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*APPLICATION NUMBER:*

**208470Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Drug Evaluation III (ODE III)

Reviewer Name(s) Theresa H. van der Vlugt, M.D.  
Review Completion Date November 16, 2016

Established Name Prasterone Vaginal Insert  
(Proposed) Trade Name INTRAROSA  
Therapeutic Class Steroid Hormone  
Applicant EndoCeutics Inc.

Formulation(s) Dehydroepiandrosterone  
Dosing Regimen Intravaginal Daily  
Indication(s) Treatment of Moderate to  
Severe Dyspareunia (b) (4)  
(b) (4) a Symptom  
of Vulvovaginal Atrophy, Due  
to Menopause

Intended Population(s) Postmenopausal Women

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This reviewer recommends approval of 6.5 mg INTRAROSA™ (prasterone) vaginal insert, administered intravaginally daily, at bedtime, for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Recommendation for approval for the treatment of moderate to severe dyspareunia, pending final agreed upon labeling for INTRAROSA™ (prasterone) vaginal insert, is based on:

1. The safety and efficacy data presented in primary 12-week clinical Trial ERC-231 included in the application, received on October 16, 2015.
2. The safety and efficacy data presented in primary 12-week clinical Trial ERC-238 included in the application, received on October 16, 2015.
3. The safety data presented in primary 52-week clinical Trial ERC-230 included in the application, received on October 16, 2015.
4. The additional safety data presented in 12-week clinical Trial ERC-234 included in the application, received on October 16, 2015.
5. The additional safety data presented in 12-week clinical Trial ERC-210 included in the application, received on October 16, 2015.
6. The 120-Day Safety Update received on May 27, 2016.
7. Additional safety data received on February 12, 2016 (requested in the Filing Communication – No Filing Review Issued Identified letter dated December 28, 2015) for actual copies of central endometrial biopsy histology reports prepared by (b) (4), the single pathologists who examined end-of-trial (or discontinuation) endometrial biopsy specimens in Trials ERC-210, ERC-230, ERC-231, and ERC-234.
8. Additional safety data received on June 30, 2016 in safety “Study ERC-237”. Study ERC-237 (protocol received on May 6, 2016, amended on May 10, 2016 and June 1, 2016) was designed at the request of the Agency (letter dated March 29, 2016) requesting a re-cut of the original endometrial biopsy specimens obtained in Trials ERC-210, ERC-230, ERC-231, and ERC-234, and a re-read by two additional, independent, blinded pathologists.
9. No outstanding Chemistry, Manufacturing and Controls (CMC) or nonclinical pharmacology/toxicology issues.
10. The supporting safety information for 6.5 mg prasterone vaginal insert administered intravaginally daily. The review of the original safety data in the application, the 120-Day Safety Update Report received on May 27, 2016, and the additional safety data received on February 12, 2016 and June 30, 2016 did not demonstrate any overall safety concerns for 6.5 mg prasterone.

## 1.2 Risk Benefit Assessment

Menopause is a natural biological process and marks the end of fertility as a result of permanent ovarian failure. Symptoms of menopause, such as vasomotor symptoms (VMS; hot flashes/hot flushes) and vulvar and vaginal atrophy symptoms [VVA; vaginal dryness, vaginal irritation/itching, and pain with sexual activity (dyspareunia)] can be debilitating with respect to a woman's ability to accomplish her normal activities including sleep. However, menopause is not a life-threatening condition. In 2000, there were an estimated 45.6 million postmenopausal women in the United States. About 40 million of them were older than age 51, the average age of natural menopause in the Western world. By the year 2020, the number of US women older than age 51 is expected to be more than 50 million.<sup>1</sup>

Current treatment options for the general indication for the treatment of moderate to severe symptoms of VVA, involve multiple estrogen products, used alone in a woman without a uterus, or in combination with a progestogen in a woman with a uterus. Most of these products were approved under estrogen class labeling, and were not supported by clinical trial data demonstrating relief of moderate to severe symptoms of vulvar and vaginal atrophy. Current treatment options for an indication for the treatment of moderate to severe dyspareunia (self-identified as most bothersome by the woman) include one intravaginally applied estrogen cream, one oral estrogen tablet, and one oral estrogen agonist/antagonist tablet.

Prasterone is a steroid vaginal insert. Prasterone is a synthetic version of dehydroepiandrosterone (DHEA). DHEA is an endogenous hormone produced by the human body. DHEA is an inactive precursor hormone but can be converted to active forms such as androgens and estrogens. No structurally similar steroid hormone is approved for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Prasterone 6.5 mg vaginal insert, administered intravaginally once daily at bedtime, demonstrated statistically significant improvement over placebo, in the relief of self-identified moderate to severe dyspareunia, in two confirmatory 12-week clinical trials. No major safety issues, related specifically to the 6.5 mg prasterone vaginal insert, were identified in this review in four 12-week, placebo-controlled clinical trials and one 12-month open-label clinical trial. Application site discharge was the most common adverse reaction identified with the use of the 6.5 mg prasterone vaginal insert. This specific adverse reaction resolved over a 12-month period in the long-term clinical trial.

With the approval of 6.5 mg INTRAROSA™ (prasterone) vaginal insert, symptomatic postmenopausal women, with moderate to severe dyspareunia, will have access to an

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<sup>1</sup> US Census Bureau. Population survey: female population by age, sex, and race and Hispanic origin: March 2002. Available at: <http://www.census.gov/poplulation/socdemo/race/api/ppl-163/tab01>.

additional vaginally administered product for this indication. Vaginally (b) (4) administered products for the treatment of moderate to severe dyspareunia, due to menopause, are recommended for this indication.

Approval of prasterone for use in the treatment of moderate to severe dyspareunia in postmenopausal women is fully supported by the available evidence of efficacy and safety.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarketing risk evaluation and mitigation strategies (REMS) are recommended.

### 1.4 Recommendations for Postmarket Requirements and Commitments

No postmarketing requirements and commitments are recommended.

EndoCeutics will be requested to provide specific focused pharmacovigilance information in the NDA Annual Report regarding the applicator approved for use with the 6.5 mg INTRAROSA™ (prasterone) vaginal insert, particularly for issues regarding difficulty of insertion and/or removal of the applicator, and subsequent vaginal abrasion and/or laceration of the vaginal wall with use of the applicator. The to-be-marketed applicator is different from the applicator used in clinical trials conducted during the prasterone development program.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

The purpose of this application is to obtain marketing authorization for prasterone [dehydroepiandrosterone (DHEA); hereafter referred to as DHEA] in the treatment of moderate to severe dyspareunia (pain at sexual activity), a symptom of vulvar and vaginal atrophy (VVA), due to menopause. The proposed dose is 6.5 mg once daily administered intravaginally at bedtime.

DHEA and its sulfate conjugate DHEA-S are C21 steroids synthesized from cholesterol and secreted by the normal human adrenal gland in the zona reticularis. Cholesterol is converted to pregnenolone by the enzyme P450 scc (side chain cleavage); CYP17A1

converts pregnenolone to 17 $\alpha$ -hydroxypregnenolone and then to DHEA. 17-ketosteroid reductase converts DHEA to androstenediol; androstenediol is converted to testosterone and dihydrotestosterone. Testosterone may be converted to estradiol and estrone.

DHEA is also produced in the theca cells of the ovary in three steps from cholesterol. DHEA is then converted by 3 $\beta$ -hydroxysteroid dehydrogenase/isomerase to androstenedione which is in turn converted to testosterone by 17 $\beta$ -hydroxysteroid dehydrogenase. In the granulosa, androstenedione is aromatized to estradiol by P450 aromatase.

Per the applicant, "The strictly local action of intravaginal DHEA (prasterone) is in line with the absence of significant systemic drug-related adverse events, thus showing the high benefit/risk ratio of this treatment essentially based upon the novel understanding of the physiology of sex steroids in women."

Vulvar and vaginal atrophy (VVA) is a condition associated with declining postmenopausal estrogen levels, and is often symptomatic and can be progressive.

The vaginal wall has estrogen receptors, mainly in the basal layers of the epithelium, but also in stromal cells and smooth muscle fibers. Estrogen affects the epithelium, connective tissue and vaginal wall elasticity. Physiologic estrogen concentrations are associated with a thickened and mature vaginal mucosa and increased vaginal blood flow, lubrication, and mechanical sensitivity. Estrogen stimulation produces glycogen used by lactobacilli. Lactic acid produced by the bacteria keeps vaginal pH levels low (from 3.5 to 4.5), which is essential for the body's natural defense against vaginal infections.

Per the applicant, the approval of INTRAROSA (hereafter referred to as Intrarosa) would offer an alternative to estrogens for the management of postmenopausal VVA and provide the only non-estrogen approved treatment for this population. (b) (4)

[Redacted text block]

**Clinical Reviewer's Comments:**

[Redacted text block] (b) (4)

(b) (4)

Two proposed proprietary names (b) (4) and (b) (4) were found to be unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA) on August 19, 2014 and April 10, 2015, respectively. The present application includes the information needed for a review of the proposed proprietary name “Intrarosa” with the accompanying evaluation from the (b) (4)

EndoCeutics received a Proprietary Name Request, Conditionally Acceptable letter from DMEPA, on December 30, 2015, stating:

“We have completed our review of the proposed proprietary name, Intrarosa and have concluded that it is conditionally acceptable. If any of the proposed product characteristics as stated in your October 16, 2015 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.”

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 shows the number of drug products approved for the treatment of moderate to severe dyspareunia (or pain with sexual activity), due to menopause.

Table 1: Currently Approved Products for the Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause

<b>Vaginal Cream Product</b>	<b>Available Dosage Strength/Dosing Regimens</b>
Premarin® (conjugated estrogens) Vaginal Cream	Cyclic Administration: 0.5 g intravaginally daily for 21 days then off for 7 days  Twice Weekly Administration: 0.5 g intravaginally twice weekly (for example, Monday and Thursday)
<b>Oral Estrogen-alone Product</b>	<b>Available Dosage Strength/Dosing Regimens</b>
Enjuvia® (synthetic conjugated estrogens, B) Tablets*	0.3 mg taken orally once daily
<b>Oral Estrogen Agonist/Antagonist Product</b>	<b>Available Dosage Strength/Dosing Regimens</b>
Osphena® (ospemifene) Tablet	60 mg tablet taken orally once daily with food

\* Teva Women’s Health, Inc. no longer manufactures or distributes Enjuvia® (synthetic conjugated estrogens, B) tablets under NDA 21443. NDA 21443 for Enjuvia® remains active. The last approved Enjuvia® (synthetic conjugated estrogens, B) tablets labeling is dated May 13, 2015.

Several estrogen-alone and estrogen plus progestin products are approved with a general indication for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause. See the “Table of Currently Available

Treatments for a Non-Specific VVA Symptom Indication”, in Subsection 9.4 of this review, for information on currently approved estrogen-alone and estrogen plus progestin products with a general indication for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, due to menopause. Most of these products approved for a general indication for the treatment of moderate to severe symptoms of VVA, were approved under estrogen class labeling, and were not supported by clinical trial data demonstrating relief of individual moderate to severe symptoms of vulvar and vaginal atrophy. Subsequent to the approval under class labeling of products for the general indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, the Division of Reproductive and Urologic Drug Products [(DRUDP), now known as the Division of Bone, Reproductive, and Urologic Products (DBRUP)] discussed the approach of approval under class labeling with its Fertility & Maternal Health Drugs Advisory Committee (AC). Taking the advice of the AC into consideration, we determined that sponsors seeking an indication for any symptom of vulvar and vaginal atrophy should conduct clinical trials in support of the indication.

### 2.3 Availability of Proposed Active Ingredient in the United States

DHEA is available in the U.S. without a prescription; 10 mg to 100 mg capsules and/or tablets and a 1% cream can be obtained over-the-counter or the internet. A prescription for DHEA is needed in Canada where DHEA is considered an anabolic steroid.

At the time of this review, no structurally similar product is approved for the proposed indication.

On December 21, 2105, Norman R. Schmuft, Ph.D., Associate Director for Science, Office of Process and Facilities (OPF) at the Food and Drug Administration (FDA) states:

“Prasterone is an endogenous steroid hormone. Prasterone is the United States Adopted Name (USAN) and the International Nonproprietary Name (INN) for dehydroepiandrosterone (DHEA) which is the both the active moiety and the active ingredient in INTRAROSA. It is marketed as a dietary supplement where it is generally known as DHEA.”

“However, it has also been marketed as a drug under the name DHEA, prompting the issuance of a number of FDA Warning Letters.” One example follows:

“June 10, 2015 Warning Letter to Daniel V. Young: Based on our review of your products’ labels and your websites, countrydoctorherbal.us and countrydoctornutritionalcenter.us, in March 2015, we have determined that the claims on your labels and websites establish that several of your firm’s products are drugs within the meaning of section 201(g)(1)(B) and/or (g)(1)(C) of the Act

[21 USC § 321(g)(1)(B) and/or (g)(1)(C)] because they are intended for use in the cure, mitigation, treatment, or prevention of disease and/or are articles (other than food) intended to affect the structure or any function of the body....

COUNTRY DOCTOR DHEA (CAPSULE ONLY)

- “[M]ay help....treat osteoporosis”

The November 4, 2015 Manual of Policies and Procedures (MaPP) entitled, “NDA Classification Codes” contains the following definition for New Molecular Entity (NME):

“An NME is an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under section 505 of the Act or has been previously marketed as a drug in the United States.”

OPF concludes:

“As evidenced by the FDA Warning Letters cited above, prasterone (aka DHEA) is an active ingredient containing an active moiety that has been previously marketed as a drug in the United States. Consequently, the prasterone active ingredient in the INTRAROSA (prasterone insert) NDA is not an NME.”

**Clinical Reviewer’s Comments:**

Although DHEA is not considered a NME by the Agency, it is a new chemical entity (NCE) proposed for the treatment of moderate to severe dyspareunia due to menopause. As an NCE for this indication, the Agency recommended that EndoCeutics adhere to the International Conference on Harmonization (ICH) E1 Guidelines for premarket patient exposure for a drug product intended for chronic use. These guidelines recommend exposure in 1500 patients overall, 300-600 patients for 6 months, and 100 patients for one year. Patient exposure must occur at the dose or dose range expected to be efficacious.

EndoCeutics complied with the ICH E1 guideline recommendations in the DHEA development program.

## 2.4 Important Safety Issues with Consideration to Related Drugs

Anabolic steroids, technically known as anabolic-androgenic steroids, are synthetically produced variants of the naturally occurring male hormone testosterone. In the U.S., anabolic steroids are Schedule III substances under the Controlled Substances Act. “A wide range of adverse effects is associated with the use or abuse of anabolic steroids. These effects depend on several factors including: age, sex, the anabolic steroid used, amount used, and duration of use. In adolescents, anabolic steroid use can stunt the

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ultimate height than an individual achieves. In boys, steroid use can cause early sexual development, acne, and stunted growth. In adolescent girls and women, anabolic steroid use can induce permanent physical changes, such as deepening of the voice, increased facial and body hair growth, menstrual irregularities, male pattern baldness, and lengthening of the clitoris. In men, anabolic steroid use can cause shrinkage of the testicles, reduced sperm count, enlargement of male breast tissue, sterility, and an increased risk of prostate cancer. In both men and women, anabolic steroid use can cause high cholesterol levels, which may increase the risk of coronary artery disease, strokes, and heart attacks. Anabolic steroid use can also cause acne and fluid retention. Oral preparations of anabolic steroids, in particular, can damage the liver.”<sup>2</sup> “Case studies and scientific research indicate that high doses of anabolic steroids may cause mood and behavioral effects. In some individuals, steroid use can cause dramatic mood swings, increased feelings of hostility, impaired judgment, and increased levels of aggression (often referred to as “roid rage”). When users stop taking steroids, they may experience depression that may be severe enough to lead one to commit suicide. Anabolic steroid use may also cause psychological dependence and addiction.”<sup>2</sup>

In Canada, DHEA is a controlled drug listed under Section 23 Schedule IV of the *Controlled Drugs and Substances Act* and as such is available by prescription only.<sup>3</sup>

In the human body, large amounts of the inactive precursor steroids DHEA and DHEA-sulfate (DHEA-S) are converted into bioactive steroid hormones such as potent androgens [testosterone and dihydrotestosterone (DHT)] and/or estrogens in peripheral tissues. Per the applicant, following their formation and availability for local intracellular action, testosterone and DHT are inactivated and transformed in the same cells into water soluble glucuronide derivatives eliminated by the kidneys.

