CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-788

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	21-788	*Submission Date(s):*	9/26/08; 10/27/08; 11/25/08
Brand Name		None proposed	
Generic Name		Synthetic Conjugated Estrogens, A (SCE-A)	
Reviewer		LaiMing Lee, Ph.D.	
Team Leader		Myong-Jin Kim, Pharm.D.	
OCP Division		Division of Clinical Pharmacology 3	
OND Division		Division of Reproductive and Urologic Products	
Sponsor		Duramed Research, Inc.	
Relevant IND and NDA		IND 65,505; NDA 20-992 Cenestin® (synthetic conjugated estrogens, A) oral tablets	
Submission Type; Code		Class 1 Resubmission (60 days)	
Formulation; Strengths; Regimen		1 gm vaginal cream containing 0.625 mg SCE-A; 1 gm of cream applied intravaginally daily for 7 days then twice a week	
Proposed Indication		Treatment of Vulvar and Vaginal Atrophy	

Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 finds NDA 21-788 acceptable provided that the final proposed label does not include the pharmacokinetics (PK) data for oral synthetic conjugated estrogens, A (SCE-A) and is the same as the final one proposed on November 25, 2008.

Review

On September 12, 2008, the Division of Reproductive and Urologic Products (DRUP) determined that NDA 21-788 cannot be approved and issued a COMPLETE RESPONSE letter to Duramed due to (1) unresolved label, acceptable proprietary name, carton, and container labeling, and (2) post-marketing commitment to evaluate lower exposure of SCE-A vaginal cream that might prove effective for the treatment of vulvar and vaginal atrophy (VVA).

A Class I Resubmission from the sponsor was submitted to the Agency on September 26, 2008. In the response, the sponsor resubmitted the September 12, 2008 version of the draft label that includes data on PK parameters for the 0.625 mg/g vaginal cream and 0.3 mg oral Cenestin® (SCE-A). The sponsor continues to state they strongly believe that the PK data for the oral and vaginal SCE-A is important to prescribing healthcare professionals when making a clinical decision to prescribe SCE-A vaginal cream.

The following is the PK data for the oral product the sponsor proposed to include in the label under Section 12.3 Pharmacokinetics:

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The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 and Clinical Review Team (Drs. Shelley Slaughter and Phill Price) removed the above PK information for the SCE-A oral product from the SCE-A vaginal cream label. As discussed in the original clinical pharmacology and clinical reviews of NDA 21-788 (DFSed September 2008), the relief of VVA symptoms was demonstrated in the clinical trial via local application of SCE-A to the vaginal area. There is no evidence that suggests the relief of VVA symptoms from this vaginal product is associated with systemic exposure to estrone, estradiol, or equilin. Additionally, there is no clinical trial data demonstrating that a lower serum level of estrogens from this vaginal cream translates into a safer profile. Moreover, PK of one dosage form (i.e. tablets) cannot be relied upon to guide the usage of a different dosage form (i.e. vaginal cream).

On October 20, 2008, the sponsor was informed that the proposed proprietary name, Bijuva®, was found unacceptable by DRUP and Division of Medication Error Prevention and Analysis (DMEPA) because of potential confusion with the marketed drug Enjuvia®. However, via written correspondence on October 27, 2008, the sponsor continued to pursue the approval of the Bijuva® name for their vaginal cream insisting that minimal overlap and confusion with Enjuvia tablet would be encountered.

On November 25, 2008, the sponsor submitted their final label, carton, and container labeling for 0.625 mg/g SCE-A vaginal cream. The sponsor accepted the Agency's removal of PK data for the oral product and proposed no proprietary name for the vaginal product.

This reviewer finds the label, including Section 12.3 Pharmacokinetics, carton, and container labeling acceptable.

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/s/

LaiMing Lee
11/28/2008 07:46:25 AM
PHARMACOLOGIST

Myong-Jin Kim
11/28/2008 09:52:48 AM
BIOPHARMACEUTICS

REVIEW OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA:	21-788
Submission Date:	March 12, 2008
Brand Name:	Bijuva® Vaginal Cream
Generic Name:	Synthetic Conjugated Estrogens, A (SCE-A)
Reviewer:	LaiMing Lee, Ph.D.
Team Leader (Acting):	Sandhya Apparaju, Ph.D.
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Reproductive and Urologic Products
Sponsor:	Duramed Research, Inc.
Relevant IND and NDA:	IND 65,505 NDA 20-992 Cenestin® (synthetic conjugated estrogens, A) oral tablets
Submission Type; Code:	Resubmission
Formulation; Strengths;	1 gm vaginal cream; 0.625 mg SCE-A
Regimen	1 gm of cream every day for 7 days then two times a week
Proposed Indication:	Treatment of Vulvar and Vaginal Atrophy

An Optional Intra-Division Level OCP Briefing was held on August 4, 2008 and was attended by Lawrence Lesko, Hae-Young Ahn, Shelley Slaughter, Sandhya Apparaju, Doanh Tran, Chongwoo Yu, Hyunjin Kim, and Ting Eng Ong.

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1 Executive Summary

Duramed Research Inc, is seeking approval of Bijuva® (synthetic conjugated estrogens, A) Vaginal Cream, 0.625 mg for the treatment of moderate to severe symptoms of Vulvar and Vaginal Atrophy (VVA) in postmenopausal women. Synthetic conjugated estrogens, A (SCE-A) is a blend of nine synthetic estrogenic substances: sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin

sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate, and sodium 17β-estradiol sulfate. SCE-A was approved as oral tablets (0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg) under Cenestin® NDA 20-992 for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause. Only the 0.3 mg Cenestin® oral tablet is approved for the treatment of moderate to severe symptoms of VVA due to menopause.

In response to the "Not Approvable" letter issued by the Agency in 2005 for the original NDA due to clinical deficiencies, Duramed completed a new Phase 3 clinical trial. In addition, a pharmacokinetic study was conducted comparing two different doses (0.625 mg and 1.25 mg) of the test product Bijuva® vaginal cream given daily for the first seven days, followed by twice weekly for the remainder of the 27-day treatment period to Cenestin® 0.3 mg oral tablet given once a day for 27 days in healthy postmenopausal women.

The PK results showed that steady-state systemic exposure (AUC_{0-24} following Day 27 dose) from once daily for 7 days, then twice weekly administration of both doses - 0.625 mg and 1.25 mg – of Bijuva® vaginal cream was lower than once daily administration of 0.3 mg Cenestin® oral tablet.

1.1 Recommendations

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed NDA 21-788 for Bijuva® synthetic conjugated estrogens (SCE- A) 0.625 mg vaginal cream submitted to the Agency on March 12, 2008. We have found this NDA acceptable from a clinical pharmacology perspective. The pending issue is agreement from the sponsor on the Agency's proposed recommendations on the label.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The results from a pharmacokinetic study submitted in the 2004 NDA submission showed that 1.25 mg Bijuva® vaginal cream given intravaginally once daily for 7 days followed by twice weekly for 3 weeks resulted in lower system exposure (AUC), compared to dosing at once daily for 21 days. Based on those pharmacokinetic findings, the sponsor conducted a new pharmacokinetic study with the once daily for 7 days, then twice weekly for 3 weeks dosing regimen to support the approval Bijuva® vaginal cream, and included a low dose group, as well as an oral Cenestin® (0.3 mg) group.

The sponsor implemented the new dosing regimen in a new pivotal Phase 3 randomized, double-blind, placebo-controlled clinical trial to compare the effects of 12 weeks treatment with vaginal cream versus placebo vaginal cream on Vulvar and Vaginal Atrophy in asymptomatic postmenopausal women to support the efficacy and the safety of Bijuva® (synthetic conjugated estrogens, A) Vaginal Cream.

PK characteristics

The sponsor conducted pharmacokinetic studies comparing two doses (1 g containing 0.625 mg synthetic conjugated estrogens and 2 g containing 1.25 mg synthetic conjugated estrogens) of Bijuva® vaginal cream to once daily dose (0.3 mg) of Cenestin® oral tablet. The subjects receiving the vaginal cream were dosed once daily for 7 days followed by twice weekly for 3 weeks, whereas the subjects receiving the oral tablets were dosed once daily for 27 days. The PK parameters were determined following the first dose (Day 1), after one week use (Day 7) and following the last dose (Day 27).

Compared to oral Cenestin® 0.3 mg, for unconjugated **equilin**, the Day 1 AUC_{0-24} was 14.3% lower for 0.625 mg and 23.5% higher for 1.25 mg Bijuva® vaginal cream. By Day 7 & 27, AUC_{0-24} was lower for both doses of Bijuva® (66.3% and 89.7% for 0.625 mg; 25.7% and 80.6% for 1.25 mg) relative to Cenestin®.

Compared to oral Cenestin® 0.3 mg, for baseline-corrected unconjugated **estrone**, the Day 1 AUC_{0-24} was 103.7% and 172.8% higher for 0.625 mg and 1.25 mg Bijuva® vaginal cream. By Day 7, AUC_{0-24} was 8.1% and 69.9% higher for both doses of Bijuva®. By Day 27, AUC_{0-24} was 52.6% and 40.6% lower for both doses of Bijuva®.

Compared to oral Cenestin® 0.3 mg, for baseline-corrected unconjugated **estradiol**, the AUC_{0-24} for 0.625 mg dose was 142.4% higher, 10.4% lower, and 0.1% lower for Days 1, 7, and 27. For 1.25 mg Bijuva® vaginal cream, AUC_{0-24} on Days 1, 7, and 27 was 206.1%, 34.4%, and 0.9% higher than Cenestin® oral tablet, respectively.

After continued use, the steady-state systemic exposure (AUC_{0-24} on Day 27) of unconjugated equilin and baseline-corrected unconjugated estrone from once daily for 7 days, then twice weekly administration of 0.625 mg and 1.25 mg Bijuva® was significantly lower (40.6% to 89.7%) than once daily administration of 0.3 mg Cenestin®. After continued use, the steady-state systemic exposure (AUC_{0-24} on Day 27) of baseline-corrected unconjugated estradiol from 0.625 mg and 1.25 mg Bijuva® was similar to 0.3 mg Cenestin®.

