
Vaginal Dryness		
n	60	72
Baseline Severity *	2.58	2.47
LS Mean Change from Baseline (SE)	-1.65 (0.144)	-1.17 (0.130)
p-value versus placebo	0.0016	
Pain during Intercourse		
n	45	41
Baseline Severity*	2.71	2.76
LS Mean Change from Baseline (SE)	-1.75 (0.208)	-0.82 (0.233)
p-value versus placebo	0.0002	

*severity was scored on a scale of 0 to 3 (0=none, 1=mild, 2=moderate and 3=severe)

See the Medical Officer and Statistical reviews for the depiction of the vaginal cytology and vaginal pH results. The mean change from baseline to week 12 in vaginal superficial and parabasal cells and vaginal pH and the most bothersome symptoms of vaginal dryness and pain with intercourse for the 1 g strength (as well as the 2 g strength) of synthetic conjugated estrogens A, vaginal cream were all highly statistically significantly different from placebo and thus criteria for efficacy as recommended in the 2003 Draft HT Clinical Trial Guidance were all met. The Medical Officer Review notes that statistical significance vs. placebo was noted as early as day 21 for the 1 g dosage strength of synthetic conjugated estrogens, A vaginal cream. The Sponsor did not seek approval for the 2 g dose and per the Medical Officer Review, this dose offered no efficacy advantage over the 1 g dosage strength. Therefore, the clinical team agrees that the 2 g dosage strength will not be recommended.

8. Safety

Overall, there were no concerning new safety signals identified in Study DR CEN-302.

There were no deaths. Treatment emergent adverse events defined as those adverse events that began or worsened on or after the first dose of study drug through study completion + 14 days, were not statistically significantly different between the synthetic conjugated A vaginal cream active groups and placebo, occurring in 49.2% and 45.7% of subjects, respectively.

Only 8 serious adverse events (SAEs) were reported during the conduct of Study DR CEN-302; 4 of these were in subjects on placebo, two were in the synthetic conjugated A vaginal cream active groups and two were in subjects not randomized to the study. The reported SAEs were: 1 subject with chronic sinusitis on 2 g synthetic conjugated A vaginal cream active groups; 1 subject with ventricular tachycardia (diagnosed as an "extra conduction

pathway'); 1 subject with deep venous thrombosis/pulmonary embolism, 1 subject with cardiac chest pain and 1 subject with hyponatremia on 2 g placebo; and 1 subject with Hodgkins Disease on 1 g placebo. One subject with diverticulitis and pancreatitis and 1 subject with cardiac chest pain and hypertension were never randomized to study drug. None of the SAEs appear to be related to active treatment with synthetic conjugated A vaginal cream.

Twelve subjects withdrew during the study because of an adverse event. Of this total, 5 were in the 2 g synthetic conjugated A vaginal cream active group, 3 were in the 1 g synthetic conjugated A vaginal cream active group, 4 were in the placebo groups. Two subjects discontinued due to an AE before randomization.

9. Advisory Committee

There were no controversial or difficult issues requiring input from an Advisory Committee

10. Pediatrics

The Sponsor requested a full waiver from the requirement to assess the safety and effectiveness of synthetic conjugated estrogens, A vaginal cream in all relevant pediatric subpopulations in Accordance with 21 CFR 314.55(c)(2). The rationale for this request is that vulvar and vaginal atrophy does not occur in pediatric patients and, therefore, use of this product prior to menarche is not indicated.

The Sponsor's rationale has been accepted for other drug products used to treat symptoms due to Menopause and the Division agrees with it. In an electronic mail communication, dated September 11, 2008, the Pediatric and Maternal Health Division in the Office of New Drugs indicated that "as a follow-up to NDA 21-788, synthetic conjugated estrogens, the PeRC members agreed with the Division to grant a full waiver of pediatric studies in 0-16 age group."

11. Other Relevant Regulatory Issues

The Medical Officer did not request Division of Scientific Investigation (DSI) audit as **acceptable** DSI audits were done for the previous Phase 3 Study DP3-2002-002 in the original cycle of review.

The Medical Officer determined that the Sponsor disclosed financial arrangements with clinical investigators were consistent with the recommendation by the Agency in the FDA Guidance for Industry on Financial Disclosure by Clinical Investigators.

12. Labeling

The proprietary name Bijuvia™ is not acceptable. The Sponsor was informed of this on July 8, 2008. As of the writing of this review, no new proprietary names have been submitted by the Sponsor.

The Physician labeling rule template was followed in the labeling review. Recommendations from SEALD submitted for labels from similar hormone therapy drug products were followed for this product. The label was updated to include information on the WHI from publications submitted through 2007.

A request to DSRCS for review of the patient labeling was sent on April 29, 2008. DSRCS provided no comments on the patient labeling.

Labeling recommendations were provided to Duramed on Monday, August 18, 2008. Duramed replied on Monday, September 8, 2008 with a version of the label that included in

section **12.2 Pharmacokinetics** *Absorption* subsection, comparator data for 0.3 mg Cenestin® data that reads as follows:

b(4)

Both the Clinical Reviewing team and OCPB strongly believe that this information should not be included in the label. The information does not help guide the physician on either choosing the product or dosing for the symptomatic indications (vaginal dryness and pain with intercourse) of vulvar and vaginal atrophy. As stated in the **Background** section of this review, Cenestin® 0.3 mg strength oral tablet received approval for the treatment of vulvar and vaginal atrophy associated with the menopause based on changes to vaginal maturation index and not symptoms. No final agreement was reached on the label for this cycle of review.

The Division of Medication Error Prevention and Analysis, HFD-420 reviewed the container and carton labeling and have concerns regarding the font size of the established name on the container label as well as the absence of the strength on the primary display panel other than the description of the active drug content. They also note that the strength is lacking on the primary display panel again other than the description of the active drug content. These comments were relayed to the Sponsor. HFD-420 had no comment on the package insert labeling.

13. **Recommendations/ Risk Benefit Assessments**

The Sponsor has demonstrated in clinical Study DR-CEN-302, efficacy and safety of the 1 g dosage strength of synthetic conjugated estrogens, A vaginal cream. Approval of the 1 g dosage strength is recommended contingent on agreement between the Sponsor and the Agency on the final label.

A 2 g dose was also studied, there appears to be little difference between the efficacy profile of the 2 g dose and the 1 g dosage strength. Approval of the 2 g dosage strength is not recommended. The Sponsor did not seek approval of this dose. The strong statistical efficacy and the onset of statistical significance as early as 2 weeks into treatments suggest that a lower dose might be effective. In order to further minimize the risk:benefit ratio of this vaginal product (it is noted that a lower systemic exposure is obtained with the0.625 mg conjugated estrogens in the vaginal cream than with 0.3 mg of the oral product), the clinical review team is requesting a Phase 4 commitment from the Sponsor to study the lowest effective dose of synthetic conjugated estrogens, A vaginal cream.

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/s/

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MEDICAL OFFICER