DHEA functions predominantly as a metabolic intermediate in the biosynthesis of androgen and estrogen sex steroids. As such, DHEA could be considered a relatively weak anabolic steroid. Published literature of short-term trials of high doses of daily DHEA report few side effects. Chang et al., 2002 reported an increased incidence of acne at a dose of 200 mg per day for 24 weeks.<sup>4</sup> Rabkin JG et al., 2006 utilized a DHEA dose up to 400 mg per day for 8 weeks with few adverse events reported.<sup>5</sup> Per the published literature, the most common reported androgenic side effects of DHEA include acne, hirsutism, deepening of voice, oily skin, and mild hair loss.

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2 Drug Enforcement Administration, Drug Fact Sheet, Steroids ([www.dea.gov](http://www.dea.gov)).

3 Health Canada, DHEA listing in the Ingredient Database (<http://webprod.hc-sc.gc.ca/nhp/ident/bdipsn/ingredReq.do?id=4639&lang=eng>).

4 Chang DM, Lan JL, Lin HY, Lou HY. Dehydroepiandrosterone treatment in women with mild-to-moderate systemic lupus erythematosus: a multicenter randomized, double-blind, placebo-control trial. *Arthritis Rheum.* 2002. 46(11): 2924-2927.

5 Rabkin JG, et al. Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS. *Am J Psychiatry.* 2006. 163(1): 59-66.

Overall, the long-term effects of exogenous DHEA use are largely unknown as DHEA use has not been studied in long-term, randomized clinical trials of sufficient size.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 78,027 for DHEA was initially submitted by EndoCeutics on July 17, 2007. The initial submission presented a 12-week, phase 3 protocol for Clinical Trial ERC-210 entitled, "Protocol ERC-210: Topical DHEA Against Vaginal Atrophy (3-Months Placebo-Controlled Double-Blind Randomized Phase III Study)" with the primary objective to determine the dose-response of vaginal mucosa parameters to the local action of DHEA in postmenopausal women suffering from vaginal atrophy.

(b) (4)



On March 31, 2009, DBRUP met with EndoCeutics (Type C Guidance Meeting). Selected EndoCeutics preclinical and clinical questions, and DBRUP responses, are presented below:

### Preclinical:

Question Number 1: "Based upon the absence of significant findings in the repeated-dose one-year oral toxicity study with DHEA in monkeys (2 and 10 mg/kg/day) and in the 26-week oral toxicity study in rats (10 and 100 mg/kg/day) as well as the absence of effect of DHEA in the three standard genotoxicity assays and the fact that [REDACTED] (b) (4) is used exclusively in postmenopausal women and the absence of significant change in serum estrogen and androgen levels, EndoCeutics believes that the current preclinical toxicology package should be acceptable for approval of [REDACTED] (b) (4) (0.5% DHEA, 6.5 mg DHEA) for the vaginal atrophy indication. Does the FDA agree?"

### **DBRUP Response:**

“We agree that the findings reported in the completed repeated-dose one-year oral toxicity study with DHEA in monkeys, the 26-week oral toxicity study in rats, and the three standard genotoxicity assays are adequate to support the submission of an NDA for 0.5% DHEA (6.5 mg of DHEA) for a vaginal atrophy indication.”

Clinical:

Question Number 1: “Very compelling data were obtained in the prospective, randomized and placebo-controlled 3-month phase III clinical trial ERC-210 (163 women treated) using 0.25%, 0.5% and 1.0% DHEA, following the completion of two highly positive phase II clinical trials.” (b) (4)

[Redacted]

[Redacted] (b) (4)

Question Number 2: “If more than one pivotal trial (ERC-210) is required, would the data from the proposed study ERC-210 (250 women treated with 0.50% intravaginal DHEA for 3 months with 3-month data estimated for December 2009) be acceptable for the vaginal atrophy indication using 0.5% DHEA (b) (4) ?”

**DBRUP Response:**

“We consider DHEA to be a new molecular entity. Therefore, we are recommending two confirmatory studies in support of safety and efficacy for a VVA indication. As stated in our response to Question 1, the analysis from ERC-210 did not adhere to our previous recommendations.”

Question Number 3: “Regarding the safety of chronic use” --- and, “considering the low dose of DHEA used (6.5 mg) and the well documented and recognized safety of DHEA, including the conclusions of the FDA following evaluation from data of the

Adverse Event Reporting System (AERS) as well as the CFSAN's post-marketing database and the medical literature, it is reasonable to assume that a post-marketing phase IV study should be acceptable to determine long term safety. Does the FDA agree?"

**DBRUP Response:**

"We do not agree that a postmarketing phase 4 study commitment would be appropriate to address the Agency's concerns regarding the safety of chronic use of the daily intravaginal administration of DHEA.

The Division generally follows the ICH guidelines for patient exposure when a drug product is used on a chronic basis. These guidelines recommend exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures must occur at the dose or dose range believed to be efficacious."

On July 12, 2013, Written Responses Only (WRO) was provided to the following selected EndoCeutics clinical questions:

Question Number 1: "Does the Agency agree that study ERC-210 (b) (4)

[REDACTED]

**DBRUP Response:**

"We do not agree that Trial ERC-210 can be considered as one of the two confirmatory 12-week clinical trials to support the effectiveness of 0.50% prasterone for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Trial ERC-210 did not assess the mean change from baseline to week 12 in the individual moderate to severe vulvar and vaginal atrophy symptom (for example, dyspareunia) self-identified by the patient as being most bothersome to her. The most bothersome symptom (MBS) calculation was based on a composite of all most bothersome symptoms scores and was not adjusted for multiple comparisons to control the overall type-1 error rate. The subsequently submitted post-hoc reanalysis of Trial ERC-210 data (analysis of the subset of the Trial ERC-210 (b) (4) data) was not based on an adequate sample size and is not acceptable."

Question Number 3: "DHEA is an endogenous precursor of sex steroids that is present at relatively high levels in men. Administration of (b) (4) results in negligible changes of systemic levels of DHEA in women when compared to existing endogenous serum levels in normal women. Furthermore, there is an absence of safety concerns raised during the conduct of the VVA studies including the lack of any safety signal of local intolerance by women exposed to higher levels and much

longer duration than men. Based on the above-described reasons, we believe that partner exposure does not require further evaluation. Does the Agency agree?"

**DBRUP Response:**

"We cannot agree at this time that you have sufficient information to support the safety of the exposed partner. This will be a review issue. At the time of the NDA submission, you should provide a thorough justification that the safety of the exposed partner has been adequately evaluated. This justification should include but is not limited to: 1) the expected drug concentration in the male partner given the daily administration of 0.50% prasterone in the female partner, 2) potential safety concerns in males that could be related to the drug exposure, and 3) actual adverse events observed in exposed male partners."

On September 5, 2013, EndoCeutics submits the following clarification questions:

Question Number 1: "Does the Agency agree that as per the International Conference on Harmonization (ICH) guidelines, women in clinical trials who receive daily treatment with 0.25% prasterone can be considered to be within an established dose range of efficacy and therefore, can be included in the total number of 1500 subjects exposed to the investigational drug? It is our understanding that we have already obtained adequate/required prasterone exposure in 1178 patients and that we only need to generate exposure data in another 322 patients to fulfill the guideline."

**DBRUP Response:**

"We accept the subjects exposed to prasterone (DHEA) 3.25 mg (0.25%) would have been considered as within the anticipated dose range of efficacy and can be included in the total number of exposed subjects. Per the information provided, the total 1178 subjects exposed to prasterone include the dose range of 3.25 mg (0.25%) to 23.4 mg (1.8%).

We agree that an additional 322 subjects, with exposure at 0.50% or greater, would meet the ICH guidelines recommendation for overall exposure of 1500 subjects.

In addition, DBRUP found acceptable subjects with "short-term exposures" including 1 week of daily administration and subject who discontinued after one dose of study medication."

On April 27, 2015, a Type B pre-NDA meeting was held with EndoCeutics to discuss the format and content of EndoCeutics' anticipated NDA application and the acceptability of CMC specifications, stability data, and qualification of an additional commercial manufacturing site. Selected questions and DBRUP responses are reviewed below:

Nonclinical:

Question Number 1: “For the Module 4 of the NDA, is it acceptable for the Agency that we include in the NDA the new study report on CYP inhibition but that cross-reference be made to the previously submitted and unchanged non-clinical study reports (Module 4.2.2.6), or if all nonclinical reports (toxicity and analytical reports) should be re-submitted in the NDA. The schematic presentation of the drug metabolism pathway will be included in the summary of clinical pharmacology (Module 2.7.2). Does the Agency agree that with the additional CYP study performed all preclinical requirements are met to support the NDA?”

**DBRUP Response:**

“Yes, you have met all nonclinical requirements to support the NDA. For ease of review, we ask that all nonclinical study reports that will be used to support the nonclinical portion of your current NDA submission be resubmitted in Module 4 of the NDA. We also ask that you provide a tabular listing of titles of studies from all INDs or NDAs that you intend to use to support the nonclinical portion of your current NDA submission. This can be included in Module 2 under Nonclinical Overview.”

Clinical:

Question Number 3: “Does the Agency agree with the proposed data and population to be used for the integrated efficacy analysis?”

**DBRUP Response:**

“No, we do not agree with your proposal to integrate efficacy data from 12-week Trial ERC-231 and 12-week Trial ERC-238 with your post-hoc analysis of Trial ERC-210 to support the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

We consider DHEA to be a new molecular entity (NME). This NME should be supported by two confirmatory adequate and well-controlled 12-week, phase 3 clinical trials for safety and efficacy. As previously conveyed to you, we do not agree that Trial ERC-210 can be considered as one of the confirmatory 12-week clinical trials to support the effectiveness of 0.50% prasterone (DHEA) for the indication as noted above. Our consideration of the efficacy of your product will be based on the results of Trial ERC-231 and Trial ERC-238, analyzed separately. Your proposed post-hoc analysis of Trial ERC- 210 could be submitted as supportive of your two confirmatory clinical trials.

The primary efficacy analyses in Trial ERC-231 and Trial ERC-238 should be based on women who meet all three of the baseline inclusion criteria: 1) less than 5% superficial cells on a lateral-wall vaginal smear, and 2) a vaginal pH greater than 5, and 3) a most bothersome moderate to severe symptom of vulvar and vaginal atrophy (defined as dyspareunia in Trials ERC-231 and ERC-238).

We agree with your definition of the ITT population as all women who have: 1) a baseline (Day 1) evaluation which meets the study entrance criteria, and 2) received at least one dose of medication (based on the woman's diary card)."

Question Number 8: "Does the Agency agree that data obtained for moderate to severe (b) (4) should be taken into account to define the proposed indication?"

**DBRUP Response:**

"No, we do not agree that secondary findings obtained in your two confirmatory clinical trials (Trial ERC-231 and Trial ERC-238) support an indication (b) (4). We continue to advise you that findings from secondary clinical trial endpoints, unless they are adequately and prospectively powered, are considered supportive and not primary."

Discussion at the meeting:

(b) (4)  
Further, the Agency reminded EndoCeutics that dyspareunia was self-selected as the most bothersome symptom in Trials ERC-231 and ERC-238. Trial ERC-234, for which a different dosing regimen was utilized (b) (4)

Additional DBRUP comments:

"We have the following additional comment on your Clinical Pharmacology development. As previously recommended during Advice (Type-C) Meetings on July 12, 2013 and April 30, 2009, provide at the time of the NDA submission, scientific justification to support: 1) dosing consideration for specific populations, such those with hepatic or renal impairment and; 2) safety in the exposed partner of the treated woman."

## 2.6 Other Relevant Background Information

This reviewer did not find evidence that prasterone (DHEA) is approved for any indication nationally or internationally. On October 19, 2005, Genelabs Technologies, Inc. withdrew its European Market Authorization Application (MAA) for its investigational systemic lupus erythematosus drug, Anastar (prasterone). Per information provided, the European Agency for Evaluation of Medicinal Products (EMA) found the data submitted not sufficient for approval. On July 28, 2002, orphan designation

(EU/3/03/156) was granted by the European Commission to Medicom Healthcare BV, the Netherlands, for prasterone (Fidelin) for the treatment of adrenal insufficiency. An orphan designation is not a marketing authorization.

On March 18, 2015, EndoCeutics received an Advice iPSP letter stating: “We also refer to your Initial Pediatric Study Plan (iPSP) submission dated December 13, 2013. We agree with your plan to waive studies in pediatric subjects and that you will submit a request for waiver from all requirements from Pediatric Research Equity Act (PREA) in a marketing application for EM-760 (prasterone, DHEA) intended for the treatment of moderate to severe dyspareunia, a symptom of vulvovaginal atrophy, due to menopause. We have completed our review of the submission, and we have no further comments to the iPSP.”

In a June 19, 2015 Agreed iPSP letter, DBRUP states: “We also refer to your amendment dated December 13, 2013, containing your Initial Pediatric Study Plan (iPSP) with a request for a waiver from the study requirements of the Pediatric Research Equity Act and to your submission dated, May 13, 2015, containing your Agreed iPSP. We have completed our review of the submission, and we confirm our agreement to your Agreed iPSP.”

In this NDA application, EndoCeutics provides information supporting their request for Priority Review Designation. DBRUP recommends that DHEA not be granted a Priority Review Designation for the following reasons:

1. “Menopause is a natural biological process and marks the end of fertility as a result of permanent ovarian failure. Moderate to severe vulvar and vaginal atrophy symptoms (for example, individual symptom of vaginal dryness, vaginal irritation/itching, or pain with sexual activity [dyspareunia] self-identified by the woman as most bothersome) due to menopause can be a serious condition which can restrict a woman’s ability to accomplish her normal activities including sexual activity. There is no indication, however, that prasterone (DHEA) vaginal insert will provide a significant improvement in safety or effectiveness over currently approved products for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy.”
2. “DHEA’s approved indication, should this NDA application be approved, would be for the treatment of the individual moderate to severe symptom of vulvar and vaginal atrophy (in this case dyspareunia), a symptom of vulvar and vaginal atrophy, due to menopause. Breast cancer survivors were not included in any of the primary efficacy clinical trials in the DHEA development program (Trials ERC-231, ERC-234, and ERC-238) or in the long-term safety trial (Trial ERC-230). Therefore, use of DHEA in this specific population (breast cancer survivors) is not warranted. No data was collected in this specific population in the DHEA development program. See the Medical Officer’s Memorandum, dated December 11, 2015, and the Clinical Filing Review, dated December 15, 2015,

for a full discussion of the information provided in support of a Priority Review Designation.”

EndoCeutics was granted a user fee waiver on September 29, 2015 under the small business waiver provision, section 736(d)(1)(D) of the Federal Food, Drug and Cosmetic Act (the Act).