Comparing both doses of Bijuva® vaginal cream, the systemic exposure (AUC_{0-24} on Day 27) was lower for the 0.625 mg dose.

Exposure (Dose)-Response Relationship

Efficacy - The sponsor compared the efficacy of two doses of Bijuva® vaginal cream (1 g containing 0.625 mg synthetic conjugated estrogens and 2 g containing 1.25 mg synthetic conjugated estrogens) compared to placebo-matched vaginal cream for the treatment of VVA symptoms.

In the Phase 3 Study DR-CEN-302 (Study No. 10716214), a dose-response study was conducted in postmenopausal women with two doses of SCE-A vaginal cream compared to placebo. The three co-primary endpoints are mean change from baseline to week 12 in: (1) vaginal maturation index; (2) lowering of vaginal pH; (3) moderate to severe symptom that has been identified by the subject as being most bothersome to her. At both doses, a statistically significant increase in the maturation index, and statistically significant decrease in vaginal pH and in the severity of

the most bothersome symptom were observed for subjects treated with Bijuva® SCE-A vaginal cream, compared with those who received the placebo cream.

Table 1. Summary of Co-primary Endpoints for Efficacy for Two Dosing Groups.

Co-Primary Efficacy Endpoints	Difference between 1.25 mg Bijuva® & 2 gm Placebo (p-value)	Difference between 0.625 mg Bijuva® & 1 gm Placebo (p-value)
Maturation Index	24.36 (<0.0001)	26.3 (<0.0001)
Vaginal pH	-1.06 (<0.0001)	-1.17 (<0.0001)
Most Bothersome Symptom	-0.67 (<0.0001)	-0.6 (<0.0001)

There is no clear dose response with both doses of Bijuva® SCE-A vaginal cream; both appear to be effective in treating symptoms of VVA. The magnitude of the response to each efficacy measure was similar for both dose groups. In fact, the data suggests that there is no benefit to using the higher 2 g dose.

Safety

Overall, Bijuva® vaginal cream appeared to be well tolerated. The most commonly reported adverse event was upper respiratory tract infection, vulvovaginal mycotic infection, urinary tract infection, headache, hot flush, genital pruritus, abdominal pain, and back pain. There is no significant difference in the incidence of adverse events with either doses of Bijuva® vaginal cream compared to the placebo-matched vaginal cream.

Additional comments and details regarding the efficacy and safety of Bijuva® vaginal cream can be found in the clinical review by Dr. Phill Price, Division of Reproductive and Urologic Products.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Synthetic conjugated estrogens, A (SCE-A) have been approved as Cenestin® oral tablets (0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg) under NDA 20-992 for the treatment of moderate to severe vasomotor symptoms due to menopause. Only the 0.3 mg Cenestin® oral tablet was approved in 2002 for the treatment of moderate to severe symptoms of VVA due to menopause. At that time approval for the VVA indication was granted based on two co-primary endpoints: statistically significant improvement in vaginal maturation index and lowering of vaginal pH from baseline to week 12. As of 2003, the Agency draft Guidance for Industry entitled,

"Estrogens and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation" recommends the additional co-primary endpoint: statistically significant improvement in the moderate to severe symptoms identified by the subject as most bothersome.

Duramed Research Inc., the NDA holder of Cenestin® (SCE-A) oral tablets, investigated the safety and efficacy of Bijuva® (SCE-A) vaginal cream under IND 65,505. On June 25, 2004, under NDA 21-788, the sponsor submitted the results from a single Phase 3 clinical trial and a Phase 1 pharmacokinetic study to support the approval of Bijuva® (SCE-A) vaginal cream, 1.25 mg.

Prior Clinical Trial (DP3-2002-002)
In the Phase 3 clinical trial of the original NDA, the sponsor evaluated the efficacy of the 1.25 mg SCE-A vaginal cream a placebo (vehicle cream) in a double-blinded, randomized, parallel, placebo-controlled, multicenter clinical trial with a twice weekly and a daily dosing regimen in symptomatic postmenopausal women over a 12 week period. A total of 278 patients were randomized to one of five treatment groups:

- 1.25 mg of SCE-A Bijuva® vaginal cream given intravaginally daily for 3 weeks, withheld for 1 week, then repeated cyclically (3 weeks on, 1 week off) for the remainder of the 12 week treatment period
- 1.25 mg of SCE-A Bijuva® vaginal cream given intravaginally daily for 7 days, then twice weekly for the remainder of the 12 week treatment period
- 1.25 mg of conjugated estrogens (CE) Premarin® vaginal cream given vaginally daily for 3 weeks, withheld for 1 week, then repeated cyclically (3 weeks on, 1 week off) for the remainder of the 12 week treatment period
- 2 g of placebo vaginal cream given once daily for 3 weeks, withheld for 1 week, then repeated cyclically (3 weeks on, 1 week off) for the remainder of the 12 week treatment period
- 2 g of placebo vaginal cream given intravaginally daily for 7 days, then twice weekly for the remainder of the 12 week treatment period

The medical officer Dr. Theresa van der Vlugt and medical officer Team Leader Dr. Scott Monroe did not recommend approval to both dosing regimens. It was concluded that both the daily and twice weekly regimens for 1.25 mg SCE-A achieved statistical superiority over placebo for the co-primary endpoints of (1) change in vaginal maturation index and (2) change in vaginal pH. However, neither dosing regimen demonstrated statistical superiority over placebo for improvement in the VVA symptom identified as most bothersome to the patient at baseline.

Prior Pharmacokinetic Study (Study 231-03)
In the 2004 NDA submission, the sponsor conducted a Phase 1, open-label, randomized, multiple-dose, single period pharmacokinetic study. A total of 30 healthy, postmenopausal women (10 subjects per group) were randomized to one of three treatment groups:

- 1.25 mg of SCE-A Bijuva® vaginal cream given intravaginally once daily for 21 days
- 0.625 mg of SCE-A Bijuva® vaginal cream given intravaginally once daily for 21 days
- 1.25 mg of SCE-A Bijuva® vaginal cream given intravaginally daily for 7 days, then twice weekly for 3 weeks

From a clinical pharmacology perspective, the original NDA was acceptable. An optional inter-division OCP briefing was held on March 21, 2005. The clinical pharmacology reviewer Dr. Stephan Ortiz concluded that (1) the systemic exposure after intravaginal application is reduced with continued application, a reduction attributed to the healing effect of estrogens on atrophied vaginal epithelium and (2) the weekly exposure ($AUC_{0\text{-}168\ hr}$) from a twice weekly regimen is considerably lower than the exposure from a daily regimen of the vaginal cream (the exposure was 73% and 77% lower for baseline-adjusted free estrone and free equilin, respectively). However, based on a cross-study comparison of 0.3 mg SCE-A oral tablet given daily and both dosing regimens of 1.25 mg SCE-A vaginal cream, the clinical pharmacology reviewer concluded that the exposure estimates are higher from vaginal administration for baseline-corrected estrone and equilin.

Based on the results from the clinical trial DP3-2002-002, the sponsor failed to demonstrate statistically significant difference between Bijuva® vaginal cream (1.25 mg) and the placebo vaginal cream treatment groups for the co-primary endpoint **"subject self-assessment of most** bothersome vulvar and vaginal atrophy symptom **at baseline". The sponsor received a NOT** APPROVABLE (NA) letter from the Agency on April 25, 2005.

On July 18, 2005, the sponsor met with the Division of Reproductive and Urologic Products (DRUP) Clinical Division to discuss information **needed for a "Complete Response" to the NA** decision issued on April 25, 2005. Based on the meeting minutes the Clinical Division provided recommendations on acceptable clinical trial designs and stated that inclusion of an active comparator group was not necessary. However, safety would be a concern if plasma concentrations of estradiol and estrone for the proposed vaginal dose(s) and dosing regimen(s) exceed those with oral administration of Cenestin® oral tablets for VVA.

In response to a request for a special clinical protocol assessment submitted to the Agency on November 8, 2005, DRUP advised the sponsor that plasma concentrations of estrone and equilin for the proposed vaginal dose(s) and dosing regimen(s) exceeding those reported with the approved oral SCE-A tablets could be a clinical review issue. DRUP recommended sparse sampling to determine Cmax and AUC estimates for estrone and equilin (both baseline-adjusted and total) be collected in the clinical trial DR-CEN-302.

On March 12, 2008, the sponsor submitted a response to the deficiencies outlined in the NA letter, which included results from a new clinical trial to support the approval of Bijuva® (SCE-A) vaginal cream, 0.625 mg. In response to the **DRUP's request for sparse sampling of Cmax** and AUC for the vaginal cream, the sponsor conducted a separate pharmacokinetics study of two doses of SCE-A vaginal cream and SCE-A oral tablet. The protocol for the new pharmacokinetic study was determined to be acceptable by the clinical pharmacology reviewer Dr. Sandra Suarez in July 2007.

<u>New Clinical Trial (DR-CEN-302)</u>
The sponsor conducted a Phase 3, randomized, multicenter, double-blind, placebo-controlled clinical trial to compare the effects of SCE-A vaginal cream versus placebo vaginal cream on

VVA in healthy postmenopausal women. A total of 622 patients were randomized to one of four treatment groups:

- 1.25 mg (in 2 g cream) of SCE-A Bijuva® vaginal cream given intravaginally daily for seven days, then twice weekly for the remainder of the 12 week treatment period
- 0.625 mg (in 1 g cream) of SCE-A Bijuva® vaginal cream given intravaginally daily for seven days, then twice weekly for the remainder of the 12 week treatment period
- 2 g placebo vaginal cream given intravaginally daily for seven days, then twice weekly for the remainder of the 12 week treatment period
- 1 g placebo vaginal cream given intravaginally daily for seven days, then twice weekly for the remainder of the 12 week treatment period

The major differences in the new clinical trial design are addition of a lower dose SCE-A vaginal cream, removal of the once daily dosing regimen (only the once daily for 3 weeks, withheld for 1 week, then repeated cyclically (3 weeks on, 1 week off) for the remainder of the 12 week treatment period, and exclusion of an active comparator. Medical Officer Dr. Phill Price reviewed results of the new clinical study.

New Pharmacokinetic Study (DR-CEN-10X)

The sponsor conducted a new Phase 1, open-label, randomized, multiple-dose, single period pharmacokinetic study. A total of 60 healthy, postmenopausal women were randomized to one of three treatment groups:

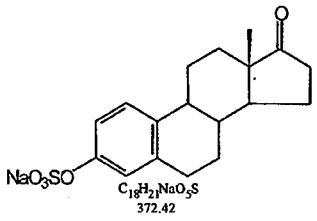
- 1.25 mg of SCE-A Bijuva® vaginal cream given intravaginally daily for 7 days, then twice weekly for 3 weeks
- 0.625 mg of SCE-A Bijuva® vaginal cream given intravaginally daily for 7 days, then twice weekly for 3 weeks
- 0.3 mg of SCE-A Cenestin® oral tablet given intravaginally daily for 27 days

The major differences in the new pharmacokinetic study design are addition of a lower dose SCE-A vaginal cream, removal of the once daily for 21 days dosing, and addition of comparator. A comparator group was not included in the earlier pharmacokinetic study nor was it requested by the previous clinical pharmacology reviewer. The newly submitted pharmacokinetic study (DR-CEN-10X) is the subject of this clinical pharmacology review.

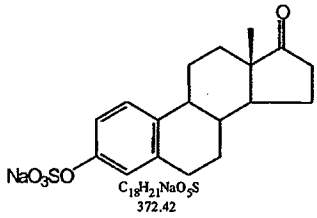
2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Synthetic conjugated estrogens, A (SCE-A) is a blend of nine synthetic estrogenic substances synthesized from soybean and Mexican yam plant starting materials with "A" denoting the first and unique combination of the specified synthetic estrogens. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate, and sodium 17β-estradiol sulfate.

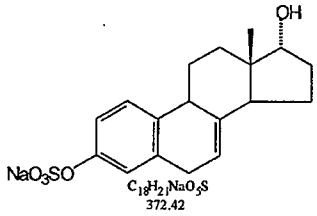
The chemical structure of the nine estrogens are:



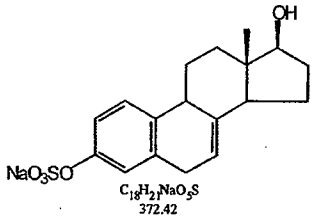
Sodium Estrone Sulfate



Sodium Equilin Sulfate



Sodium 17α-Dihydroequilin Sulfate



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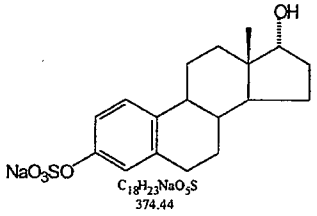
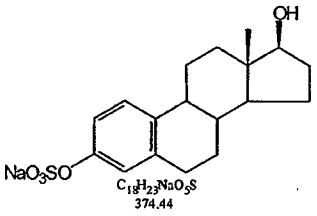


Sodium 17α-Estradiol Sulfate



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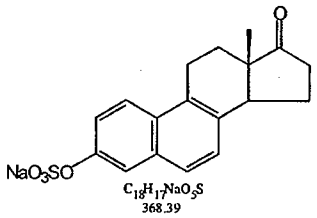
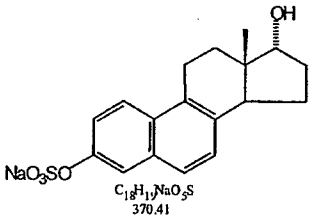
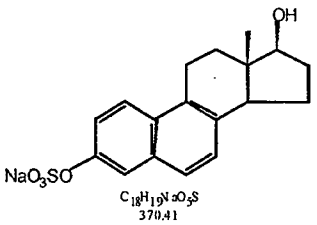


Sodium Equilenin Sulfate



Sodium 17α-Dihydroequilenin Sulfate



Sodium 17β-Dihydroequilenin Sulfate

The formulation of the proposed product is composed of the following:

Ingredient	Concentration (% w/w)
Synthetic Conjugated Estrogens, A in Glycerin	
Purified water, USP	
Glycerin, USP	
Sodium Laurel Sulfate, NF	
Benzyl Alcohol	
Sodium Phosphate Dibasic Anhydrous, USP	
Cetyl Esters Wax, NF	
Light Mineral Oil, NF	
Propylene Glycol Monostearate	
Cetyl Alcohol, NF	
Methyl Stearate	
White Wax, NF	
Glyceryl Monostearate, NF	
Sodium Hydroxide, NF	

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2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 mcg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

Currently available estrogen-containing vaginal products for the treatment of vulvar and vaginal atrophy include Premarin® (0.625 mg conjugated estrogens) vaginal cream, Estrace® (0.1 mg estradiol) vaginal cream, Estring® (7.5 µg/24 hr estradiol) vaginal ring, Femring® (50 and 100 µg/24 hr estradiol) vaginal ring, and Vagifem® (25 µg estradiol) vaginal tablet.

The sponsor is seeking approval of 0.625mg Bijuva® (synthetic conjugated estrogens, A) Vaginal Cream for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. The product will be available in a tube containing 30 g cream

(0.625 mg SCE-A per gram of cream) with eight re-usable applicators. The proposed dosage administration is 0.625 mg (one applicator full) intravaginally once a day for 7 days followed by 0.625 mg (one applicator full) intravaginally twice a week.

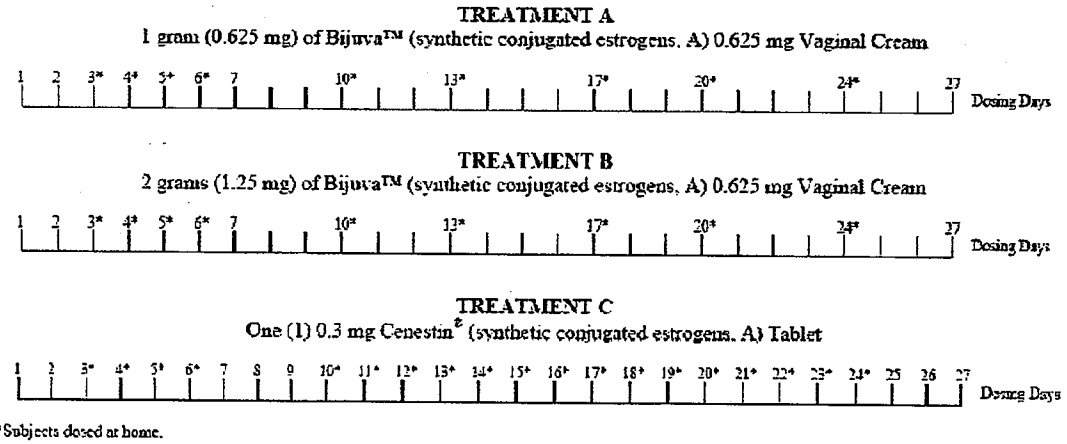
2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A Phase 1 randomized, multiple-dose, three treatment, parallel design study (No. 10716214) was conducted to compare the pharmacokinetic profiles of two difference doses (0.625 mg and 1.25 mg) of Bijuva® vaginal cream, compared to 0.3 mg Cenestin® oral tablets. Women who are naturally or surgically (bilateral oophorectomized) postmenopausal with 30 to 70 years of age were recruited for the study. Sixty (twenty subjects per cohort) healthy, postmenopausal women were randomized to one of three treatment groups:

- 0.625 mg of SCE-A Bijuva® vaginal cream given intravaginally daily for 7 days, then twice weekly for 3 weeks
- 1.25 mg of SCE-A Bijuva® vaginal cream given intravaginally daily for 7 days, then twice weekly for 3 weeks
- 0.3 mg of SCE-A Cenestin® oral tablet given intravaginally daily for 27 days

At the conclusion of the study (Day 29) for all dose groups, each subject with a uterus received a 14 day course of oral Prometrium® (progesterone) 200 mg/day (as a single 200 mg capsule at bedtime).



*Subjects dosed at home.

Blood samples (10 mL with EDTA) were collected from 48 hours prior to initial study dosing (Day -2), at regular intervals throughout the study, and over 48 hours after the final study dosing on Day 27. The blood draw collection times follow and was the same for all three treatment groups:

- Approximately -48 hours*, -24 hours* prior to the first dose on Day 1.
- Day 1: Pre-dose (within 1 hour of prior of dosing) and 1.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16 and 24 hours (Day 2) after dosing.

- Day 7: Pre-dose (within 1 hour of prior on Day 7) and 1.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16 and 24 hours (Day 8) after dosing.
- Day 9*: Approximately 48* hours after the Day 7 dosing time and prior to dosing if the subject is randomized to the Cenestin® 0.3 mg tablet dosing regimen.
- Day 25*: Prior to the study drug dosing on that day.
- Day 26*: Prior to the study drug dosing on that day.
- Day 27: Pre-dose (within 1 hour prior to dosing on Day 27) and 1.5, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16 and 24 hours (Day 28) after dosing.
- Day 28*: 36 hours* after dosing on Day 27.
- Day 29*: 48 hours* after dosing on Day 27.

* Samples were taken as outpatients.

The plasma concentrations were determined for unconjugated estradiol, unconjugated estrone, unconjugated equilin, total estrone, and total equilin. Statistical analysis evaluated both baseline corrected and non-baseline corrected pharmacokinetics to compare the relative bioavailability of the two test doses of vaginal cream to the one reference oral tablet.