The Agency has reviewed 22 commercial and 62 research INDs for DHEA. Four (4) of the 22 commercial INDs and 1 of the research INDs were pre-submissions. Three (3) of the 22 commercial INDs are currently active [2 sponsored by EndoCeutics (IND (b) (4) (b) (4) and IND 78027 for dyspareunia), and 1 sponsored by (b) (4)

Seven (7) of the 62 research INDs are currently active with the following trial objectives: (b) (4)

One (1) NDA submission for DHEA has previously been reviewed in the Agency. (b) (4)

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

The applicant conducted numerous internal audits at participating centers during the DHEA development program. Trial-specific audit certificates are available in the application for phase 1 pharmacokinetic Trial ERC-213. Trial-specific audit certificates are also available for the following phase 3 clinical Trials: Trial ERC-210 (seven clinical sites audited); Trial ERC-231 (7 separate sites including 2 sites visited after site closure; Sites 5 and 8); Trial ERC-234 (eight clinical sites audited); Trial ERC-230 (seven clinical

## Clinical Review

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

NDA 208470

INTRAROSA (prasterone) vaginal insert

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sites audited); and Trial ERC-238 (ten clinical sites audited). No corrective action appears to have resulted from these internal audits.

The mandatory Biomedical Research (BIMO) information requested by the Office of Scientific Investigations (OSI) is included in the application for 12-week, primary efficacy clinical Trials ERC-231 and ERC-238, and 12-month, primary safety clinical Trial ERC-230.

On February 4, 2016, DBRUP requested clinical site inspection by OSI, Division of Good Clinical Practice Compliance (DGCPC) for the following clinical sites in the U.S. and Canada:

- Priority 1; Site #15: David Portman, MD, Northern California Research, 3840 Watt Ave., Bldg. E, Sacramento, CA 95821. Site #15 participated in the two primary 12-week safety and efficacy clinical trials (ERC-231 and ERC-238). In addition, Site #15 participated in the primary 52-week safety clinical trial (ERC-230).
- Priority 2; Site #21: Douglas Young, MD, Northern California Research, 3840 Watt Ave., Bldg. E, Sacramento, CA 95821. Site #21 participated in the two primary 12-week safety and efficacy clinical trials (ERC-231 and ERC-238). In addition, Site #21 participated in the primary 52-week safety clinical trial (ERC-230).
- Priority 3; Site #02: Céline Bouchard, MD, Clinique de Recherche en Santé des Femmes, 1000, chemin Ste-Foy, suite 304, Quebec (QC) GIS 2L5, Canada. Site #02 participated in the two primary 12-week safety and efficacy clinical trials (ERC-231 and ERC-238). In addition, Site #02 participated in the primary 52-week safety clinical trial (ERC-230).
- Priority 4; Site #81: Scott E. Eder, MD, Women's Health research CTR., 666 Plainsboro Road, Bldg. 100, Suite D, Plainsboro, NJ 08536, P: 609.799.5010, F: 609.799.0819. Site #81 participated in 12-week Clinical Trial ERC-238.
- Priority 5; Site #60: Samuel N. Lederman, Altus Research, 4671 S. Congress Avenue, Suite 100-B, Lake Worth, FL 33 461, P: 561.641.0404, F: 561.641.0345. Site #60 participated in 12-week Clinical Trial ERC-238.

### **Clinical Reviewer's Comments:**

OSI/DGCPC inspected Site #15 (Dr. David Portman) from March 7-17, 2016, Site #02 (Dr. Celine Bouchard) from April 25-28, 2016, and Site #21 (Dr. Douglas Young) from May 9-13, 2016. The two additional recommended sites (Sites #81 and #60) were not inspected by OSI/DGCPC.

On June 15, 2016, OSI/DGCPC provided an evaluation of clinical inspection for Site #15 (Dr. David Portman). Dr. Portman received a letter indicating "...we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of

human subjects.” A Form FDA 483 was not issued at the conclusion of the inspection. Site #15 received a NAI classification.

On July 13, 2016, OSI/DGCPC provided evaluations of clinical inspections for Site #02 and Site #21. Drs. Bouchard and Young each received letters indicating “...we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.” No Form FDA 483 was issued at either site at the conclusion of the inspections. Sites #02 and #21 received NAI classifications.

### 3.2 Compliance with Good Clinical Practices

Twelve-week clinical Trial ERC-231 and clinical Trial ERC-238, and 52-week clinical Trial ERC-230 (also includes a 40-week open-label extension clinical trial following 12-week Trial ERC-231) all appear to have been conducted in accordance with the ethical principles originating from the Declaration of Helsinki and undertaken in accordance with the principles of Good Clinical Practice (GCP) as set forth in the International Conference on Harmonization Guidelines for GCP (ICH-E6). Written informed consent, approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), was obtained for all women participating in the respective trials.

The Debarment Certification, dated September 18, 2015, available in the application states: “EndoCeutics hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.”

### 3.3 Financial Disclosures

Form FDA 3454 (4/13), dated September 11, 2015 states: “As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).”

A detailed tabular listing is available in the application of investigators who participated in clinical Trials ERC-210, ERC-213, ERC-230, ERC-231, ERC-234, and ERC-238.

**Clinical Reviewer's Comments:**

This reviewer concludes that the applicant has adequately disclosed financial agreements for participating investigators/subinvestigators in the clinical trials conducted to support this NDA application.

The overall integrity of supporting data was confirmed following inspection of selected clinical sites.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

Per the NDA application, prasterone is the international non-proprietary name (INN) for dehydroepiandrosterone (DHEA) which is the active ingredient in EM-760 (code name) for this drug product (CAS Name: Androst-5-en-17-one, 3-hydroxy-, (3 $\beta$ )-). Throughout the drug development program, as well as in the current application, the drug product is referred to as: Intrarosa (conditionally approved proprietary name), prasterone vaginal (b) (4) DHEA vaginal (b) (4) EM-760 (b) (4) intravaginal prasterone, intravaginal DHEA or (b) (4). On June 9, 2015, EndoCeutics requested that the American Medical Association assign "Prasterone" as the United States Adopted Name (USAN) designation for DHEA.

EndoCeutics received a letter from the USAN Council, dated October 28, 2015, stating:

- "I am pleased to inform you that the USAN Council has adopted **prasterone** as a USAN."
- "After January 1, 2016, the USAN information on **prasterone** will be scheduled for posting on the USAN Web site ([www.ama-assn.org/go/usan](http://www.ama-assn.org/go/usan))."
- "At the same time, the USAN information on **prasterone** will be submitted to the United States Pharmacopeial Convention, Inc., for publication in the *USP Directory of USAN and International Drug Names*."

Intrarosa is a drug-device combination product. EndoCeutics was advised on March 15, 2016 that the dosage form term "insert" not (b) (4) is the recommended dosage form term from both the Center for Drug Evaluation and Research (CDER) and the United States Pharmacopeia (USP). The DHEA vaginal insert is a hard fat insert containing 6.5 mg (0.50%) of DHEA and Witepsol (b) (4), a compendial grade of hard fat (USP/NF). The weight of the insert is approximately (b) (4) mg with an approximate volume of 1.3 mL.

The DHEA insert is to be administered vaginally daily, preferably at bedtime, using a vaginal applicator (Class I device; single use; manufactured by (b) (4)

The combination product is presented in a carton box containing 28 vaginal inserts (4 strips of 7 inserts) packed in a smaller carton box plus 28 applicators (Class I device) wrapped (b) (4) The vaginal inserts and applicators are co-packaged.

On December 22, 2015, Chemistry, Manufacturing and Controls (CMC) requested clarification regarding the (b) (4) batches described in Table 2 of 3.2.S.4.4 and inclusion in both DMF (b) (4) and DMF (b) (4). Per the response received on January 5, 2016, "...supporting information for the (b) (4) batches described in the NDA is only contained in DMF (b) (4) for which the Letter of Authorization is in the NDA."

The Agency's December 28, 2015 Filing Communication – No Filing Review Issues Identified letter includes information requests from CMC regarding dissolution issues and environmental assessment. See the December 28, 2015 letter for detailed information.

CMC expressed specific concerns regarding the environmental analysis, section 1.12.14, citing inappropriate categorical exclusion: "The appropriate exclusion(s) must be cited and the relevant data specifically applied to the respective exclusion. Supporting data should include readily available environmental assessment literature and reports addressing both the active ingredient and substances with similar environmental toxicological modes of action, including assessments submitted to other domestic and foreign agencies." "The explicit categorical exclusion(s) and specifically applied supporting data are particularly important given that this product has estrogenic and androgenic activity. As noted in the FDA's recently released draft guidance on hormonally active products, Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity (April 2015), drugs with such activity have the potential to cause developmental or reproductive effects in the aquatic environment at concentrations below 1 ppb."

EndoCeutics' response received February 12, 2016 states:

- "The Environmental Analysis, section 1.12.14, has been updated to refer to the adequate categorical exclusion and to include the assessment submitted to the European Medicine Agency. The total number of (b) (4) per year has been adjusted based on recent market estimates."
- "In accordance with 21 CFR 25.31(b), EndoCeutics claims a categorical exclusion from the requirement to prepare an Environmental Assessment, since the action (New Drug Approval) would increase the use of the active moiety

prasterone (INN), but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). Indeed, the Expected Introduction Concentration Calculation (EIC), calculated per Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications, is of (b) (4) **ppb.**”

- “Moreover, as per 21 CFR 25.21, to EndoCeutics’ knowledge **no extraordinary circumstance exist**, such as indication that the NDA may significantly affect the quality of the environment or adversely affect an endangered wild flora or fauna species, since the intracrine enzymes able to transform inactive DHEA into androgens and/or estrogens are not present in flora, not present in insects, and not present in fish.”
- “The Activated Sludge Test revealed that PRASTERONE has **no anti-microbial activity**. The Agency may wish to consult the environmental risk assessment submitted to the European Medicines Agency by EndoCeutics on December 18, 2015, along with its Marketing Authorization Application, showing the following properties of prasterone and its metabolites:
  - Bioaccumulation and toxicity are very unlikely;
  - No anti-microbial activity;
  - Unlikely to represent a risk to the aquatic environment;
  - Unlikely to represent a risk to microorganisms.”

The Office of Pharmaceutical Quality (OPQ) sent an IR request to EndoCeutics on May 26, 2016 and held a teleconference meeting with EndoCeutics on May 31, 2016 (meeting minutes are dated June 13, 2016) to discuss the following CMC issues:

- Dissolution specification of Q (b) (4) % at 180 minutes for Intrarosa for both release and stability. OPQ recommended incorporation of tighter specifications in internal controls.

(b) (4)

- Manufacturing three (3) new registration batches using established process and controls.

On June 28, 2016, EndoCeutics submitted a revised process validation report for the (b) (4) manufacturing site in (b) (4), and a revised packaging batch record for the (b) (4) manufacturing site. On July 15, 2016, EndoCeutics submitted a quality information amendment providing a copy of “an executed batch record (under Module 3.2.R) for one of three new registration batches as well as the information regarding

yield and reconciliation (under Module 3.2.P.5.4) for the three new registration batches manufactured at (b) (4) site in June/July 2016.”

**Clinical Reviewer’s Comments:**

See the CMC Review for a complete discussion of the aforementioned CMC issues. An inspection of the (b) (4) manufacturing site was conducted (b) (4). An inspection of the (b) (4) manufacturing site was conducted (b) (4).

(b) (4)

The inspection outcome for the (b) (4) manufacturing site is classified VAI.

(b) (4)

“The firm’s management stated that corrective actions will be implemented and committed to send a written response to FDA within 15 business days.”

FDA recommended the facility as “acceptable”. The inspection outcome for the (b) (4) manufacturing site is classified VAI.

**Clinical Reviewer’s Comments:**

See the final OPQ review for a full discussion of the corrections made at the [REDACTED] (b) (4) and [REDACTED] (b) (4) manufacturing sites and the Agency's acceptance.

#### 4.2 Clinical Microbiology

The DHEA drug product does not contain anti-microbial preservatives. The Microbiological reviewer evaluated the microbial burden and limit testing and states that, "Information provided for control of microbiology for the drug product is found adequate per microbiology review # 1. Therefore, NDA 208470 is recommended for approval from a microbiology perspective."

#### 4.3 Preclinical Pharmacology/Toxicology

The applicant performed a series of nonclinical studies in rodents to study the pharmacologic effects of DHEA in the vagina. Per the applicant, rat or mouse adrenals do not secrete DHEA or DHEA-sulfate (DHEA-S); therefore, exogenous administration of DHEA to rodents represents the only source of this steroid.

The most pertinent nonclinical study was performed in ovariectomized (OVX) female rats administered intravaginal DHEA at daily doses of 0.33 mg, 0.66 mg or 1 mg for two weeks. The objective was to induce local vaginal effects without systemic action. The applicant states, "Since DHEA has no intrinsic androgenic or estrogenic activity, the effects observed after DHEA treatment reflect its intracrine conversion by the steroidogenic enzymes into active sex steroids having estrogenic and/or androgenic action."

Per the application, this preclinical study showed that the morphological effects of DHEA on the vaginal mucosa were "observed at the lowest dose used (0.33 mg DHEA insert) and consisted mainly of a typical androgenic effect of epithelial mucification, high compactness of delicate, finely woven lamina propria collagen fibers and moderate increase in muscularis thickness." "No change in morphological features related to cell proliferation was observed at any DHEA dose used (up to 1 mg DHEA/suppository) on the uterus, mammary gland and skin. Immunohistochemistry for androgen, estrogen alpha and progesterone receptors did not reveal any significant systemic effects in the uterus, mammary gland and skin except some suggestion of increased androgen receptor labeling in mammary gland and skin at the highest DHEA dose."

Other short- and long-term nonclinical studies in rodents were performed with DHEA administered orally, subcutaneously, intravenously (IV), by local application on the vaginal mucosa or by percutaneous administration on the dorsal skin in order to avoid

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the first passage of DHEA through the liver, and to evaluate the effect of DHEA on the skin, bone, lipids, adipose tissue, mammary glands, uterus, vagina and tumor growth.

In these pharmacokinetic studies, serum levels of DHEA and of its most important metabolites were measured using validated GC-MS and LC-MS/MS methods, per the application.

In addition to the pharmacologic studies, two repeat-dose toxicity studies were performed in rats and monkeys. The objective of the first toxicity study (LREM-1375) was to assess the toxicity of DHEA, administered orally by gavage to monkeys for 52 weeks. Male and female cynomolgus monkeys received vehicle or 2 or 10 mg DHEA/kg of body weight/day (mg/kg/day). Monkey adrenal glands secrete DHEA and DHEA-S. In control female monkeys, exposure to DHEA ranged from 143 to 171 ng.hr/ml and exposure to DHEA-S ranged from 1.48 to 2.19 µg.hr/ml (based on serum concentrations at Days 1, 184 and 359). Per the application, these exposure results are “approximately 3-7 times that achieved with a 0.50% DHEA vaginal suppository in women (Study report: ERC-213).” Similar concentrations of DHEA and DHEA-S were detected in control male monkeys.

Groups of male and female monkeys also received 10 mg DHEA/kg/day in combination with estradiol or 10 mg DHEA/kg/day in combination with estradiol and the estrogen agonist/antagonist acolbifene in Study LREM-1375. Per the application, DHEA alone and in combination with estradiol and/or acolbifene was well tolerated in monkeys of both sexes. “There were no toxicologically significant changes in clinical, hematological or biochemical parameters and no unexpected macroscopic or histological changes (Study report: LREM-SN-1375).”