The AUC_{weekly} at steady state following the Day 27 dosing was estimated to allow a more direct comparison of the relative bioavailability for the two different dosage forms of synthetic conjugated estrogens, A. For the vaginal cream, the $AUC_{0\text{-}84}$ was calculated by using the elimination rate from the last measurable concentration (t=48 hour post Day 27 dose), then AUC_{weekly} is 2 times the $AUC_{0\text{-}84}$. For the oral tablet, $AUC_{0\text{-}24}$ following the Day 27 dose was calculated, then AUC_{weekly} is 7 times $AUC_{0\text{-}24}$.

2.2.2 What are the clinical endpoints measured in clinical pharmacology and clinical studies?

As outlined in the Agency's 2003 draft Guidance for Industry "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation", the sponsor conducted a 12-week Phase 3 clinical trial in 622 postmenopausal women age 42 to 78 years with VVA to assess the efficacy of Bijuva® vaginal cream using three co-primary efficacy endpoints. For an estrogen alone drug product intended to treat moderate to severe symptoms of VVA due to menopause, the sponsor must demonstrate statistically significant improvement versus placebo in the mean change from baseline to week 12 in all three of the following co-primary endpoints:
(1) vaginal maturation index - increase in superficial cells and decrease in parabasal cells (for study inclusion, subjects would have no greater than 5% superficial cells on a vaginal smear);
(2) vaginal pH (for study inclusion, subjects should have a vaginal pH > 5.0);
(3) moderate to severe symptom that has been identified by the subject as being most bothersome to her

2.2.3 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Bijuva® (synthetic conjugated estrogens, A) is a blend of nine synthetic conjugated estrogens. The major estrogenic substances consist are sodium salts of sulfate esters of estrone and equilin with both making up the majority of the total active drug substances (——— and

b(4)

——— %, respectively). The minor estrogenic substances are sodium salts of sulfate esters of 17α-dihydroequilin, 17α-estradiol, 17β-estradiol, 17α-dihydroequilenin, 17β-dihydroequilenin, 17β-dihydroequilin, and equilenin. b(4)

The pharmacokinetic parameters were assessed for unconjugated estradiol, unconjugated estrone, unconjugated equilin, total estrone, and total equilin.

2.2.4 Exposure-Response Evaluation

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The sponsor conducted a Phase 3 clinical study to assess the effectiveness of two doses of Bijuva® vaginal cream to treat moderate to severe symptoms of VVA. Patients were treated with one of the two Bijuva® doses (1 g cream containing 0.625 mg and 2 g cream containing 1.25 mg synthetic conjugated estrogens, A) compared to placebo matched vaginal cream or matching placebo once daily for the first seven days and followed twice weekly for up to 12 weeks. Patients treated with both active doses showed a statistically significant increase in the maturation index, and statistically significant decreases in vaginal pH and in the severity of the most bothersome symptom, compared with those who received the placebo cream.

Table 1: Change in Vaginal Maturation Index - Comparison Between Bijuva® SCE-A Vaginal Cream vs. Placebo Vaginal Cream.

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Ranked Data)***
2g Bijuva™	146	29.20	33.27	1.191	24.36	<.0001
2g Placebo	135	30.34	8.91	1.222		
1g Bijuva™	135	31.31	31.46	1.221	26.3	<.0001
1g Placebo	140	31.84	5.16	1.205		

Change = Change in Maturation Index (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on ranked data analysis. Normality test: p-value=0.0001.*

Following 12 weeks of treatment, the vaginal maturation index increased by a mean of 33.27 for the 1.25 mg Bijuva® treatment group compared to 8.91 for the 2 gm placebo group (p-value < 0.0001). Similarly, for the 0.625 mg Bijuva® treatment group, the mean increase in the vaginal maturation index was 31.46 compared to 5.16 for the matching placebo group (p-value < 0.0001).

Table 2: Change in Superficial Cells - Comparison Between Bijuva® SCE-A Vaginal Cream vs. Placebo Vaginal Cream.

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Ranked Data)***
2g Bijuva™	146	0.97	26.79	1.237	21.79	<.0001
2g Placebo	135	1.08	5.00	1.271		
1g Bijuva™	135	1.13	25.16	1.270	22.05	<.0001
1g Placebo	140	1.31	3.11	1.256		

Change = Change in Superficial Cells (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on ranked data analysis. Normality test: p-value=0.0001.*

For the 1.25 mg Bijuva® treatment group, there was a statistically significant (p-value <0.0001) increase in the percentage of superficial cells was 26.79 compared with 5.00 for the placebo matched group. The increase in the percentage of superficial cells was 25.16 for the 0.625 mg Bijuva® group compared to 3.11 for the placebo matched group.

Table 3: Change in Parabasal Cells - Comparison Between Bijuva® SCE-A Vaginal Cream vs. Placebo Vaginal Cream.

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Ranked Data)***
2g Bijuva™	146	42.56	-39.82	1.796	-26.97	<.0001
2g Placebo	135	40.41	-12.85	1.844		
1g Bijuva™	135	38.51	-37.75	1.842	-30.55	<.0001
1g Placebo	140	37.64	-7.20	1.818		

Change = Change in Parabasal Cells (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on ranked data analysis. Normality test: p-value=0.0001.*

There was statistically significant (p-values < 0.0001) decrease in parabasal cells for the 1.25 mg treatment and placebo groups (39.82 versus 12.85) and for the 0.625 mg treatment and placebo groups (37.75 versus 7.20).

Table 4: Change in Vaginal pH - Comparison Between Bijuva® SCE-A Vaginal Cream vs. Placebo Vaginal Cream.

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value (Raw Data)***
2g Bijuva™	146	6.35	-1.44	0.071	-1.06	<.0001
2g Placebo	135	6.30	-0.38	0.073		
1g Bijuva™	135	6.32	-1.48	0.073	-1.17	<.0001
1g Placebo	140	6.27	-0.31	0.072		

Change = Change in Vaginal pH (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on raw data analysis. Normality test: p-value=0.0515.*

The vaginal pH at baseline ranged from 6.27 to 6.35. At the end of the treatment period, the mean decrease in vaginal pH for the 1.25 mg Bijuva® group was 1.44 pH units, compared with 0.38 pH unit for the matching placebo group. For the 0.625 Bijuva® group, the mean decrease in vaginal pH was slightly greater at 1.48 pH units, compared with 0.31 pH units for the matching placebo group. The overall difference in vaginal pH change was similar and statistically significant (p-value <0.0001) for both treatment groups.

Table 5: Most Bothersome Symptom as Identified by the Subject - Comparison Between Bijuva® SCE-A Vaginal Cream vs. Placebo Vaginal Cream.

Treatments	N	Baseline	LS Mean Change*	Standard Error	Difference**	P-Value***
2g Bijuva™	146	2.61	-1.77	0.085	-0.67	<.0001
2g Placebo	135	2.59	-1.10	0.087		
1g Bijuva™	135	2.62	-1.71	0.087	-0.6	<.0001
1g Placebo	140	2.55	-1.11	0.086		

Change = Change in the Severity of Most Bothersome Symptom (Day 0 to Day 84 [or End-of-Treatment]).
**Difference = Difference between active treatment group and matching placebo.*
***P-Value: Significance between active treatment group and matching placebo was tested on raw data analysis.*

The most bothersome symptom was identified by the subject from five different symptoms (vaginal dryness, vaginal irritation/itching, vaginal soreness, pain during intercourse, and bleeding after intercourse) of vaginal and vulvar atrophy at the baseline visit. Statistically significant mean reduction in the severity of the most bothersome symptom for both dose groups of Bijuva® vaginal cream, compared to the respective placebo groups. For the 1.25 mg Bijuva® treatment group, the mean reduction was 1.77 in the most bothersome symptom versus 1.10 for the matching placebo group (p-value <0.0001). For the 0.625 mg Bijuva® treatment group, the mean reduction was 1.71 in the most bothersome symptom versus 1.11 for the matching placebo group (p-value <0.0001). Both treatment groups demonstrated similar magnitude of treatment effect.

Table 6. Summary of Co-primary Endpoints for Efficacy for Two Dosing Groups.

Co-Primary Efficacy Endpoints	Difference between 1.25 mg Bijuva® & 2 gm Placebo (p-value)	Difference between 0.625 mg Bijuva® & 1 gm Placebo (p-value)
Maturation Index	24.36 (<0.0001)	26.3 (<0.0001)
Vaginal pH	-1.06 (<0.0001)	-1.17 (<0.0001)
Most Bothersome Symptom	-0.67 (<0.0001)	-0.6 (<0.0001)

There is no clear dose response with both doses of Bijuva® vaginal cream; both appear to be effective in treating symptoms of VVA. The magnitude of the response to each efficacy measure was similar for both dose groups. In fact, the data suggests that there is no benefit to using the higher 1.25 mg dose.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Overall, Bijuva® synthetic conjugated estrogens vaginal cream was well tolerated with the incidence of adverse events reported in the study were comparable for the treatment and placebo groups. The incidence rate for treatment emergent adverse events was 49.2% and 45.7% for the active treatment and the placebo groups, respectively. The most commonly reported adverse event was upper respiratory tract infection – 4.18% for both Bijuva® vaginal cream and placebo vaginal cream. Compared to 0.625 mg Bijuva® group, abdominal pain (7 vs. 1), back pain (6 vs. 0), and genital pruritus female (5 vs.4) appeared more frequently for the 1.25 mg Bijuva® dose. A clear dose response for safety was not readily apparent for all AEs. For additional details, refer to the clinical review.

Table 1. Adverse Events: Incidence of Treatment-Emergent Adverse Events Occurring in 3% or More of Patients (Safety Cohort).

MedDRA System Organ Class	2g Bijuva (N=161)		1g Bijuva (N=150)		2g Placebo (N=156)		1g Placebo (N=155)		Total (N=622)	
and Preferred Term	N	%	N	%	N	%	N	%	N	%
GASTROINTESTINAL DISORDERS										
ABDOMINAL PAIN	7	4.35	1	0.67	0	0.00	1	0.65	9	1.45
INFECTIONS AND INFESTATIONS										
UPPER RESPIRATORY TRACT INFECTION	6	3.73	7	4.67	6	3.85	7	4.52	26	4.18
URINARY TRACT INFECTION	5	3.11	3	2.00	6	3.85	2	1.29	16	2.57
VULVOVAGINAL MYCOTIC INFECTION	3	1.86	7	4.67	2	1.28	5	3.23	17	2.73
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS										
BACK PAIN	6	3.73	0	0.00	2	1.28	0	0.00	8	1.29
REPRODUCTIVE SYSTEM AND BREAST DISORDERS										
GENITAL PRURITUS FEMALE	5	3.11	4	2.67	1	0.64	0	0.00	10	1.61
NERVOUS SYSTEM DISORDERS										
HEADACHE	2	1.24	6	4.00	6	3.85	0	0.00	14	2.25
VASCULAR DISORDERS										
HOT FLUSH	2	1.24	5	3.33	5	3.21	2	1.29	14	2.25
HYPERTENSION	0	0.00	1	0.67	5	3.21	1	0.65	7	1.13

2.2.4.3 Does this drug prolong the QT or QTc interval?

Not applicable, due to long established use and knowledge of estrogens.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response?

Yes. Patients treated with both active doses (0.625 mg and 1.25 mg) of Bijuva® vaginal cream showed a statistically significant increase in the maturation index, and statistically significant decreases in vaginal pH and in the severity of the most bothersome symptom, compared with those who received the placebo cream. There is no clear dose response with both doses of Bijuva® vaginal cream; both appear to be effective in treating symptoms of VVA. The most commonly reported adverse event was upper respiratory infection - 7 events were reported for the 0.625 mg and 6 events were reported 1.25 mg Bijuva® group. However, adverse events such as abdominal pain, back pain, genital pruritus appeared more frequently for the 1.25 mg Bijuva® group. Overall, there was no significant dose-related difference in the incidence of treatment-related adverse events.

Cenestin® synthetic conjugated estrogens, A administered orally at 0.3 mg daily is currently approved for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy. The weekly dose of synthetic conjugated estrogens, A at steady state is: 2.1 mg (7 x 0.3 mg) for oral Cenestin®, 1.25 mg (2 x 0.625 mg) for vaginal Bijuva®, and 2.5 mg (2 x 1.25 mg) for vaginal Bijuva®. The systemic exposure, based on the estimated AUC_{weekly} comparison, was considerably lower for Bijuva® vaginal cream, compared to Cenestin® oral tablet (see sections 2.2.5.1 and 2.2.5.2). Systemic exposure from 0.625 mg was lower than 1.25 mg Bijuva®.

The results from the Phase 3 clinical study showed that both doses of vaginal cream were equally efficacious in treating the VVA (see section 2.2.4.1) and well tolerated. The product is intended for the local (vaginal) treatment of VVA symptoms therefore limiting systemic exposure is desirable. Given the efficacy, safety, and pharmacokinetic data, the dosing recommendation is 0.625 mg.

Premarin® 0.625mg/g conjugated estrogens (CE) vaginal cream is currently approved for the treatment of VVA. The usual dosage range for Premarin® vaginal cream is 0.5 to 2.0 g of cream (0.313 to 1.25 mg CE) administered intravaginally daily for 3 weeks on and one week off (cyclic) for 3 to 6 months or the shortest duration needed. The proposed dosing regimen of 0.625 mg Bijuva® daily for 7 days then twice weekly is justified based on the observed dose-response for safety and efficacy, and is within the dosing range for Premarin®.

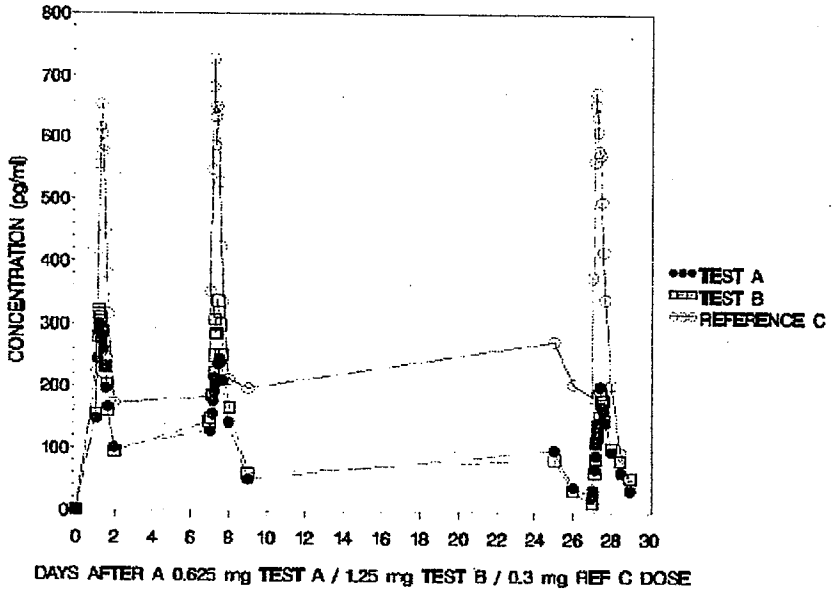
2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the single dose and multiple dose PK parameters?

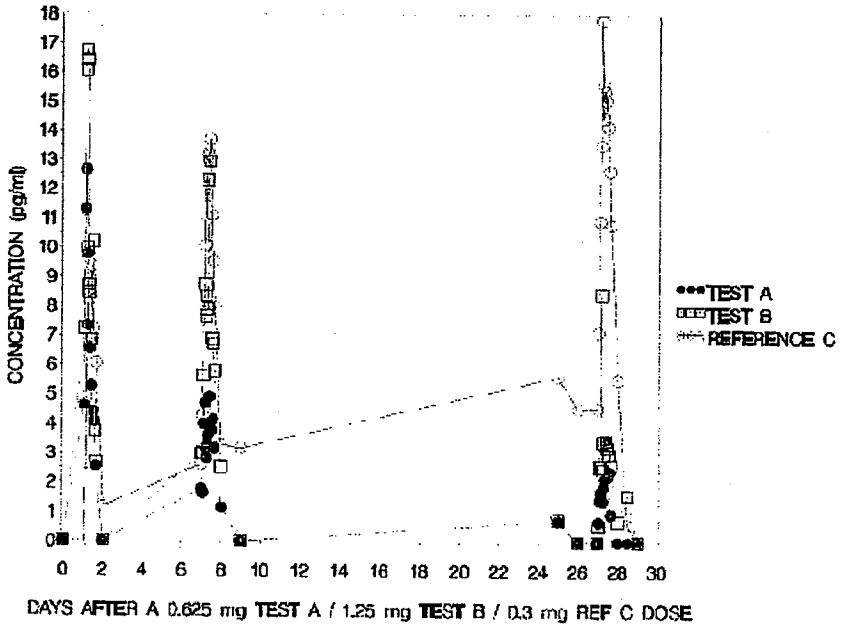
In the new Phase 1 pharmacokinetics study, sixty (twenty subjects per cohort, 59 completed the study) healthy postmenopausal women were randomized to one of three dosing regimens:
(A) 0.625 mg of Bijuva® vaginal cream applied intravaginally once daily for seven days followed by twice weekly for the next three weeks
(B) 1.25 mg of Bijuva® vaginal cream applied intravaginally once daily for seven days followed by twice weekly for the next three weeks
(C) 0.3 mg Cenestin® oral tablet administered orally once daily for 27 consecutive days.

The following figures and summary tables highlight the decreased exposure to equilin, estrone, and estradiol (baseline-adjusted of total & unconjugated) following twice weekly dosing of Bijuva® vaginal cream compared to daily dosing Cenestin® oral tablet.

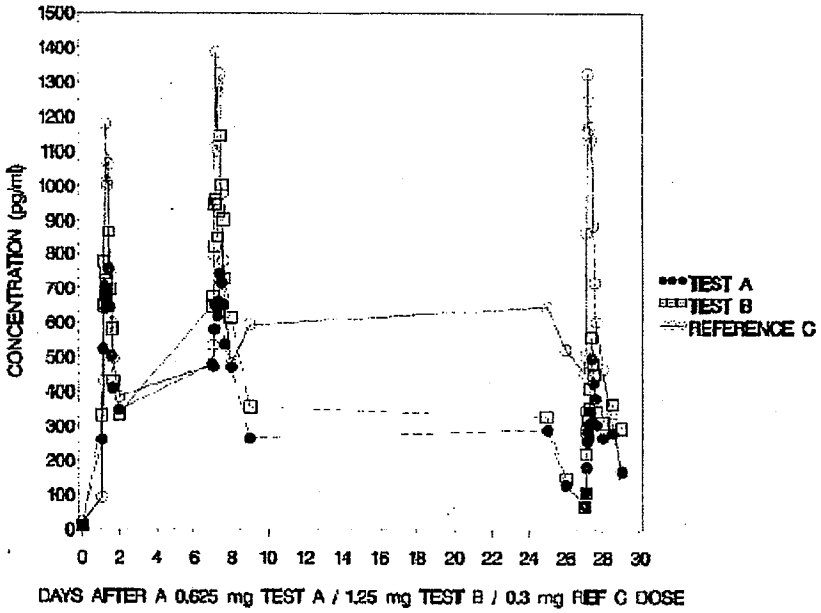
Total Equilin (no baseline adjustment – pre-dose levels were below limit of quantitation)