The objective of the second study (LREM-1376) was to assess the toxicity of DHEA administered orally by gavage to rats for 26 weeks. Male and female Sprague-Dawley rats received vehicle or 10 or 100 mg DHEA/kg of body weight/day (mg/kg/day). Groups of male and female rats also received 100 mg DHEA/kg/day in combination with estradiol or 100 mg DHEA/kg/day in combination with estradiol and the estrogen agonist/antagonist acolbifene in this study. Per the application, “the rat adrenal glands do not secrete large amounts of DHEA or DHEA-sulfate (DHEA-S) and these steroids were generally not quantifiable in the serum of control rats.” Exposure to DHEA and DHEA-S in rats dosed with 10 or 100 mg DHEA/kg/day was dose-related in both sexes and at least 5 times higher in female rats compared to male rats. “DHEA was well tolerated in male and female rats. Lower serum bilirubin concentrations and higher serum alkaline phosphatase values were noted in both male and female rats dosed with 100 mg DHEA/kg/day. These were attributed to DHEA effects on liver and bone, respectively. Increased urine production, attributed to the high serum concentrations of DHEA-S, was observed in female rats dosed with 10 or 100 mg DHEA/kg/day.” Per the application, “the exposure to DHEA and DHEA-S achieved in rats dosed with 100 mg

DHEA/kg/day is 8-16 times that achieved with a 0.50% DHEA vaginal suppository in women.”

The genotoxicity of DHEA was evaluated in three different assays:

- a bacterial mutagenicity assay (Study 7220-105),
- a human blood lymphocyte assay (Study 7220-106), and
- *in vivo* mouse bone marrow micronucleus assay (Study 7220-107).

Results obtained from these three genotoxicity assays with DHEA are summarized in the corresponding study reports in the application. Per the applicant, “DHEA was considered negative in the three genotoxicity assays.”

No carcinogenicity study was performed with DHEA. A waiver of carcinogenicity studies was granted in IND [REDACTED]<sup>(b) (4)</sup>, Advice/Information Request letter, dated January 24, 2014:

“We have reviewed your submissions, and agree that no carcinogenicity studies are needed for DHEA. *In vivo* carcinogenicity studies can be waived for DHEA vaginal suppository provided you agree to add wording regarding the carcinogenicity of estrogens and androgens in the product labeling. This wording would be similar to product labeling for Premarin vaginal cream and topical androgens such as AndroGel and Fortesta.”

**Clinical Reviewer’s Comments:**

Per the Pharmacology/Toxicology Review, dated August 9, 2016:

“According to the International Agency for research on Cancer (IARC, member of the World Health Organization), postmenopausal estrogen therapy is carcinogenic to humans. Furthermore IARC states: there is sufficient evidence for the carcinogenicity of testosterone in experimental animals and in the absence of adequate data in humans, it is reasonable, for practical purposes, to regard testosterone as if it presented a carcinogenic risk to humans.”

The Pharmacology/Toxicology Reviewer recommends the following labeling text under Section 13 Nonclinical Toxicology, Subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility, Carcinogenesis:

“Long-term studies in animals to evaluate carcinogenic potential have not been conducted with prasterone. Two metabolites of prasterone, testosterone and estradiol, are carcinogenic in animals.”

On August 10, 2016, EndoCeutics received an Advice/Information Request letter stating:

“Section 13.1 of labeling will include the following information on carcinogenicity:

Long-term studies in animals to evaluate carcinogenic potential have not been conducted with prasterone. Two metabolites of prasterone, estradiol and testosterone, are carcinogenic in animals.”

Reproductive and development toxicity studies were not performed in the DHEA development program; per the applicant “prasterone vaginal (b) (4) is intended to be used in postmenopausal women where pregnancy should not occur.”

The local tolerance to intravaginal DHEA administration was evaluated in a single 2-week, nonclinical study in rats following daily administration of a vaginal insert containing 0.33 mg, 0.66 mg or 1 mg of DHEA dissolved in the hard fat base Witepsol (b) (4). Per the application, no local tolerance issues were observed (see Berger, El-Alfy, et al., 2008 in the application).

#### 4.4 Clinical Pharmacology

##### 4.4.1 Mechanism of Action

Per the applicant, “Sex steroids in the human are from two sources, namely of gonadal and adrenal origins. In fact, humans, along with other primates, are unique among animal species in having adrenals that secrete large amounts of the inactive precursor steroid dehydroepiandrosterone (DHEA) which is converted into not only estrogens but also into potent androgens in peripheral target tissues. The local synthesis and action of sex steroids in peripheral target tissues has been called intracrinology. DHEA (prasterone) is a natural (endogenous) compound inactive by itself with no estrogenic, androgenic or other hormonal activity.” “Since DHEA has no intrinsic androgenic or estrogenic activity, the histological changes observed after DHEA treatment reflect its intracrine conversion into active sex steroids having estrogenic and/or androgenic action. The tissue-specific conversion of DHEA in individual cells and tissues permits adjustments according to local anatomical and functional requirements, thus illustrating the new sector of endocrinology called intracrinology.”

Per the applicant, “The local biosynthesis of active sex steroids in most peripheral tissues is supported by the local presence of enzymes required for the conversion of the inactive adrenal precursor dehydroepiandrosterone (DHEA) into estradiol (E2) and androgens which exert their activity locally by means of the estrogen receptors (ERs) present in estrogen- sensitive cells or androgen receptors expressed in androgen-sensitive cells (see Labrie and Labrie 2013 in the application).” “The enzymes

responsible for E2 formation as well as estrogen receptors are expressed mainly in the superficial layer of the stratified epithelium as well as the muscle layer of the vagina.”

In addition, per the applicant:

1. “The classical endocrine organs, like the ovary, synthesize E2 from cholesterol and distribute E2 to all tissues of the body through the general circulation. Intracrinology, on the other hand, permits to each cell in each tissue to synthesize locally from the inactive DHEA active estrogens and androgens which act physiologically intracellularly without a biologically significant release of active steroids into the circulation.” See Module 2.7 Clinical Summaries, 2.7.2 Summary of Clinical Pharmacology Studies in the application, Figure 10A and 10B, page 29 of 32.
2. “The physiological requirement for an efficacious and safe treatment of menopause is to keep the blood concentrations of E2 and testosterone within the postmenopausal range or up to the 95th centile of 9.3 pg/mL and 260 pg/mL for these two sex steroids, respectively.” See Labrie, Cusan et al. 2008a; Labrie, Cusan et al. 2008b; Labrie, Martel et al. 2013 in the application.

**Clinical Reviewer’s Comments:**

This application contains numerous preclinical studies conducted in support of the formation of androgen and estrogen sex steroids peripherally in target tissue. Per the applicant, “We have shown in preclinical studies in rats that DHEA administration causes a complete reversal of the vaginal atrophy observed after oophorectomy. The morphological changes observed in the rat vagina after DHEA treatment reflects its local conversion into active sex steroids having androgenic and estrogenic action through intracrine mechanisms. In addition, in the rat study performed with vaginal DHEA suppositories, we have shown that DHEA exerts beneficial effects limited to the vagina.”

This reviewer has not found published literature that refutes this observation by the applicant in preclinical studies.

4.4.2 Pharmacodynamics

In nonclinical studies, the applicant studied the vaginal effects of intravaginal administration of DHEA at daily doses of 0.33 mg to 1 mg in ovariectomized female rats for two weeks, showing that serum DHEA, DHEA-sulfate (DHEA-S), and androst-5-ene-3 $\beta$ -diol (5-DIOL) were increased over a 4 hour time period, but serum testosterone, estradiol, estrone and dihydrotestosterone (DHT) remained below detectable levels. Per the application, after 2 weeks of daily treatment, the placebo insert produced minimal epithelial thickening limited to the vaginal distal half. Per the trial report, the

morphological effects of DHEA on vaginal mucosa were observed at the 0.33 mg DHEA dose and consisted mainly of a typical androgenic effect of epithelial mucification.

The applicant also studied the possible time-dependent differential effects of 1, 3, and 6 months of percutaneous (30 mg applied twice daily to the dorsal skin area) and intravaginal DHEA treatment of ovariectomized rats on vaginal and uterine histopathology. Per the trial report available in the application, stratification as well as keratinization and mucification of the vaginal epithelium was observed.

The results of 12-week, primary, phase 3 clinical Trials ERC-231 and ERC-238 are reported in Section 6 Review of Efficacy in this review.

#### 4.4.3 Pharmacokinetics

Clinical Trial ERC-213 was a randomized, placebo-controlled, double-blind phase 1 trial conducted at the Hormonal Treatment Clinic of the CHUL Research Center in the province of Quebec, Canada. The trial design compared a placebo vaginal insert and 3 dosage strengths of DHEA vaginal inserts over 7 days:

- 0.50% DHEA insert (6.5 mg of DHEA)
- 1.0% DHEA insert (13 mg of DHEA)
- 1.8% DHEA insert (23.4 mg of DHEA)

The trial population consisted of 40 postmenopausal women with self-assessed vaginal atrophy and vaginal dryness. The primary objective of Trial ERC-213 was to evaluate serum levels of DHEA and its metabolites after intravaginal administration of the trial medication. Bioavailability parameters, as well as safety and tolerance parameters, were evaluated at Day 1 and Day 7. Vaginal maturation index and value and vaginal pH were also evaluated at Day 1 and Day 7 to obtain an indication of the local effect of DHEA. The inserts were vaginally applied daily in the evening, between 22:00 and 23:00, for 1 week.

Pharmacokinetic parameters were calculated on Day 1 and Day 7, including  $AUC_{0-24}$  and  $C_{max}$ , and summarized using means, standard of error mean (SEM), median, minimum and maximum values, and coefficients of variation. Confidence intervals (95% two-tailed) were calculated for  $AUC_{0-24}$ , basal and average serum steroid levels,  $C_{max}$ , vaginal maturation value and vaginal pH. Differences between Day 1 and Day 7 were summarized in the same manner. Statistical analysis of the Day 7 minus Day 1 differences was performed using paired t-tests within each treatment group without adjustment for multiple comparisons.

In ERC-213, serum estradiol and testosterone, as well as DHEA and nine of its other metabolites, were assayed at ten time intervals over 24 h following the 1<sup>st</sup> and 7<sup>th</sup>

vaginal administration of DHEA or placebo vaginal inserts. Per the final trial report, daily intravaginal application of 0.50%, 1.0% and 1.8% DHEA or placebo inserts led to a progressive increase in serum DHEA with AUC<sub>0-24</sub> values on Day 7 of  $56.2 \pm 8.9$  ng.h/ml ( $p < 0.05$ ),  $76.2 \pm 10.3$  ng.h/ml ( $p < 0.01$ ) and  $114.3 \pm 9.96$  ng.h/ml ( $p < 0.01$ ), or  $24.8 \pm 4.8$  ng.h/ml, respectively. There was thus 127%, 207% and 361% increases over placebo at the 0.50%, 1.0% and 1.8% doses of DHEA, respectively.

Per the final trial report, the 24 hour mean ( $\pm$  SEM) serum estradiol concentrations ( $C_{ave}$ ) showed no significant change from baseline with a value of  $2.77 \pm 0.29$  pg/ml for the placebo vaginal insert, and  $4.04 \pm 0.69$  pg/ml (not significant versus baseline) on Day 7 for 0.50% DHEA vaginal insert. Per the applicant, this 0.50% DHEA value is below the mean ( $\pm$  SD) serum estradiol concentration reported as  $4.17 \pm 3.29$  pg/ml in normal intact postmenopausal women, aged 55 to 65 years of age (see Labrie, Cusan et al. 2008a, and Labrie, Cusan et al 2009b in the application). Per the applicant, all of the 24 hour average estradiol concentration for 0.50%, 1.0%, and 1.8% DHEA inserts were below the 95<sup>th</sup> centile of 9.27 pg/mL observed in untreated postmenopausal women.

The AUC<sub>0-24</sub> value of serum testosterone shows no significant change at the 0.50% DHEA dose ( $2.79 \pm 0.30$  ng.h/ml on Day 7) versus  $2.58 \pm 0.33$  ng.h/ml in the placebo group at Day 7. Per the application, these values translate into average serum testosterone levels over the 24h period of  $0.11 \pm 0.01$  for the placebo group, and  $0.12 \pm 0.01$  for the 0.50 DHEA group [N.S., (not significant)],  $0.19 \pm 0.04$  (N.S.) and  $0.25 \pm 0.03$  ( $p < 0.01$ ) ng/ml, respectively, in the placebo and 0.5%, 1.0% and 1.8% DHEA concentration groups

Serum DHT increased from an AUC<sub>0-24</sub> value of  $0.58 \pm 0.07$  ng.h/ml in the placebo group on Day 7 to  $0.93 \pm 0.11$  (N.S.) for 0.50% DHEA vaginal insert on Day 7. These values correspond to average serum DHT levels of  $0.02 \pm 0.01$  for the placebo vaginal insert, and  $0.04 \pm 0.01$  for the 0.50% DHEA vaginal insert, both lower than the normal serum DHT levels of  $0.07 \pm 0.03$  observed in premenopausal women, per the application.

Per the final trial report, at Day 7, vaginal maturation value was significantly increased (increased by 107% [ $p < 0.01$ ] for 0.50% DHEA) and vaginal pH was significantly decreased (decreased from  $6.29 \pm 0.21$  to  $5.75 \pm 0.27$  [ $p < 0.05$ ] for 0.50% DHEA). Per the final trial report, there were no drug-related adverse events or clinically significant changes in laboratory parameters, except one urinary infection at screening only.

**Clinical Reviewer's Comments:**

The range for serum estradiol concentration in the normal postmenopausal women is often cited in textbooks and the published literature as 0-40 pg/mL. In 2006, in a clinical trial of 377 healthy postmenopausal women aged 55 to 65 years, the applicant reports a baseline (untreated) mean  $\pm$  standard deviation

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(SD) serum estradiol concentration of  $4.17 \pm 3.29$  pg/mL (median of 3.44 pg/mL) measured by mass spectrometry-based assay. The 5<sup>th</sup>-95<sup>th</sup> centiles range reported for estradiol was 1.0-9.27. The baseline (untreated) testosterone mean  $\pm$  SD in postmenopausal women was reported, in this same trial, as  $0.14 \pm 0.07$  ng/mL (median of 0.13 ng/mL) with a 5<sup>th</sup>-95<sup>th</sup> centile range reported as 0.06-0.26. Testosterone was also measured by mass spectrometry assay. Other published literatures cite these reported findings.

Per the applicant, in order to avoid the risks of systemic exposure, serum estradiol and testosterone concentrations (both measured by mass spectrometry-based assays) should remain below the 95<sup>th</sup> centiles measured at 9.3 pg/ml and 0.26 ng/ml for estradiol and testosterone in normal postmenopausal women. In Trial ERC-213, the estradiol and testosterone values remained below the above stated values.

See the Clinical Pharmacology Review for a full discussion of the pharmacokinetics findings in Trial ERC-213.

Pharmacokinetic parameters were also collected in other completed DHEA clinical trials:

1. In clinical Trial ERC-210, the serum levels of DHEA and eleven of its metabolites were measured following daily intravaginal administration of inserts containing 0.25% DHEA (3.25 mg of DHEA), 0.50% DHEA (6.5 mg of DHEA) or 1.0% DHEA (13 mg of DHEA) or placebo to 218 postmenopausal women at Screening, Day 1, and Weeks 2, 4, 8, and 12. Results obtained from this trial showed a statistically significant 70.7% increase of DHEA observed with the 1.0% DHEA dose. Per the applicant, the serum DHEA concentration of  $3.14 \pm 0.17$  ng/mL is “well within the normal postmenopausal range (5<sup>th</sup>-95<sup>th</sup> centiles of 0.56 and 3.99 ng/mL), and below the mean value of  $4.47 \pm 2.19$  ng/mL (5<sup>th</sup>-95<sup>th</sup> centiles of 1.53 and 9.14 ng/mL) observed in normal premenopausal women.” In addition, the metabolites of androgens [androsterone glucuronide (ADT-G), androstane-3 $\alpha$ , 17 $\beta$ -diol 3-glucuronide (3 $\alpha$ -diol-3G) and androstane-3 $\alpha$ , 17 $\beta$ -diol 17-glucuronide (3 $\alpha$ -diol-17G) and estrogens (estrone sulfate) were unchanged or minimally changed after intravaginal DHEA administration.
2. Clinical Trial ERC-231 was a 12-week, multicenter (a total of 30 sites; 21 in the US and 9 in Canada), placebo-controlled, double-blind, randomized phase 3 clinical trial which enrolled 255 postmenopausal women (222 completers) to investigate the efficacy of daily intravaginal administration of 0.25% DHEA insert (3.25 mg), 0.50% DHEA insert (6.5 mg) compared with placebo. Postmenopausal women with moderate to severe dyspareunia, self-identified as most bothersome were randomized into treatment groups in a 1:1:1 ratio. Blood samples for pharmacokinetic parameters were collected on Day 1 and Week 12 (or at discontinuation visit, if applicable) for measurement of DHEA and related

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steroids. Per the trial report, serum steroids remained well within reference normal postmenopausal concentrations.

3. Clinical Trial ERC-238 was a 12-week, multicenter (38 sites; 24 in the US and 14 in Canada), phase 3, placebo-controlled, double-blind, prospective trial which randomized a total of 558 postmenopausal women (463 postmenopausal women completed this trial) with moderate to severe dyspareunia self-identified as most bothersome in a 2:1 ratio between 0.50% DHEA insert (6.5 mg DHEA) and placebo. Blood samples for pharmacokinetic parameters were collected on Day 1 and Week 12 (or at discontinuation visit, if applicable) for measurement of DHEA and related steroids. Per the clinical trial report, the 12-week serum estradiol concentration was measured at 22% below the average normal postmenopausal value (3.26 vs 4.17 pg/mL in untreated women); serum estrone sulfate, showed similar serum levels observed in normal postmenopausal women (219 versus 220 pg/mL). Serum ADT-G, the major metabolite of androgens, remained within normal postmenopausal values.
4. In the 52-week open-label safety trial ERC-230, a total of 435 non-hysterectomized women (422 with end-of-trial endometrial biopsy reports) were exposed to daily administration of 0.50% DHEA (6.5 mg DHEA) for 52 weeks (including those women who received 0.50% DHEA in Trial ERC-231 and continued at this dose in Trial ERC-230). Serum samples were obtained at baseline and after 12, 26 and 52 weeks of treatment. Per the clinical trial report, “all serum steroids remained within normal postmenopausal values with no significant differences between different durations of treatment, thus indicating the absence of change over time in the metabolism of DHEA and its derivatives.” “For the most relevant estrogen-related compounds, namely estrone (E1), estradiol (E2), and estrone sulfate (E1-S), the values in the DHEA-treated group at 52 weeks were -3.4%, -9.1% and +1.8%, respectively, compared to the normal postmenopausal values found in untreated women.”
5. Clinical Trial ERC-234, was a 12-week, multicenter (a total of 40 sites; 30 in the US and 10 in Canada), phase 3, placebo-controlled, double-blind, randomized trial designed to analyze the efficacy with respect to moderate to severe vaginal dryness, as self-identified most bothersome symptom, following the intravaginal administration of 0.25% DHEA insert (3.25 mg DHEA), 0.50% DHEA insert (6.5 mg DHEA) compared to placebo utilizing a reduced dosing regimen of daily administration for 2 weeks followed by twice-weekly (on Monday and Thursday) for 10 weeks (383 completers). Blood samples were collected at Day 1 and at Week 12 (or at discontinuation visit, if applicable) for measurement of DHEA and related steroids. All steroid assays were performed with validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays. Per the clinical trial report, for the Safety-S population, which include only the women having steroid measurements at both baseline and Week 12, all steroid values are well within the limits of normal postmenopausal women.

### **Clinical Reviewer’s Comments:**

The following summary of pharmacology and clinical pharmacokinetics is available in the Clinical Pharmacology Review:

“DHEA (prasterone) is an endogenous steroid precursor that is secreted in the adrenal gland and is converted into active androgens and/or estrogens in peripheral tissues. The mechanism of action of prasterone vaginal insert in postmenopausal women with VVA has not been fully established.

The clinical pharmacokinetics of prasterone is summarized as follows:

**Pharmacology and Clinical Pharmacokinetics:**

**Absorption:** The absolute bioavailability of DHEA following administration of prasterone vaginal insert was not measured. Daily administration of 6.5 mg prasterone vaginal insert for 12 weeks increased the trough concentration ( $C_{\text{trough}}$ ) of DHEA from 1.81 ng/mL at baseline to 2.67 ng/mL.

**Distribution and elimination:** Human steroidogenic enzymes such as hydroxysteroid dehydrogenases, 5 $\alpha$ -reductases and aromatases, transform DHEA into androgens and estrogens and their inactive metabolites. Androgen and estrogen metabolites transformed from DHEA are excreted as glucuronide or sulfone metabolite forms from systemic circulation. The treatment with 6.5 mg prasterone vaginal insert once daily for 12 weeks increased the  $C_{\text{trough}}$  of testosterone from 148.1 pg/mL to 178.9 pg/mL and increased estradiol (E2) from 2.76 pg/mL to 3.28 pg/mL in postmenopausal women with VVA.”

**Outstanding Issues:**

Daily application of 6.5 mg prasterone vaginal insert leads to additional systemic exposure to testosterone and estrogens with DHEA. The mean serum  $C_{\text{trough}}$  of DHEA, testosterone, estrone (E1) and E2 increased by 47%, 21%, 24% and 19% from baseline after treatment for 12 weeks in two phase 3 studies. The concentrations of those hormones in most subjects appeared to be within the normal ranges reported in postmenopausal women. However, it is not known whether the additional systemic exposures to androgen and estrogen metabolites following the use of prasterone vaginal insert in postmenopausal women would lead to any safety risk, including cardiovascular disorders and endometrial and breast cancer. It may warrant that a long-term safety monitoring in a larger population be evaluated, particularly for patients with a risk factor of hormone dependent disease.”

The Clinical Pharmacology Reviewer recommends modifications to the applicant’s proposed labeling for Intrarosa to include the pharmacology and pharmacokinetic information stated above.

See the Clinical Pharmacology Review for a full discussion of pharmacology and clinical pharmacokinetics.

The applicant also performed a combined analysis of steroid data using the 12-week data from 5 out of 6 trials in the DHEA development program, excluding the data from the one-week trial ERC-213. The following clinical trials were pooled for the combined analysis of DHEA and related steroids:

- Placebo: ERC-210, ERC-231, ERC-234 and ERC-238
- 0.25% DHEA: ERC-210, ERC-231 and ERC-234
- 0.50% DHEA: ERC-210, ERC-230 (Week 12 data), ERC-231, ERC-234 and ERC-238
- 1.0% DHEA: ERC-210

The mean change from baseline for DHEA and related steroids in the combined analysis for the Safety-S population (those women having steroid measurements performed at baseline and up to 12-weeks post-baseline) are shown on Table 2.

Table 2: Mean Change from Baseline for DHEA and Related Steroids: Safety-S Population

Dehydroepiandrosterone (DHEA) and related steroids parameters and units of measure	Treatment Groups							
	Placebo N = 474				0.50% DHEA (6.5 mg) N = 1196			
	N <sup>1</sup>	BL <sup>2</sup>	PB <sup>3</sup>	Change from BL <sup>4</sup>	N <sup>1</sup>	BL <sup>2</sup>	PB <sup>3</sup>	Change from BL <sup>4</sup>
DHEA (pg/mL)	402	1842.42	1867.46	25.04	980	1965.33	2677.15	711.82
Androst-5-ene-3 $\beta$ , 17 $\beta$ -diol (pg/mL)	407	255.04	254.41	-0.63	1001	273.96	417.12	143.16
Androstenedione (pg/mL)	403	381.06	382.5	1.44	981	394.14	445.1	50.96
Testosterone (pg/mL)	401	145.87	145.94	0.08	991	154.44	179.34	24.9
Dihydrotestosterone (pg/mL)	403	38.98	39.22	0.24	998	42.4	58.05	15.64
Estrone (pg/mL)	405	15.33	16.24	0.91	991	16.27	18.57	2.3
Estradiol (pg/mL)	404	3.63	4.28	0.65	992	4.72	4.63	-0.09
Dehydroepiandrosterone sulfate (ng/mL)	412	628.42	629	0.58	1007	681.78	750.16	68.39
Estrone sulfate (pg/mL)	410	189.20	199.20	10.06	1007	214.75	246.42	31.67
Androsterone glucuronide (ng/mL)	409	13.17	13.04	-0.13	1006	14.39	18.13	3.74
Androstane-3 $\alpha$ , 17 $\beta$ -diol 17-glucuronide (pg/mL)	390	541.19	552.95	11.96	986	602.08	764.41	162.33

Source: Adapted from NDA 208470, 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 1, page 8 of 13.

<sup>1</sup> N= the number of women who had the serum parameter of interest measured at baseline and up to 12 weeks.

<sup>2</sup> BL= baseline mean

<sup>3</sup> PB= post-baseline mean (up to 12 weeks).

<sup>4</sup> Change from BL= the mean change from baseline.

**Clinical Reviewer’s Comments:**

As shown in Table 2 of combined 12-week trials, the DHEA mean change from baseline in the 0.50% DHEA treatment group exceeds that reported in the placebo treatment group (711.82 pg/mL versus 25.04 pg/mL, respectively). The same mean change from baseline is demonstrated for testosterone (24.9 pg/mL for 0.50% DHEA versus 0.08 pg/mL for placebo) and estrone sulfate (31.67 pg/mL for 0.50% DHEA versus 10.06 pg/mL for placebo). This data demonstrates an increase in the serum concentrations of DHEA, testosterone, and estrone sulfate, over that demonstrated in placebo, following administration of 0.50% DHEA vaginal inserts. The reported results for estradiol, however, shows a mean decrease at 12-weeks in the 0.50% DHEA treatment group (-0.09 pg/mL) in the Safety-S population.

See the Clinical Pharmacology Review for a full discussion of the pharmacokinetics findings in the DHEA development program.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 3: Listing of Clinical Trials in the DHEA Development Program

<b>Trial Identifier Type of Trial</b>	<b>Objective(s) of the Trial</b>	<b>Trial Design and Type of Control</b>	<b>Test Product Dosage Regimen: Route of Administration</b>	<b>Number of Enrolled Postmenopausal Women with Vaginal Atrophy</b>	<b>Duration of Treatment</b>
ERC-213 PK	Evaluation of the systemic bioavailability of DHEA and its metabolites and the PK of four different vaginal inserts	Randomized Double-blind Placebo- controlled	Placebo vaginal insert once daily  0.50% DHEA, 1.0% DHEA, 1.8% DHEA vaginal insert once daily	40	7 Days
ERC-210 Efficacy/Safety	To determine the dose-response of vaginal mucosa parameters to the local action of DHEA	Randomized Double-blind Placebo- controlled	Placebo vaginal insert once daily  0.25% DHEA, 0.50% DHEA, 1.0% DHEA vaginal insert	218	12 Weeks

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			once daily		
ERC-231 Efficacy/Safety  Primary	To confirm the efficacy of DHEA vaginal insert on moderate to severe dyspareunia as the most bothersome (MBS) symptom	Randomized Double-blind Placebo-controlled	Placebo vaginal insert once daily  0.25% DHEA, 0.50% DHEA vaginal insert once daily	255	12 Weeks
ERC-238 Efficacy/Safety  Primary	To confirm the efficacy of DHEA vaginal insert on moderate to severe dyspareunia as the most bothersome (MBS) symptom	Randomized Double-blind Placebo-controlled	Placebo vaginal insert once daily  0.50% DHEA vaginal insert once daily	558	12 Weeks
ERC-234 Efficacy/Safety	To confirm the efficacy of DHEA vaginal insert on moderate to severe vaginal dryness as the most bothersome (MBS) symptom	Randomized Double-blind Placebo-controlled	Placebo vaginal insert once daily for 2 weeks, then twice weekly for 10 weeks  0.25% DHEA, 0.50% DHEA vaginal insert once daily for 2 weeks, then twice weekly for 10 weeks	450	12 Weeks
ERC-230 Safety  Primary	To assess the long-term safety of DHEA vaginal insert	Open-label	0.50% DHEA vaginal insert once daily	530	52 Weeks

Source: Adapted from NDA 208470, Subsection 2.7.6 Synopses of Individual Studies, Table 1, pages 2 through 5 of 45.

## 5.2 Review Strategy

The available clinical data in primary 12-week, phase 3, safety and efficacy clinical Trials ERC-231 and ERC-238 provide the basis for consideration regarding the efficacy of 0.50% DHEA vaginal insert for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Efficacy information from clinical Trials ERC-231 and ERC-238 were reviewed separately. Trials ERC-210 and ERC-234 are not considered supportive of efficacy for the treatment of moderate to severe dyspareunia. Trial ERC-210 did not provide data for all of the recommended co-primary endpoints for a VVA indication. Trial ERC-234 was conducted in support of moderate to severe vaginal dryness as the most-bothersome VVA symptom.

The available clinical data in phase 1 Trial ERC-213; 12-week, placebo-controlled phase 3 clinical Trials ERC-210, ERC-231, ERC-234; and ERC-238 and 52-week, open-label phase 3 clinical Trial ERC-230 provide safety data for consideration for the 0.50% DHEA vaginal insert. Safety data from these trials were pooled in integrated analyses (See Section 7 Review of Safety).

### 5.3 Discussion of Individual Studies/Clinical Trials

#### 5.3.1 Trial ERC-231:

##### 5.3.1.1 Objectives

**Primary:**

The primary objective of Trial ERC-231 was to assess the local activity of DHEA vaginal insert by measuring changes in the percent of superficial and parabasal cells, vaginal pH, and pain at sexual activity self-identified by trial participants as her most-bothersome symptom as co-primary endpoints.

**Secondary:**

The secondary objectives of Trial ERC-231 include:

- Self-assessment of vaginal dryness and vaginal and/or vulvar irritation/itching
- Sexual dysfunction and quality of life analyzed by the Menopause Specific Quality of Life (MENQOL), Female Sexual Function Index (FSFI), McCoy Female Sexual Questionnaire (MFSQ) and Female Sexual Distress scale (FSDS-R) questionnaires as well by the Daily Diary of Sexual Activity.
- Examining the tolerance to local administration of DHEA vaginal insert. In addition, the site investigator reported observations at the time of vaginal examination at screening, Day 1, and Weeks 6 and 12 (see Subsection 7.4.3.2.2 in Trial ERC-231 trial report in the sNDA application for a full description of the investigator observations).