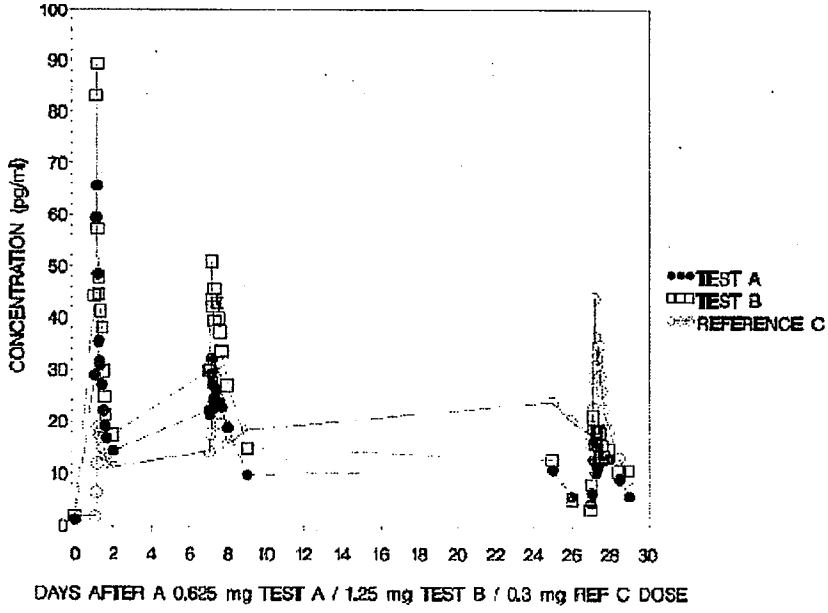
Unconjugated Equilin (no baseline adjustment – pre-dose level were below limit of quantitation)



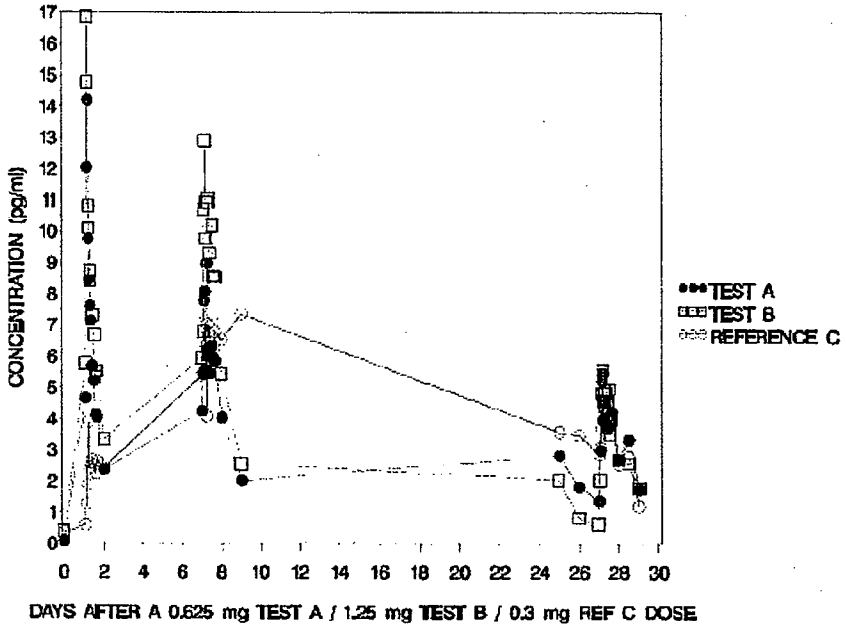
Total Estrone (baseline-adjusted)



Unconjugated Estrone (baseline-adjusted)



Unconjugated Estradiol (baseline-adjusted)



Following a single dose of Bijuva® or Cenestin®, the Day 1 pharmacokinetic parameters Cmax, Tmax, and AUC0-24 was calculated and is presented in the following table. For unconjugated equilin, unconjugated estrone (baseline-corrected), and unconjugated estradiol (baseline-corrected), the time to reach peak plasma concentration ranged from 6.0 to 6.8 hours following 0.625 mg Bijuva® vaginal cream and was 5 hours following 1.25 mg Bijuva® vaginal cream. With the exception of unconjugated equilin from 0.625 mg Bijuva®, the systemic exposure (AUC0-24) to estrogens was higher from the administration of vaginal cream compared to oral tablet after a single dose (Table 1).

Table 1. Mean Single Dose Pharmacokinetic Parameters at Day 1 Comparing Bijuva® Vaginal Cream and Cenestin® Oral Tablet

PK Parameter Arithmetic mean (±SD)	**Unconjugated Estrogen**	**Bijuva® 0.625 mg**	**Bijuva® 1.25 mg**	**Cenestin® 0.3 mg**
Cmax (pg/mL)	Equilin	14.3 ± 13.2	24.0 ± 22.8	11.9 ± 4.2
	Estrone*	74.4 ± 65.3	98.5 ± 64.0	24.3 ± 13.6
	Estradiol*	16.1 ± 13.7	8.6 ± 11.5	5.6 ± 7.9
Tmax (hr)	Equilin	6.0 ± 3.9	5.0 ± 2.9	8.4 ± 3.4
	Estrone*	6.8 ± 5.1	5.0 ± 3.0	10.7 ± 6.6
	Estradiol*	6.6 ± 4.1	5.0 ± 2.5	12.5 ± 6.4
AUC0-24 (pg.hr/mL)	Equilin	94.9 ± 88.6	136.7 ± 129.1	110.7 ± 56.8

	Estrone*	622.7 ± 400.8	834.0 ± 476.3	305.7 ± 198.3
	Estradiol*	131.6 ± 74.8	166.2 ± 74.7	54.3 ± 34.5

*Baseline Corrected

After seven consecutive days of multiple dose administration, the systemic exposure to baseline-corrected unconjugated estrone and estradiol from the 0.625 mg Bijuva® vaginal cream and the 0.3 mg Cenestin® oral tablet became more similar. At Day 7, the exposure to equilin was lower for both doses of Bijuva® compared to Cenestin® (Table 2).

Table 2. Mean Multiple Dose Pharmacokinetic Parameters at Day 7 Comparing Bijuva® Vaginal Cream and Cenestin® Oral Tablet

PK Parameter Arithmetic mean (±SD)	**Unconjugated Estrogen**	**Bijuva® 0.625 mg**	**Bijuva® 1.25 mg**	**Cenestin® 0.3 mg**
Cmax (pg/mL)	Equilin	7.4 ± 4.5	15.6 ± 20.7	15.7 ± 5.8
	Estrone*	38.5 ± 23.1	57.2 ± 22.1	36.8 ± 15.9
	Estradiol*	12.7 ± 12.7	15.3 ± 9.0	9.8 ± 18.8
Tmax (hr)	Equilin	10.1 ± 4.6	7.7 ± 4.2	7.7 ± 2.3
	Estrone*	8.3 ± 11.0	6.6 ± 3.9	12.1 ± 12.9
	Estradiol*	8.9 ± 6.0	6.4 ± 4.0	12.8 ± 12.9
AUC_{0-24} (pg.hr/mL)	Equilin	65.4 ± 70.9	144.0 ± 143.7	193.8 ± 73.5
	Estrone*	560.7 ± 340.4	881.7 ± 457.0	518.8 ± 228.5
	Estradiol*	139.7 ± 60.5	209.6 ± 151.1	155.9 ± 327.3

*Baseline Corrected

The sponsor states that due to differences in dose and dosing regimen with Bijuva® vaginal cream and Cenestin® oral tablet, estimating the AUC_{weekly} for the estrogens at steady state following the Day 27 dosing would allow a more direct comparison of the relative bioavailability for the two different dosage forms of synthetic conjugated estrogens, A. Compared to the oral 0.3 mg daily dose of Cenestin®, the steady state systemic exposure (AUC_{weekly} Day27) of unconjugated equilin, baseline-corrected unconjugated estrone, and baseline-corrected unconjugated estradiol from both doses of Bijuva® vaginal cream was significantly lower. Comparing both Bijuva doses, the systemic exposure (AUC_{0-24} and AUC_{weekly}) was lower for 0.625 mg.

For unconjugated equilin, the AUC_{weekly} was lower by 96% and 91% for 0.625 mg and 1.25 mg Bijuva® vaginal cream, respectively. For baseline-corrected unconjugated estrone, the AUC_{weekly} was lower by 71% and 62% for 0.625 mg and 1.25 mg Bijuva® vaginal cream, respectively. For baseline-corrected unconjugated estradiol, the AUC_{weekly} was lower by 46% and 45% for 0.625 mg and 1.25 mg Bijuva® vaginal cream, respectively (Table 3). The

systemic exposure from once daily then twice weekly administration of 0.625 mg and 1.25 mg synthetic conjugated estrogens vaginal cream was significantly lower than once daily administration of 0.3 mg oral synthetic conjugated estrogens. It is believed that systemic absorption of estrogens through the vaginal wall is impeded as the proportion of superficial to parabasal cells changes (improvement in the maturation index), which was observed as early as 14 days after initiating therapy.

Table 3. Mean Multiple Dose Pharmacokinetic Parameters at Day 27 Comparing Bijuva® Vaginal Cream and Cenestin® Oral Tablet

PK Parameter Arithmetic mean (±SD)	**Unconjugated Estrogen**	**Bijuva® 0.625 mg**	**Bijuva® 1.25 mg**	**Cenestin® 0.3 mg**
Cmax (pg/mL)	Equilin	5.5 ± 6.9	11.5 ± 21.7	20.1 ± 8.4
	Estrone*	24.0 ± 11.5	31.4 ± 9.7	46.8 ± 28.1
	Estradiol*	7.9 ± 7.3	7.7 ± 3.7	6.7 ± 3.5
Tmax (hr)	Equilin	10.5 ± 4.2	9.3 ± 8.4	7.4 ± 3.1
	Estrone*	12.0 ± 8.7	10.9 ± 13.2	7.6 ± 3.2
	Estradiol*	12.3 ± 9.8	9.1 ± 9.9	11.6 ± 7.3
AUC_{0-24} (pg.hr/mL)	Equilin	27.3 ± 37.1	51.7 ± 50.7	265.8 ± 112.5
	Estrone*	293.8 ± 136.0	367.7 ± 167.1	619.4 ± 308.8
	Estradiol*	92.5 ± 82.4	93.4 ± 61.4	92.6 ± 49.0
**AUC_{weekly} (pg.hr/mL)	Equilin	66.8 ± 97.1	171.7 ± 198.4	1860.4 ± 787.4
	Estrone*	1246.4 ± 572.73	1635.7 ± 776.1	4335.5 ± 2161.9
	Estradiol*	350.2 ± 370.0	357.5 ± 240.5	648.1 ± 343.0

*Baseline Corrected

**AUC_{weekly} (AUC_{0-168}) at steady state was estimated using AUC_{0-24} for Cenestin (AUC_{0-24} x7) and AUC_{0-48} for Bijuva (AUC_{0-84} x2, where AUC_{0-84} was extrapolated from AUC_{0-48})

Though the sponsor states that the pharmacokinetic parameter AUC_{weekly} for the Bijuva® vaginal cream and Cenestin® oral tablet provides a direct comparison of systemic exposure following 7 days of product use, the use of AUC_{0-48} to extrapolate AUC_{0-84} can result in over- or under-estimation if the elimination phase after 48 hours is non-linear. Additionally, an error in estimating AUC_{0-84} can be carried further to the AUC_{weekly} value; therefore, this reviewer recommends comparison of the AUC_{0-24} following Day 27 dose for a more accurate assessment of systemic exposure.

The following table is a cross study comparison of 1.25 mg Bijuva® given intravaginally once daily for 7 days, then twice weekly for three weeks. The pharmacokinetic data from the prior pharmcokinetic study was extracted from the clinical pharmacology review dated April 8, 2005.

As expected with a cross study comparison, the absolute values are not the same; however, given the level of variability, the values are similar. Both pharmacokinetic studies show that there was a decrease in systemic exposure (AUC_{0-24}) for unconjugated equilin, unconjugated baseline-corrected estrone, and unconjugated baseline-correct estradiol with continued use of Bijuva® vaginal cream.

Table 4: Mean AUC_{0-24} for 1.25 mg Bijuva® Vaginal Cream

		AUC_{0-24} (pg.hr/mL) Arithmetic mean (±SD) 1.25 mg Bijuva® vaginal cream	
Unconjugated Estrogen	**Time**	**Prior PK study (No. 231-03)**	**New PK study (DR-CEN-10X)**
Equilin	Day 1	249.7	136.7 ± 129.1
	Day 7	180.3	144.0 ± 143.7
	Day 27	97.3	51.7 ± 50.7
Estrone*	Day 1	964.1	834.0 ± 476.3
	Day 7	875.5	881.7 ± 457.0
	Day 27	440.5	367.7 ± 167.1
Estradiol*	Day 1	172.2	166.2 ± 74.7
	Day 7	184.4	209.6 ± 151.1
	Day 27	80.8	93.4 ± 61.4

*baseline-corrected

Comments as it relates to pharmacokinetic data in the label:

- Pharmacokinetic data to be included in the label will be discussed at the time of labeling discussions.
- Equilin is one of several important estrogenic substances and contributes toward the overall clinical effect of Bijuva®. As such, the reviewer recommends adding the pharmacokinetic data for unconjugated equilin in the label.

2.2.5.2 What does the PK characteristics of the drug and its major metabolite?

The pharmacokinetics of unconjugated estradiol, unconjugated estrone, and total estrone were calculated for the baseline-corrected and uncorrected levels. For unconjugated equilin and total equilin, the pre-dose values were below the limit of quantitation so no baseline correction for these analytes were performed. The mean pharmacokinetic parameters for the mentioned estrogenic substances are presented in the following source tables.

Test A: 0.625 mg of Bijuva® vaginal cream applied intravaginally once daily for seven days followed by twice weekly for the next three weeks
Test B: 1.25 mg of Bijuva® vaginal cream applied intravaginally once daily for seven days followed by twice weekly for the next three weeks
Test C: 0.3 mg Cenestin® oral tablet administered orally once daily for 27 consecutive days

Unconjugated Estradiol (No Baseline Correction)

Pharmacokinetic Parameter	Units	Arithmetic Mean values		
		Test A	Test B	Reference C
AUC D1 (0-24)	pg·hr/ml	248.7795	285.7653	288.3140
Cmax D1	pg/ml	21.0353	23.6300	17.0810
AUC D7 (0-24)	pg·hr/ml	256.8059	329.1191	356.4928
AUC D27 (0-24)	pg·hr/ml	208.9236	211.7148	196.9973
Cmax D27	pg/ml	12.7900	12.7255	11.0710
Tmax D27	hr	13.5263	9.1000	11.6750
Cmin	pg/ml	6.6123	6.0123	7.4708
Cav	pg/ml	8.7051	8.8214	8.2082

Unconjugated Estradiol (Baseline Corrected)

Pharmacokinetic Parameter	Units	Arithmetic Mean values		
		Test A	Test B	Reference C
AUC D1 (0-24)	pg·hr/ml	131.5842	166.1650	54.7263
Cmax D1	pg/ml	16.1421	18.6400	5.5950
AUC D7 (0-24)	pg·hr/ml	139.6882	209.5625	155.8538
AUC D27 (0-24)	pg·hr/ml	92.5039	93.3975	92.5900
Cmax D27	pg/ml	7.9000	7.7350	6.6450
Tmax D27	hr	12.2632	9.1000	11.5526
Cmin	pg/ml	2.0035	1.1650	3.3033
Cav	pg/ml	3.8543	3.8916	3.8579

Unconjugated Estrone (No Baseline Correction)

Pharmacokinetic Parameter	Units	Arithmetic Mean values		
		Test A	Test B	Reference C
AUC D1 (0-24)	pg·hr/ml	1199.5297	1420.4000	958.3759
Cmax D1	pg/ml	98.5105	122.9000	52.4650
AUC D7 (0-24)	pg·hr/ml	1138.3737	1465.5725	1127.4963
AUC D27 (0-24)	pg·hr/ml	868.9579	945.1588	1142.7263
Cmax D27	pg/ml	48.0684	55.8850	68.4550
Tmax D27	hr	12.0000	10.8500	7.7000
Cmin	pg/ml	30.3796	30.9517	41.9250
Cav	pg/ml	36.2066	39.3816	47.6136

Unconjugated Estrone (Baseline Corrected)

Pharmacokinetic Parameter	Units	Arithmetic Mean values		
		Test A	Test B	Reference C
AUC D1 (0-24)	pg·hr/ml	622.6947	833.9863	305.6789
Cmax D1	pg/ml	74.4368	98.4500	24.3368
AUC D7 (0-24)	pg·hr/ml	560.7211	881.6525	518.7776
AUC D27 (0-24)	pg·hr/ml	293.7526	367.6963	619.3526
Cmax D27	pg/ml	23.9947	31.4350	46.8316
Tmax D27	hr	12.0000	10.8500	7.5789
Cmin	pg/ml	6.8561	6.9567	20.5158
Cav	pg/ml	12.2397	15.3207	25.8064

Total Estrone (No Baseline Correction)

Pharmacokinetic Parameter	Units	Arithmetic Mean values		
		Test A	Test B	Reference C
AUC D1 (0-24)	pg·hr/ml	19143.8974	19028.2938	25074.8138
Cmax D1	pg/ml	1210.2632	1268.0000	1782.9000
AUC D7 (0-24)	pg·hr/ml	20813.5263	25763.6750	27956.4750
AUC D27 (0-24)	pg·hr/ml	14324.9842	14178.1575	25089.8750
Cmax D27	pg/ml	866.6316	845.3000	1754.8000
Tmax D27	hr	14.9474	14.4500	6.3000
Cmin	pg/ml	452.9070	421.2967	813.3000
Cav	pg/ml	596.8743	590.7566	1045.4115

Total Estrone (Baseline Corrected)

Pharmacokinetic Parameter	Units	Arithmetic Mean values		
		Test A	Test B	Reference C
AUC D1 (0-24)	pg·hr/ml	12012.5263	13101.7375	15065.3421
Cmax D1	pg/ml	911.8947	1020.3500	1321.9474
AUC D7 (0-24)	pg·hr/ml	14116.8158	19843.5000	20170.7105
AUC D27 (0-24)	pg·hr/ml	7252.3158	8337.3000	19103.5526
Cmax D27	pg/ml	568.2632	597.6500	1502.3684
Tmax D27	hr	14.9474	14.4500	6.4211
Cmin	pg/ml	162.4386	180.8667	540.4386
Cav	pg/ml	302.1798	347.3875	795.9814

Unconjugated Equilin (No Baseline Correction)

Pharmacokinetic Parameter	Units	Arithmetic Mean values		
		Test A	Test B	Reference C
AUC D1 (0-24)	pg·hr/ml	94.8699	136.6681	110.6845
Cmax D1	pg/ml	14.2737	23.9590	11.8640
AUC D7 (0-24)	pg·hr/ml	65.3622	143.9699	193.7998
AUC D27 (0-24)	pg·hr/ml	27.3284	51.6720	265.7690
Cmax D27	pg/ml	5.4926	11.4505	20.0850
Tmax D27	Hr	10.4545	9.2667	7.4000
Cmin	pg/ml	0.2407	0.2475	4.9198
Cav	pg/ml	1.1387	2.1530	11.0737

Total Equilin (No Baseline Correction)

Pharmacokinetic Parameter	Units	Arithmetic Mean values		
		Test A	Test B	Reference C
AUC D1 (0-24)	pg·hr/ml	4677.4184	4877.8875	9233.4050
Cmax D1	pg/ml	370.4632	394.1500	796.3500
AUC D7 (0-24)	pg·hr/ml	4629.8158	5877.9750	10670.6713
AUC D27 (0-24)	pg·hr/ml	3007.2461	3081.8250	10357.2825
Cmax D27	pg/ml	224.6211	208.6350	785.6000
Tmax D27	hr	11.3158	10.3000	5.9000
Cmin	pg/ml	54.6632	44.2567	221.4150
Cav	pg/ml	125.3019	128.4094	431.5534

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pharmacokinetics of Bijuva® were studied in asymptomatic healthy postmenapausal women. No pharmacokinetics were evaluated in the Phase 3 study

2.2.5.3 What are the characteristics of drug absorption?

Conjugated estrogens are water soluble and are well absorbed through the skin, mucous membranes, and the GI tract. The intended route of administration with Bijuva® synthetic conjugated estrogens is intravaginal and the desired site of delivery is also the vagina for local treatment of VVA; however, but systemic absorption through the vaginal epithelium was observed as seen from the systemic pharmacokinetic data presented earlier. Absorption of estrogens from the vagina decreased over time as observed with lower AUC following extended use (Day 1 versus Day 27).