##### 5.3.1.2 Enrollment Criteria

**Inclusion Criteria:**

Postmenopausal women were eligible for inclusion if they met the following inclusion criteria:

1. Postmenopausal women, between 40 and 75 years of age, (non-hysterectomized and willing to have an endometrial biopsy or hysterectomized) must satisfy either a or b or c:
  - a. No menses for at least one year, or

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- b. FSH levels > 40 IU/mL (within 60 days prior to day 1) in women with no menses > 6 months but < 12 months, or hysterectomized women who were premenopausal at the time of hysterectomy, or
  - c. Six weeks (of Screening visit) or more following bilateral oophorectomy.
2. Have self-identified at baseline pain at sexual activity as moderate to severe and the most bothersome vaginal symptom.
3. Have  $\leq 5\%$  of superficial cells on vaginal smear at baseline.
4. Have a vaginal pH above 5 at baseline.
5. Have a normal mammogram within 9 months of trial start, and normal breast examination.
6. Have a normal Pap smear (which includes inflammatory changes) within the last 12 months. For hysterectomized women, the Pap smear will consist of at least one slide of the vaginal vault.
7. Be willing to participate in the trial and sign an informed consent form.
8. Absence of former or present narcotic addiction or alcoholism.
9. Body weight within the range of 18.5 and 35 of ideal body weight according to body mass index (BMI).
10. No hepatic or renal impairment or condition known to affect drug or steroid metabolism.
11. Normal baseline hematology, clinical chemistry, and urinalysis.

### **Exclusion Criteria:**

Postmenopausal women were eligible for inclusion if they met inclusion criteria did not have the following exclusion criteria:

1. Undiagnosed abnormal genital bleeding.
2. Previous diagnosis of cancer, except skin cancer (non-melanoma).
3. Active or history of thromboembolic disease.
4. Significant metabolic or endocrine disease.
5. Clinically significant gastrointestinal, liver or gallbladder disease.
6. Recurrent migraine headache not controlled by conventional therapy.
7. Diabetes mellitus not controlled by conventional therapy.
8. Significant complication on previous hormonal therapy.
9. Use of estrogen alone injectable drug therapy or progestin implant within 6 months prior to study entry (screening visit).
10. Use of estrogen pellet or progestin injectable drug within 6 months prior to study entry (screening visit).
11. Oral estrogen, progestin or DHEA exposure or intrauterine progestin therapy in the 8 weeks prior to baseline assessments (screening visit).
12. Vaginal hormonal products (rings, creams, gels or tablets) or transdermal estrogen alone or estrogen/progestin products in the 8 weeks prior to baseline assessment (screening visit).

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Women can washout as follows, but the questionnaire on vaginal atrophy must be answered after the required washout period:

- At least an eight-week washout period for prior oral estrogen, DHEA and/or progestin therapy.
  - At least an eight-week washout period for prior transdermal hormone therapy.
  - At least an eight-week washout period for locally delivered hormone replacement therapy for vaginal dryness (rings, creams, gels or tablets).
  - At least 6 months for prior estrogen pellet therapy or progestin injectable drug therapy.
  - Eight weeks or longer for prior intrauterine progestin therapy.
  - Six months or longer for prior progestin implants and estrogen alone injectable drug therapy.
13. Cardiac failure or manifest coronary heart disease.
  14. Hypertension equal to or above 140/90 mm Hg or not controlled by standard therapy.
  15. Confirmed clinically significant depression or confirmed history of severe psychiatric disturbance.
  16. The administration of any investigational drug within 30 days of screening visit.
  17. Previous treatment with androgens or anabolic steroids within 3 months prior to screening visit.
  18. Clinically relevant abnormal serum biochemistry, urinalysis or hematology.
  19. Baseline cervical cytology showing low-grade squamous intraepithelial lesion (LGISIL) or worse.
  20. Smoking: more than 10 cigarettes a day.
  21. Drugs that interfere with the metabolism of estrogen (e.g., ketoconazole), sex steroid formation or active inhibitors.
  22. SERMs or drug interacting with steroid receptors.
  23. Known presence of uterine fibroma or palpable at gynecological exam.
  24. Palpable fibroids or Grade 2 uterine prolapse by gynecologic exam.
  25. Coagulation disorders or on anticoagulant drug therapy.
  26. Endometrial hyperplasia or cancer at biopsy performed at screening.

### ***Allowed and Excluded Medications:***

Medications necessary for the woman's well-being were allowed during the trial with the exception (see Appendix 19.2 of the trial protocol) of:

- Estrogen hormone therapy
- Progestogen medication
- Natural oral "estrogenic" products
- Vaginal cream or gel
- Vaginal lubricant
- Vaginal douching

### 5.3.1.3 Trial Design and Conduct

Clinical Trial ERC-231 entitled: “DHEA Against Vaginal Atrophy (Placebo-Controlled, Double-Blind and Randomized Phase III Study of 3-Month Intravaginal DHEA)” was a multicenter (total of 33 clinical sites; 24 in the US and 9 in Canada), randomized, double-blind, placebo-controlled trial conducted between November 30, 2010 (first woman enrolled) and July 29, 2011 (last woman completed the trial) conducted to support the indication “Treatment of moderate to severe dyspareunia (pain at sexual activity), a symptom of vulvovaginal atrophy, due to menopause.”

Two hundred and fifty-five (255) postmenopausal women were randomized in a 1:1:1 ratio to receive:

- 0.25% DHEA vaginal insert (87 women),
- 0.50% DHEA vaginal insert (87 women), or
- Placebo vaginal insert (82 women).

Trial ERC-231 was divided into two phases, a screening period up to 6 weeks and a treatment period of 12 weeks. Trial participants were instructed to apply one intravaginal insert daily before bedtime (usually in the evening) during the 12-week trial.

(b) (4) distributed trial medication to the US clinical sites (medication was sent to (b) (4) from EndoCeutics’ Drug Control Unit) while EndoCeutics’ Drug Control Unit distributed trial medication to the Canadian clinical sites.

The trial population consisted of postmenopausal women (non-hysterectomized or hysterectomized), between 40 and 75 years of age, having  $\leq 5\%$  of superficial cells on a lateral wall vaginal smear, a vaginal pH above 5, and who self-identified moderate to severe vaginal pain associated with sexual activity (dyspareunia) as their MBS of VVA.

Efficacy information on vulvar and vaginal atrophy symptoms and signs was collected as follows:

- Vaginal cell maturation:  
Vaginal smears were obtained from the middle or second third of the side wall of the vagina and sent to a central laboratory. All samples were examined by an experienced cytopathologist blinded to the treatment regimens. A 100-cell count was performed (parabasal (including basal), intermediate, and superficial). The mean change from baseline to Weeks 6 and 12 (percentages of parabasal and superficial cells) was evaluated.
- Vaginal pH:

A pH strip was applied to the lateral wall of the vagina. The mean change in vaginal pH from baseline to Weeks 6 and 12 was evaluated.

- Self-assessment of vaginal symptoms:

The self-assessment of symptoms was evaluated by a questionnaire (English and French) at screening, baseline, and Weeks 6 and 12. The severity of symptoms of dyspareunia, vaginal dryness and vaginal irritation/itching was recorded as none, mild, moderate or severe, and was analyzed using score values of 0, 1, 2 or 3, respectively. The symptoms questionnaire is as follows:

- **Vaginal dryness:** No lubrication or secretions noted, or after wiping.
  - **None:** No sensation of dryness.
  - **Mild:** Feels dryness episodically, dryness does not interfere with activities of daily living.
  - **Moderate:** Sensation of dryness most of the time, dryness does not interfere with activities of daily living.
  - **Severe:** Sensation of dryness all the time, dryness interferes with activities of daily living.
- **Irritation/itching (vulvar and/or vaginal):** Sand-paper type feeling, and/or itching, uncomfortable with clothing or undergarments touching sexual organ.
  - **None:** No sensation of irritation/itching.
  - **Mild:** Feels irritation/itching episodically, does not interfere with activities of daily living.
  - **Moderate:** Sensation of irritation/itching most of the time, does not interfere with activities of daily living.
  - **Severe:** Sensation of irritation/itching all the time, interferes with activities of daily living.
- **Vaginal pain associated with sexual activity: Pain at penetration during intercourse or after sexual activity.**
  - **Not sexually active.**
  - **None:** Comfortable sexual activity, no pain during sexual activity.
  - **Mild:** Episodically occurs, not all the time, occasionally causes stop of sexual activity.
  - **Moderate:** Most of the time, minimal satisfaction from sexual activity, often must stop sexual activity.
  - **Severe:** Occurs all the time, cannot enjoy sexual activity, often must stop sexual activity. May be abstinent because of pain.
- Among the 3 symptoms, which one is the most bothersome to you?
  - Vaginal dryness.
  - Irritation/itching (vulvar and/or vaginal).
  - Vaginal pain associated with sexual activity.

#### 5.3.1.4 Assessment of Efficacy

##### **Primary Efficacy Variable:**

The original proposed primary efficacy endpoint was the mean change from baseline to weeks 6 and 12 in the moderate to severe symptom that was identified by the woman as being the most bothersome to her. Change from baseline to Weeks 6 and 12 in vaginal pH and vaginal superficial and parabasal cells were originally considered as secondary efficacy variables.

After input from the Agency, the final ERC-231 protocol reflected the co-primary endpoints of:

- Compared to placebo, a statistically significant improvement from baseline to week 12 in moderate to severe dyspareunia, self-identified by the woman as her most bothersome moderate to severe vaginal atrophy symptom at baseline (Day 1), **and**
- Compared to placebo, a statistically significant decrease in vaginal pH from baseline to week 12, **and**
- Compared to placebo, a statistically significant increase compared to placebo in percentage of superficial cells and a statistically significant decrease in percentage of parabasal cells on a smear from the vaginal wall.

#### 5.3.1.5 Assessment of Safety

Throughout the trial, vital signs, physical examination, gynecological examination including Papanicolaou (Pap) smear, mammogram (unless performed within 9 months prior to Day 1 with written documentation), and clinical laboratory tests (hematology including a complete blood count; coagulation parameters including prothrombin time, activated partial thromboplastin time; blood chemistry including glucose, electrolytes, blood urea nitrogen (BUN), creatinine, aspartate transaminase (AST), alanine transaminase (ACT), alkaline phosphate, total bilirubin, total serum protein, lactate dehydrogenase (LDH); lipid profile including total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), lipoprotein B; and urinalysis) were performed. Adverse events (AEs) were recorded for safety evaluation according to acceptable criteria and then coded into system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1.

For non-hysterectomized women, an endometrial biopsy was obtained at screening and at end-of-trial.

Endometrial assessment was to be conducted according to the Agency's 2003 draft clinical evaluation Guidance for Industry as follows:

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- Endometrial biopsies, and not uterine ultrasounds, were to be used for the evaluation of endometrial hyperplasia.
- The endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the trial, and at the end-of-trial was to be processed in the same manner by a central laboratory.
- A single pathologist reader (any one of the three blinded pathologists) was to initially assess the slides from the endometrial biopsies obtained at screening or because of participant bleeding while on trial drug (safety reading).
- Three independent expert pathologists, blinded to treatment group and to each other's readings, were to determine the diagnosis for endometrial biopsy slides during the conduct of the trial for women who have an end-of-trial biopsy or have biopsy because of participant bleeding while on trial drug (safety reading).
- Curricula vitae for participating pathologists were to be provided to the Agency in order to document expertise in gynecologic pathology.
- Participating trial pathologists were to be selected from different institutions with independent fiduciary and organizational reporting
  - Pathologists were not to meet to review slides before or during the conduct of the clinical trial.
- Standardized criteria as provided in Blaustein's pathology text (Pathology of the Female Genital Tract) were to be used for the diagnosis of endometrial hyperplasia.
- Endometrial polyps were to be fully characterized as to the glandular proliferation and atypia.
- Women found to have endometrial hyperplasia or adenocarcinoma of the endometrium were to be excluded from further drug treatment (if discovered during trial drug treatment period) and referred for *standard of care* clinical management and followed to complete resolution, and the report of any medical or surgical procedures and the resultant pathology be provided to the FDA.
- If hyperplasia is diagnosed by the single safety reader for a woman who has bled while on trial drug, the slides become part of the slide set given to the two other pathologists for reading.
- For the evaluation, the concurrence of two of the three pathologists will be accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis (i.e., atypical hyperplasia > complex hyperplasia > simple hyperplasia > benign endometrium) would be used as the final diagnosis.
- The slide set will be distributed to each of the three pathologists for the end-of-trial pathology review incorporate control slides representing a randomly selected 10 percent of the screening normal slides and all slides from women excluded for the diagnosis of hyperplasia or cancer to insure quality control.
- All slides and reports will be maintained by the sponsor and be made available upon the Agency's request.

- Any endometrial polyp(s) detected during the course of the trial were removed in its entirety and submitted for pathological analysis.

Histologic description was according to the Agency's 2003 draft Guidance for Industry (See Subsection 7.3.5.1).

**Clinical Reviewer's Comments:**

The above-noted protocol evaluation procedures for endometrial biopsies and histologic characteristics assessments comply with the Agency's 2003 draft clinical evaluation Guidance for Industry. However, the protocol-specified endometrial biopsies evaluation procedures were not followed in the conduct of Trial ERC-231. See Subsection 7.3.5.1 for discussion of the endometrial assessment.

5.3.1.6 Statistical Methodology

Unless otherwise stated, statistical analyses were performed at the two-sided significance (alpha) level of 0.025. The co-primary objectives analyzed are the changes in % of parabasal and superficial cells, vaginal pH and severity score of pain at sexual activity (dyspareunia). Efficacy analyses were performed primarily on the Intent-to-Treat (ITT) population (all women who received at least one dose of trial drug with a baseline (Day 1) evaluation meeting the entry criteria), with additional secondary analysis done on the Per-Protocol (PP) population (a subset of the ITT population that completed the 12-week trial with no major protocol violations that could compromise the efficacy data). The primary analysis was performed using analysis of covariance (ANCOVA), with the treatment group as the main factor and the baseline value as the covariate. The ITT population consists of a total of 237 women: 77, 79 and 81 per treatment group for placebo vaginal insert, 0.25% and 0.50% DHEA vaginal inserts, respectively.

Safety analyses were performed on the safety population consisting of women who received any amount of trial medication and have any safety information available. Demographics and baseline characteristics were summarized and presented by treatment groups. The change from baseline (Day 1) to post-baseline assessments as well as differences from placebo was used for analysis. Analyses of differences between the placebo vaginal insert and 0.25% and 0.50% DHEA vaginal inserts were performed using an analysis of covariance with baseline as the covariate. All available safety data were used for analysis. For adverse events and laboratory data, standard methods of analysis were used. The safety population consists of a total of 253 women: 80, 86 and 87 per treatment group for placebo vaginal insert, 0.25% and 0.50% DHEA vaginal inserts, respectively.

Per the trial report for Trial ERC-231 in the application, following the blinded review of steroid data for DHEA and its metabolites, the applicant developed a strong suspicion that some women had taken exogenous estrogens (an excluded concomitant medication) as indicated by finding marked elevations of serum estrogens (estradiol, estrone, estrone-sulfate) without parallel changes in serum DHEA as well as ADT-G, the main androgen metabolite. Prior to trial unblinding, the applicant established criteria to identify women for whom there was suspicion of having taken exogenous estrogens:

1. Women having  $\geq 2$  fold differences in serum estradiol (E2) levels (between Baseline and Week 12) where E2 levels are  $\geq 10.0$  pg/mL (for an upper 95% tolerance limit and 95% certainty, the 95th centile of normal postmenopausal women being 9.3 pg/mL) accompanied by parallel changes in estrone-sulfate (E1-S) levels, with  $\leq$  one SD change (1.18 ng/mL) of serum DHEA [if accompanied in the same direction by at least a 0.5 SD change in serum ADT-G (0.5 SD = 6.23 ng/mL)] (see Labrie, Cusan et al. 2008 in the application).
2. Women having serum E2 levels  $\geq 12.4$  pg/mL at baseline (for an upper 99% tolerance limit with 95% confidence) with serum DHEA  $\leq 3.13$  ng/mL (mean  $\pm$  one SD) (see Labrie, Cusan et al. 2008 in the application).