2.3 Intrinsic Factors

Absorption

Synthetic conjugated estrogens, A, are soluble in water and are well absorbed from the gastrointestinal tract after release from the Cenestin® Tablet drug formulation. After oral administration of Cenestin® tablet, synthetic conjugated estrogens, A, are slowly released over a period of several hours. Maximum plasma concentrations of conjugated and free estrogens are attained within 4 to 16 hours after oral administration. After intravaginal application of Cenestin® Cream, mean Tmax values ranged from 6.5 to 12.3 hours for baseline-adjusted free estradiol, from 6.8 to 12.0 hours for baseline-adjusted free estrone, and from 6.0 to 10.5 hours for free equilin.

After intravaginal application of Cenestin® cream, absorption of synthetic conjugated estrogens, A, is lower, compared to the absorption after oral administration. Absorption is further reduced after continued daily application. Relative systemic exposure after twice weekly application is considerably low, compared to systemic exposure from daily application.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone binding globulin (SHBG) and to a lesser degree to albumin. Conjugated estrogens bind mainly to albumin while the free estrogens bind to both albumin and sex hormone binding globulin (SHBG).

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both are converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women

a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active free estrogens.

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The apparent terminal elimination half-life ($t_{1/2}$) of conjugated estrone ranges from 4 to 18.5 hours and conjugated equilin from 4 to 17 hours, after oral administration. After 0.625 mg Bijuva twice weekly intravaginal application, the mean elimination half-lives at steady-state (Day 27) were 22.1 hours for baseline-adjusted free estradiol, 34.1 hours for baseline-adjusted free estrone, and 15.7 hours for free equilin.

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

The sponsor did not conduct formal studies to evaluate the impact of intrinsic factors on the pharmacokinetic of Bijuva®.

Age

89% (53 of the 59) of subjects who completed the pharmaokinetic study were between the age of 41 to 64 years. The age of all the subjects ranged from 39 to 70 years. For the clinical trial, the age range for 622 enrolled patients was 42 to 78 years.

Gender

Bijuva® is indicated for the treatment of vulvar and vaginal atrophy; only postmenopausal women were enrolled in the pharmacokinetic study.

Race

The majority (82%) of subject were Black (27/59) or Caucasian (21/59). No subgroup analysis was performed.

Renal insufficiency and hepatic insufficiency

In vitro and *in vivo* studies have shown that oral estrogens are metabolized partially by cytochrome P450 3A4; therefore hepatic impairment may affect the pharmacokinetics of orally administered estrogens. Delivery of estrogens by the vaginal route bypasses first pass metabolism by the liver. The current label for Cenestin® SCE-A oral tablets states that no pharmacokinetic studies were conducted in patients with renal or hepatic impairment. The new pharmacokinetic study did not include these special populations.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

The sponsor did not study the effect of other vaginally delivered products on Bijuva® exposure.

2.4.2 Drug-Drug Interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

In vitro and *in vivo* studies have shown that oral estrogens are metabolized partially by cytochrome P450 3A4; therefore inducers or inhibtors of CYP3A4 may affect drug metabolism. In the case of Bijuva®, the site of action is the vaginal epithelium where limited systemic absorption was observed and thus a much lower risk of systemic drug-drug interactions. The sponsor did not conduct drug-drug interactions with other vaginal products.

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility and permeability support this classification?

Conjugated estrogens are water soluble and are well absorbed through the skin, mucous membranes, and the GI tract. The permeability of estrogens across the vaginal epithelium has not been evaluated. The BCS classification of Bijuva® has not been determined.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed formulation is the same as the one used in the pivotal Phase 3 clinical trial.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Bijuva® is a vaginal cream indicated for the treatment of VVA, as such the effect of food on the bioavailability from the vaginal tissue is not relevant.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

The pharmacokinetic study was conducted by _____ The plasma samples were prepared from blood samples collected from the subjects enrolled in PK study 10716214 and were sent to _____ The quantitation of unconjugated 17β-estradiol, unconjugated estrone, unconjugated equilin, total estrone, and total equilin concentrations in human plasma was done using high performance liquid chromatography with mass spectroscopy/mass spectroscopy detection (HPLC with MS/MS).

b(4)

2.6.2 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy, precision and selectivity at these limits?

The quantitation of unconjugated 17β-estradiol, unconjugated estrone, unconjugated equilin, total estrone, and total equilin concentrations in human plasma was done using high performance liquid chromatography with mass spectroscopy/mass spectroscopy detection (HPLC with MS/MS). The lower and upper limits of quantitation is listed in the table below.

	Total estrone	Total equilin	Unconjated estrone	Unconjugated equilin	Unconjugated 17β-estradiol
LLOQ (pg/mL)	10.0	10.0	5.00	5.00	1.00
ULOQ (pg/mL)	5000	5000	500	500	100

For total estrone (E1) and total equilin (EQ), the precision and accuracy were evaluated by analyzing quality control pools prepared in surrogate matrix and human serum at 25.0, 60.0, 225, 725, and 3800 pg/mL. The % difference from theoretical concentration for total estrone and total equilin ranged from ——— and ———, respectively. b(4)

For unconjugated estrone, the precision and accuracy were evaluated by analyzing quality control pools prepared in surrogate matrix and human serum at 10.0, 20.0, 50.0, 125, and 375 pg/mL. The % difference from theoretical concentration ranged from ——— b(4)

For unconjugated equilin, the precision and accuracy were evaluated by analyzing quality control pools prepared in surrogate matrix and human serum at 10.0, 20.0, 50.0, 125, and 375 pg/mL. The % difference from theoretical concentration ranged from ——— b(4)

For unconjugated 17β-estradiol, the precision and accuracy were evaluated by analyzing quality control pools prepared in surrogate matrix and human serum at 2.00, 4.00, 10.0, 25.0 and 75.0 pg/mL. The % difference from theoretical concentration ranged from ——— b(4)

The bioanalytical method supports this application, and were accurate, precise, selective, sensitive, and reproducible. Method validation reports were submitted with the NDA.

2 Detailed Labeling Recommendations

The sponsor proposed to include in the label the pharmacokinetic data comparing the vaginal cream to the oral tablet. The pharmacokinetic information for the Cenestin® oral tablets provides limited comparative information to the prescriber or user as Bijuva® is intended to deliver estrogens to the vagina, not the systemic circulation, for a local effect. Additionally, at steady state (Day 27), the systemic exposure for Bijuva® vaginal cream is lower than the Cenestin® oral tablet, which may suggest that the vaginal cream is safer than the oral tablet. The sponsor did not conduct a clinical study comparing the safety of the vaginal cream to the oral tablet. This reviewer recommends omitting the PK data for the oral product from the label. The reviewer also recommends replacing Figure 1 (PK vs. time profile comparing the vaginal cream to the oral tablet) in the sponsor's propose label with a PK vs. time profile for Bijuva vaginal cream following the Day 27 dose for baseline-adjusted free estradiol, baseline-adjusted free estrone, and free equilin.

Though the sponsor states that the pharmacokinetic parameter AUC_{weekly} for the Bijuva® vaginal cream and Cenestin® oral tablet provides a direct comparison of systemic exposure following 7 days of product use, the use of AUC_{0-48} to extrapolate AUC_{0-84} can result in over- or under-estimation if the elimination phase after 48 hours is non-linear. Additionally, an error in estimating AUC_{0-84} can be carried further to the AUC_{weekly} value; therefore, this reviewer

recommends comparison of the AUC0-24 following Day 27 dose for a more accurate assessment of systemic exposure. The reviewer recommends replacing Table 2 (PK parameters comparing the vaginal cream to the oral tablet) in the sponsor's proposed label with the following table:

Table 2: Pharmacokinetic parameters for baseline-adjusted free estrone, baseline-adjusted free estradiol, and free equilin at Day 1, Day 7 and Day 27 following the recommended dosing regimen of 1 gm Tradename Vaginal Cream.

Pharmacokinetics of Unconjugated Estrogens									
	Day 1			Day 7			Day 27		
	C_{max} (pg/mL)	T_{max} (hr)	AUC_{0-24} (pg.hr/mL)	C_{max} (pg/mL)	T_{max} (hr)	AUC_{0-24} (pg.hr/mL)	C_{max} (pg/mL)	T_{max} (hr)	AUC_{0-24} (pg.hr/mL)
Baseline-adjusted Estrone	74.4	6.8	622.7	38.4	8.3	560.7	24.0	12.0	293.8
Baseline-adjusted Estradiol	16.1	6.6	131.6	12.7	8.9	139.7	7.9	12.3	92.5
Equilin	14.3	6.0	94.9	7.4	10.1	65.4	5.5	10.5	27.3

Equilin is one of several important estrogenic substances and contributes toward the overall clinical effect of Bijuva®. As such, the reviewer recommends adding the pharmacokinetic data for unconjugated (free) equilin in the label.

See Appendix in Section 4 for additional labeling recommendations. (~~Strikethrough text~~ is recommended to be deleted and <u>underlined text</u> is recommended to be added)
These comments have been communicated to the sponsor.

4 APPENDICES

4.1 Proposed Package Insert with reviewer's recommended revision

b(4)

4 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

X Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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