Per the applicant, all women meeting one of the above criteria were excluded from the PP analyses as this was considered a major protocol violation. The applicant also performed supportive analyses of the ITT and safety population excluding the women suspected of concomitant use of estrogens “in order to examine unbiased results.” The analyses sets excluding these women are listed in Table 4 and are identified as “corrected ITT population” (cITT) and “corrected safety population” (cSafety). In addition, for analysis of steroid data in Trial ERC-231, the applicant identified additional subpopulations by adding the suffix “-S” (for example ITT-S, cITT-S, Safety-S and cSafety-S) for those women having steroid measurements at both baseline and Week-12.

Table 4: List of Women Suspected by the Applicant of Concomitant Use of Estrogens and Inclusion/Exclusion of their Data in the Applicant’s Various Analysis Sets in Trial ERC-231

Randomization Number	Group	ITT Analysis Set	Safety Analysis Set	PP analysis Set	Corrected ITT Analysis Set	Corrected Safety Analysis Set
231-17-005	Placebo	Yes	Yes	No	No	No
231-18-013	Placebo	Yes	Yes	No	No	No
231-30-017	0.25% DHEA	Yes	Yes	No	No	No
231-30-024 <sup>1</sup>	0.25% DHEA	Yes	Yes	No	No	No
231-05-040	0.50% DHEA	No	Yes	No	No	No
231-15-005	0.50%	Yes	Yes	No	No	No

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Source: Adapted NDA 208470, Trial ERC-231 Clinical Trial Report, Table 7-1, page 54 of 591.

Abbreviations: ITT = Intent-to-Treat; PP = Per Protocol

<sup>1</sup>Not included in the ITT-S and Safety-S analysis sets for steroid data.

**Clinical Reviewer’s Comments:**

Per the application, following a blinded review of steroid data for DHEA and its metabolites, the applicant established criteria to identify women suspected of having taken exogenous estrogen which was identified as an excluded concomitant medication per protocol. See the Note to File, dated September 11, 2012, for Trial ERC-231 in the application. Following the unblinding of data, any women meeting one of the two “established criteria” described above were excluded from one or more of Trial ERC-231 data analyses sets.

However, the cITT, cSafety, ITT-S, cITT-S, Safety-S, and cSafety-S analyses were not pre-specified analyses in the original Trial ERC-231 protocol dated October 25, 2010, the amended Trial ERC-231 protocol dated March 7, 2011, or the Trial ERC-231 Statistical Analysis Plan dated September 11, 2011.

Therefore, this reviewer and the Statistical Reviewer did not consider the cITT population in determining the effectiveness of 0.50% DHEA vaginal insert to relieve moderate to severe dyspareunia due to menopause. All women in Trial ERC-231 are included in the safety analyses.

See the Medical Officer’s Review of Trial ERC-231, dated June 26, 2009 and October 27, 2009, and review of amendments dated January 31, 2011 and April 12, 2011, for a full description of the trial protocol.

5.3.1.7 Results

**Demographics:**

The demographics and baseline characteristics of the safety cohort in Trial ERC-231 are shown in Table 5.

Table 5: Demographics of Trial ERC-231: Safety Population

Parameters	Placebo N = 80	0.25% DHEA N = 86	0.50% DHEA N = 87	Total N = 253
<b>Age (Years)</b>				
Mean	58.81	50.37	57.51	58.55
Median	59	60	57	59
Range (Min – Max)	45 - 73	40 - 75	41 - 69	40 - 75
<b>Anthropometric measurements (mean)</b>				
Body Mass Index (kg/m <sup>2</sup> )	25.82	26.34	26.07	26.08
Height (cm)	161.14	160.63	160.51	160.75
Weight (kg)	67.15	68.12	67.18	67.49

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<b>Race (Number of Women, %)</b>				
Caucasian	69 (86%)	81 (94%)	83 (95%)	233 (92%)
African American	9 (11%)	4 (5%)	3 (3%)	16 (6%)
Asian	1 (1%)	0	1 (1%)	2 (1%)
Other	1 (1%)	1 (1%)	0	2 (1%)
<b>Ethnicity (Number of Women, %)</b>				
Not Hispanic or Latino	79 (99%)	81 (94%)	78 (90%)	238 (94%)
Hispanic or Latino	1 (1%)	5 (6%)	9 (10%)	15 (6%)

Source: Adapted from NDA 208470, Trial ERC-231 Clinical Trial Report, Table 8-3, page 70 of 591.

**Clinical Reviewer’s Comments:**

The demographic and baseline characteristics of the women enrolled in Trial ERC-231 in the different treatment groups are similar. The trial population consisted mainly of Caucasian and non-Hispanic postmenopausal women.

***Disposition of Participating Women:***

The overall disposition of women in Trial ERC-231 is summarized in Table 6. A total of 255 women were enrolled in Trial ERC-231, 222 women completed the trial, and 33 (12.9%) women discontinued prematurely.

Table 6: Disposition of Women in Trial ERC-231: ITT Population

	Placebo N = 81	DHEA 0.25% N = 87	DHEA 0.50% N = 87	Total N = 255
Number Completed Trial	72 (88.8%)	74 (85.0%)	76 (87.3%)	222 (87.0%)
Total Discontinued	9 (11.1%)	13 (14.9%)	11 (12.6%)	33 (12.9%)
Reason Discontinued				
- Adverse Event	1 (1.2%)	4 (4.5%)	2 (2.2%)	7 (2.7%)
- Non-Compliance	1 (1.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
- Withdrew Consent	4 (4.9%)	0 (0.0%)	2 (2.2%)	6 (2.3%)
- Investigator’s Decision	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.3%)
- Other	3 (3.7%)	8 (9.1%)	7 (8.0%)	18 (7.0%)

Source: Adapted from NDA 208470, Trial ERC-231 Clinical Trial Report, Figure 8-1, page 66 of 591.

Definition: ITT = Intent-to-Treat

The most common reason for premature discontinuation overall in Trial ERC-231 was “Other”. Trial participants completed the self-assessment questionnaire and had a vaginal smear and vaginal pH performed on Day 1 prior to drug administration. If the trial participant no longer met the inclusion criteria she was discontinued from the trial. Of these women (identifying “Other” as the reason for premature discontinuation, three (3) women were discontinued from the placebo treatment group because they did not meet inclusion criterion number 4 ( $\leq 5\%$  of superficial cells on a vaginal smear). Eight (8) of the women discontinuing for “Other” reasons, were discontinued from the 0.25% DHEA treatment group. One (1) woman had a uterine polyp at screening; 1 woman reported lack of efficacy; 1 woman did not meet inclusion criterion number 5 (vaginal pH

greater than 5.0); and 5 women did not meet inclusion criterion number 4 (defined above).

Seven (7) of the women discontinuing for “Other” reasons, were discontinued from the 0.50% DHEA treatment group. One (1) woman did not meet inclusion criterion number 2 (moderate to severe dyspareunia as her MBS); 4 women did not meet inclusion criterion number 3 (defined above); 1 woman did not meet inclusion criterion number 5 (defined above), and 1 woman reported lack of efficacy.

**Clinical Reviewer’s Comments:**

The percentage of women who completed the trial was similar across treatment groups (85% - 89%). Likewise, the percentage of women discontinuing the trial was similar across treatment groups (11% - 14%). The slightly higher discontinuation rate for the 0.25% DHEA treatment group over the 0.50% DHEA treatment group is not fully explained.

***Primary Efficacy Analyses:***

Two hundred fifty-five (255) healthy postmenopausal women, with and without an intact uterus, 40 to 75 years of age [mean age 58.84 ± 0.38 years (mean ± standard error of the mean)], were enrolled in Trial ERC-231 (81, 87 and 87 per treatment group for placebo, 0.25% DHEA and 0.50% DHEA, respectively). Two hundred thirty-seven (237) women were included in the ITT population, which consists of all women who received at least one dose of trial drug (based on diary) with a baseline (Day 1) evaluation meeting the entry criteria (77, 79 and 81 per treatment group for placebo, 0.25% DHEA and 0.50% DHEA, respectively). Two hundred and four (204) women were included in the PP population which is a subset of the ITT population that completed the trial with no major protocol violations considered to compromise efficacy data. The PP population is a supportive population for efficacy data analysis.

A woman with a uterus, who completed 12-week Trial ERC-231, was considered for entrance into long-term safety Trial ERC-230. See Section 7 Summary of Safety.

Two hundred fifty-three (253) women are included in the safety population which includes all women who received any amount of trial medication (based on diary), and who had any safety data available (80, 86 and 87 per treatment group for placebo, 0.25% DHEA and 0.50% DHEA, respectively). See Section 7 Summary of Safety.

See Section 5.3.1.4 for a discussion of the co-primary primary endpoints in Trial ERC-231.

The primary efficacy results obtained in the ITT population for Trial ERC-231 are shown in Table 7. These reported primary efficacy analyses are based on women who met all three of the baseline inclusion criteria: ≤ 5% superficial cells on a vaginal smear, a

vaginal pH greater than 5.0, and dyspareunia self-identified as moderate to severe and most bothersome.

Table 7: Applicant-Reported Primary Efficacy Summary in Trial ERC-231: ITT Population

	Placebo N = 77	0.025% DHEA N = 79	0.50% DHEA N = 81
<b>%Superficial Cells</b>			
- Baseline Mean (SD)	0.73 (1.33)	0.68 (1.18)	0.68 (1.10)
- Week 12 Mean (SD)	1.64 (2.88)	5.43 (5.08)	6.30 (5.33)
- Mean Change from Baseline (SD)	0.91 (2.69)	4.75 (5.15)	5.62 (5.49)
- P-value <sup>a</sup>	-	<0.0001	<0.0001
- P-value <sup>b</sup>	-	<0.0001	<0.0001
<b>% Parabasal Cells</b>			
- Baseline Mean (SD)	68.48 (38.66)	65.72 (40.55)	65.05 (41.69)
- Week 12 Mean (SD)	66.86 (38.32)	28.43 (32.16)	17.65 (25.87)
- Mean Change from Baseline (SD)	-1.62 (28.22)	-37.29 (37.00)	-47.40 (42.50)
- P-value <sup>a</sup>	-	<0.0001	<0.0001
- P-value <sup>b</sup>	-	<0.0001	<0.0001
<b>Vaginal pH</b>			
- Baseline Mean (SD)	6.51 (0.59)	6.48 (0.58)	6.47 (0.64)
- Week 12 Mean (SD)	6.31 (0.81)	5.70 (0.96)	5.43 (0.94)
- Mean Change from Baseline (SD)	-0.21 (0.69)	-0.77 (0.90)	01.04 (1.00)
- P-value <sup>a</sup>	-	<0.0001	<0.0001
- P-value <sup>b</sup>	-	<0.0001	<0.0001
<b>Dyspareunia</b>			
- Baseline Mean (SD)	2.58 (0.50)	2.56 (0.50)	2.63 (0.49)
- Week 12 Mean (SD)	1.71 (1.00)	1.54 (1.04)	1.36 (1.10)
- Mean Change from Baseline (SD)	-0.87 (0.95)	-1.01 (1.02)	-1.27 (0.99)
- P-value <sup>a</sup>	-	<0.0001	<0.0001
- P-value <sup>b</sup>	-	0.3423	0.0132

Source: Adapted from NDA 208470, Trial ERC-231 Clinical Trial Report; Table 9-6 on page 84 of 591, Table 9-2 on page 76 of 591, Table 9-8 on page 88 of 591, and Table 9-12 on page 95 of 591.

Abbreviations: DHEA = dehydroepiandrosterone, SD = Standard Deviation

<sup>a</sup>P-value from a paired t-test (p-value versus baseline).

<sup>b</sup>ANCOVA test with treatment group as the main factor and baseline value as the covariate (p-value versus placebo).

**Clinical Reviewer's Comments:**

From the data shown in Table 7, the 0.50% DHEA dose demonstrated significantly greater improvement over placebo at week 12 in the:

- Increase in the percentage of superficial epithelial cells (p<0.0001)
- Decrease in the percentage of parabasal epithelial cells (p<0.0001)
- Decrease in vaginal pH (p<0.0001)
- Decrease in the severity of the MBS of dyspareunia (p=0.0132)

The 0.25% DHEA dose demonstrated significantly greater improvement over placebo at week 12 in the:

- Increase in the percentage of superficial epithelial cells ( $p < 0.0001$ )
- Decrease in the percentage of parabasal epithelial cells ( $p < 0.0001$ )
- Decrease in vaginal pH ( $p < 0.0001$ )

However, the 0.25% DHEA dose did not demonstrate significantly greater improvement over placebo at Week 12 in the decrease in the severity of the MBS of dyspareunia ( $p = 0.3423$ ).

The reader is encouraged to also review the Statistical Review of Dr. Dwyer, dated July 1, 2016.

The applicant also performed additional analyses of co-primary endpoints and the MBS of dyspareunia for the cITT population removing those women who demonstrated a pattern of serum sex steroids at Week 12 that would be typical of women taking estrogens. See page 51 of this review for a description of the cITT population. The outcomes reported for the cITT population in the four co-primary endpoints do not differ from the ITT Population. Only the 0.50% DHEA dose demonstrated statistically significant improvement in the co-primary endpoints for Trial ERC-231.

***Secondary Efficacy Analyses:***

See the secondary objectives of Trial ERC-231 on page 44 of this review.

The symptom score parameters of moderate to severe vaginal dryness and vulvovaginal irritation/itching were evaluated at Baseline and Weeks 6 and 12 and tested statistically as second-order and third-order to the primary symptom score parameter of pain at sexual activity (dyspareunia). Sexual dysfunction and quality of life questionnaires were completed at Baseline and Weeks 6 and 12. Site investigators evaluated and reported on the signs of vulvar and vaginal atrophy (for example vaginal secretion, vaginal epithelial integrity, vaginal epithelial surface thickness, and vaginal color) at the time of vaginal examination at Screening and Weeks 6 and 12 to evaluate the vaginal mucosa and the local tolerance of administration of DHEA and placebo vaginal inserts. Analysis was performed to assess treatment difference and change from baseline.

**Clinical Reviewer's Comments:**

EndoCeutics was advised that no secondary endpoints would be considered in evaluating the effectiveness of the DHEA vaginal insert to relieve moderate to severe dyspareunia due to menopause, and that the reported finding of secondary endpoints would not appear in product labeling.

***Safety Analyses:***

Refer to Section 7 for discussion.

### 5.3.2 Trial ERC-238

#### 5.3.2.1 Objectives

**Primary:**

The primary objectives of Trial ERC-238 were to:

- Confirm the efficacy of intravaginal DHEA on moderate to severe pain at sexual activity (dyspareunia) as most bothersome symptom (MBS) of vulvovaginal atrophy (VVA) due to menopause.
- Collect further data on women exposed to intravaginal DHEA at the dose or dose range believed to be efficacious in order to meet the ICH E1 guideline requirement so that the "total number of individuals treated with the investigational drug, including short term exposure, will be about 1500".

**Secondary:**

Secondary objectives of Trial ERC-238 were to:

- Examine the tolerance to intravaginal administration of DHEA
- Investigate a possible influence of treatment on the male partner
- Evaluate the efficacy on the other two symptoms of VVA (dryness and irritation/itching)
- Evaluate the efficacy on arousal/lubrication, the woman's subjective arousal, desire, satisfaction and orgasm by the FSFI questionnaire according to the indicated priority design
- Obtain information on the usability of the applicator used to insert the medication

#### 5.3.2.2 Enrollment Criteria:

**Inclusion Criteria**

Postmenopausal women were eligible for inclusion if they met the following inclusion criteria:

1. Postmenopausal women (non hysterectomized or hysterectomized) must satisfy either a or b or c:
  - a) No menses for at least one year for non-hysterectomized women, or
  - b) Follicle stimulating hormone (FSH) levels >40 IU/L or > postmenopausal value of the laboratory where the FSH assay is performed (a woman with previously measured elevated serum FSH meets the inclusion criteria) in women with no menses >6 months but <12 months, or in hysterectomized women who were premenopausal at the time of hysterectomy, or
  - c) Six months or more of Day 1 visit following bilateral oophorectomy with or without hysterectomy.

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2. Women who have self-identified at screening and baseline (Day 1) pain at sexual activity as moderate to severe and as the most bothersome vulvovaginal atrophy symptom.
3. Women between 40 and 80 years of age.
4. Women having  $\leq 5\%$  of superficial cells on vaginal smear at screening and baseline (Day 1).
5. Women having a vaginal pH above 5 at screening and baseline (Day 1).
6. Women who currently have intercourse or other sexual activity (masturbation, etc.) at least once a month (with or without a partner), or who had intercourse or other sexual activity at least once a month in the past but later decreased sexual activity due to excessive pain or vaginal dryness.
7. Normal mammogram (American College of Radiology Breast Imaging-Reporting and Data System (BI-RADS) category 1 or 2 within 9 months of trial start (Day 1), and normal breast examination.
8. A normal PAP smear (which includes inflammatory changes) within the last 12 months (of Day 1) for both non-hysterectomized and hysterectomized women following specimen collection.
9. Willing to participate in the trial and sign an informed consent.
10. No former or present narcotic addiction or alcoholism.
11. For non-hysterectomized women, willing to have an endometrial biopsy during the screening period to exclude endometrial pathology.

### **Exclusion Criteria:**

Postmenopausal women were eligible for inclusion if they met inclusion criteria and did not have the following exclusion criteria:

1. Previous enrollment in ERC-210, ERC-213, ERC-230, ERC-231 or ERC-234.
2. Previous diagnosis of cancer, except skin cancer (non-melanoma).
3. Active or history of thromboembolic disease.
4. Clinically significant metabolic or endocrine disease.
5. Use of estrogen alone injectable drug therapy or progestin implant within 6 months prior to study entry (screening visit).
6. Use of estrogen pellet or progestin injectable drug within 6 months prior to study entry (screening visit).
7. Oral estrogen, progestin or DHEA exposure or intrauterine progestin therapy in the 8 weeks prior to baseline assessments (screening visit).
8. Vaginal hormonal products (rings, creams, gels or tablets) or transdermal estrogen alone or estrogen/progestin products in the 8 weeks prior to baseline assessment (screening visit).
9. Previous treatment with androgens or anabolic steroids within 6 months prior to screening visit.
10. Natural oral estrogenic products in the 4 weeks prior to baseline assessments.

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Regarding exclusion criteria 5 to 10, women can washout as follows, but the questionnaire on VVA must be answered after the required washout period:

- At least an eight-week washout period for prior oral estrogen, DHEA and/or progestin therapy.
  - At least an eight-week washout period for prior transdermal hormone therapy.
  - At least an eight-week washout period for locally delivered hormone replacement therapy for vaginal dryness (rings, creams, gels or tablets).
  - At least 6 months for prior estrogen pellet therapy or progestin injectable drug therapy.
  - Eight weeks or longer for prior intrauterine progestin therapy.
  - Six months or longer for prior progestin implants and estrogen alone injectable drug therapy.
  - Four weeks or longer for prior natural oral “estrogenic” products.
11. Confirmed clinically significant depression or confirmed history of severe psychiatric disturbance.
  12. The administration of any investigational drug within 30 days of screening visit.
  13. Previous treatment with androgens or anabolic steroids within 3 months prior to screening visit.
  14. Clinically relevant abnormal serum biochemistry, urinalysis or hematology.
  15. Baseline cervical cytology showing low-grade squamous intraepithelial lesion (LGSIL) or worse.
  16. Palpable fibroids or Grade 2 uterine prolapse by gynecologic exam.
  17. Endometrial polyps
  18. Have vulvar lichen sclerosis or had an endometrial ablation.
  19. Endometrial hyperplasia or cancer at biopsy performed at screening.

### ***Allowed and Excluded Medications:***

Medications necessary for the woman's well-being were allowed during the trial with the exception of:

- Estrogen hormone therapy
- Progestogen medication
- Natural oral "estrogenic" products
- Vaginal cream or gel
- Vaginal lubricant
- Vaginal douching

### 5.3.2.3 Trial Design and Conduct

Clinical Trial ERC-238 entitled: “Intravaginal Prasterone (DHEA) Against Vulvovaginal Atrophy Associated With Menopause (Placebo-Controlled, Double-Blind and Randomized Phase III Study” was a multicenter (total of 38 clinical sites; 24 in the US

and 14 in Canada), randomized, double-blind, placebo-controlled clinical trial conducted between February 11, 2014 (first woman enrolled) and January 6, 2015 (last woman completed the trial) to support the indication “Treatment of moderate to severe dyspareunia (pain at sexual activity), a symptom of vulvovaginal atrophy, due to menopause.”

Five hundred and fifty-eight (558) postmenopausal women were randomized in a 2:1 ratio to receive:

- 0.50% DHEA vaginal insert (376 women randomized; 356 completers), or
- Placebo vaginal insert (182 women randomized; 171 completers).

The clinical trial was divided into two phases, a screening period up to 8 weeks followed by a treatment period of 12 weeks.

Efficacy information on vulvar and vaginal atrophy symptoms and signs was collected as follows:

1. Vaginal cell maturation:

Vaginal smears were obtained from the middle or second third of the side wall of the vagina and sent to a central laboratory. All samples were examined by an experienced cytopathologist blinded to the treatment regimens. A 100-cell count was performed (parabasal (including basal), intermediate, and superficial). The mean change from baseline to weeks 6 and 12 (percentages of parabasal and superficial cells) was evaluated.

2. Vaginal pH:

A pH strip was applied to the lateral wall of the vagina. The mean change in vaginal pH from baseline to weeks 6 and 12 was evaluated.

3. Self-assessment of vaginal symptoms:

The self-assessment of symptoms were evaluated by a questionnaire (English and French) at each visit. The mean change from baseline to weeks 6 and 12 in the moderate to severe symptom that was identified by the patient as being the most bothersome to her was evaluated as the primary efficacy endpoint.

#### 5.3.2.4 Assessment of Efficacy

**Primary Efficacy Variable:**

The co-primary endpoints of Trial ERC-238 were:

1. A statistically significant improvement over placebo from baseline (Day 1) to Week 12 for moderate to severe vaginal pain at sexual activity self-identified by the woman as the most bothersome VVA symptom to her at screening and at baseline (Day 1).

2. A statistically significant decrease from baseline (Day 1) to Week 12 compared to placebo in vaginal pH, and
3. A statistically significant increase from baseline (Day 1) to Week 12 compared to placebo in percentage of superficial cells and a statistically significant decrease in percentage of parabasal cells on a smear of the vaginal wall.

**Secondary Efficacy Variable:**

Secondary efficacy variables included:

1. Vaginal mucosa
  - Vaginal secretions
  - vaginal epithelial integrity
  - Vaginal epithelial surface thickness
  - Vaginal color recorded as no atrophy, mild, moderate, severe and analyzed using values of 1, 2, 3, and 4, respectively
2. Tolerance to administration of DHEA.

5.3.2.5 Assessment of Safety

**Adverse Events:**

Information was collected, throughout the trial, on vital signs, physical examination, gynecological examination including a Pap smear, mammogram (unless performed within 9 months prior to Day 1 with written documentation), and clinical laboratory tests (hematology including a complete blood count; coagulation parameters including prothrombin time, activated partial thromboplastin time; blood chemistry including glucose, electrolytes, BUN, creatinine, AST, ACT, alkaline phosphate, total bilirubin, total serum protein, LDH; lipid profile including total cholesterol, triglyceride, HDL, LDL, lipoprotein B; and urinalysis). AEs were recorded for safety evaluation and then coded into system organ class and preferred terms using MedDRA version 16.1).

**Endometrial Assessment:**

For non-hysterectomized women, an endometrial biopsy was done at screening to document the endometrial histological status and exclude women with endometrial pathology from trial participation. Screening endometrial biopsies obtained in Trial ERC-238 were evaluated at the University of Rochester Medical Center (URMC) in Rochester, NY utilizing the same endometrial histological characteristics previously described under phase 3 Trial ERC-231.

**Applicator Use:**

Usability of the inset applicator was evaluated by a questionnaire filled out at the end-of-trial. This questionnaire included 7 questions.

See Subsection 7.3.5.3 for a more detailed discussion of the reported findings of the applicator use questionnaire.

**Male Partner Safety:**

The potential influence of DHEA on the woman's male partner (related to intercourse) was evaluated, on a voluntary basis, by a questionnaire filled by partners at screening and at Week 12.

See Subsection 7.3.5.4 for a more detailed discussion of the reported findings.

5.3.2.6 Statistical Methodology

Unless otherwise stated, statistical analyses were performed at two-sided significance (alpha) level of 0.05. The co-primary endpoints analyzed were the changes in percent of parabasal cells, percent of superficial cells, and vaginal pH in combination with pain at sexual activity self-identified by women as being her most bothersome symptom (MBS) of VVA. Efficacy analyses were performed primarily on the Intent-to-Treat (ITT) population defined as all women who received at least one dose of trial drug (based on the diary card) with a baseline (Day 1) evaluation meeting the trial entry criteria ( $\leq 5\%$  of superficial cells on vaginal smear, a vaginal pH above 5, and who have self-identified moderate to severe dyspareunia as their MBS).

The ITT population consists of a total of 482 women: 157 and 325 per treatment group for placebo vaginal insert and 0.50% DHEA vaginal insert, respectively. The primary analysis was performed using ANCOVA, with the treatment group as the main factor and the baseline value as the covariate. The p-value for the baseline adjusted least square mean (LSM) difference between groups was presented (specifically, p-values for the placebo versus 0.50% DHEA). Additionally, change from baseline for each treatment group was presented and assessed via a 1-sample t-test.

Based on Trial ERC-238 inclusion criterion number 6, it was expected that women would have sexual activity at least once during the trial evaluation period. Some women did not report sexual activity at evaluations conducted at Weeks 6 and 12. Therefore, the applicant conducted an additional analysis on a modified ITT population (mITT) composed of women from the ITT population who had post-baseline sexual activity at least once before Weeks 6 and 12 (or discontinuation).

As in Trial ERC-231, women having a serum estrogen "signature" in Trial ERC-238 were excluded by the applicant from the PP analyses as this was considered a major protocol violation. In addition, the applicant performed supportive analyses of the ITT and safety population excluding the women suspected of concomitant use of estrogens "in order to examine unbiased results." The analyses sets excluding these women are listed in Table 8 and are identified as "corrected ITT population" (cITT) and "corrected safety population" (cSafety). In addition, for analysis of steroid data in Trial ERC-238,

the applicant identified additional subpopulations by adding the suffix “-S” (for example ITT-S, cITT-S, Safety-S and cSafety-S).

Table 8: List of Women Suspected by the Applicant of Concomitant Use of Estrogens and Inclusion/Exclusion of their Data in the Applicant’s Various Analysis Sets in Trial ERC-238

Randomization Number	Group	Safety Analysis Set	Corrected Safety Analysis Set	ITT Analysis Set	Corrected ITT Analysis Set	PP Analysis Set
238-21-021	Placebo	Yes	No	Yes	No	No
238-30-048		Yes	No	No	No	No
238-36-029		Yes	No	Yes	No	No
238-73-011		Yes	No	No	No	No
238-73-013		Yes	No	No	No	No
238-74-023		Yes	No	Yes	No	No
238-01-015	0.50% DHEA	Yes	No	No	No	No
238-12-001		Yes	No	Yes	No	No
238-12-015		Yes	No	Yes	No	No
238-21-040		Yes	No	No	No	No
238-30-001		Yes	No	Yes	No	No
238-54-005		Yes	No	No	No	No
238-73-002		Yes	No	Yes	No	No
238-73-026		Yes	No	Yes	No	No
238-74-026		Yes	No	Yes	No	No
238-75-014		Yes	No	No	No	No
238-77-035		Yes	No	Yes	No	No
238-85-025		Yes	No	No	No	No

Source: NDA 208470, Trial ERC-238 Clinical Trial Report; Table 7-1, page 63 of 601.  
Abbreviations: ITT = Intent-to-Treat; PP = Per Protocol

**Clinical Reviewer’s Comments:**

As previously stated, this reviewer and the Statistical Reviewer did not consider the cITT population in determining the effectiveness of 0.50% DHEA vaginal insert to relieve moderate to severe dyspareunia due to menopause. All women in Trial ERC-238 are included in the safety analyses.

Safety analyses were performed on the safety population consisting of women who received any amount of trial medication based on the diary card and/or trial drug accountability. Demographics and baseline characteristics were summarized and presented by treatment groups. The change from baseline (Day 1) to post-baseline assessments as well as differences from placebo was used for analysis. Analyses of differences between 0.50% and placebo vaginal inserts were performed using an ANCOVA with baseline as the covariate. All available safety data were used for analysis. For adverse events and laboratory data, standard methods of analysis were used. Information on the usability of the applicator used for the administration of treatment as well as on the potential influence of DHEA on woman’s male partner was

collected and analyzed primarily from women in the per protocol population (and their male partners). The safety population consists of a total of 554 women: 180 and 374 per treatment group for placebo vaginal insert and 0.50% DHEA vaginal insert, respectively.

**Clinical Reviewer's Comments:**

See the Medical Officer's Review of Trial ERC-238, dated February 18, 2014, for a full description of the trial protocol.

5.3.2.7 Results:

**Demographics**

The demographics and baseline characteristics of the safety cohort in Trial ERC-238 are shown in Table 9.

Table 9: Demographics of Trial ERC-238: Safety Population

Parameters	Placebo	0.50% DHEA	Total
	N = 180	N = 374	N = 554
<b>Age (Years)</b>			
Mean	59.6	59.5	59.5
Median	59.0	59.0	59.0
Range (Min – Max)	47 – 75	40 – 80	40 = 80
<b>Anthropometric measurements (mean)</b>			
Body Mass Index (kg/m <sup>2</sup> )	26.0	26.7	26.4
Height (cm)	161.7	161.0	161.2
Weight (kg)	67.8	69.2	68.7
<b>Race (Number of Women, %)</b>			
Caucasian	163 (91%)	338 (90%)	501 (90%)
African American	13 (7%)	28 (7%)	41 (7%)
Asian	2 (1%)	4 (1%)	6 (1%)
Other	2 (1%)	4 (1%)	6 (1%)
<b>Ethnicity (Number of Women, %)</b>			
Not Hispanic or Latino	166 (92%)	330 (88%)	496 (90%)
Hispanic or Latino	14 (8%)	44 (12%)	58 (10%)

Source: Adapted from NDA 208470, Trial ERC-238 Clinical Trial Report, Table 8-3, page 87 of 601.

**Clinical Reviewer's Comments:**

The demographics and baseline characteristics of the women enrolled in the two treatment groups in Trial ERC-238 are similar. The trial population consisted mainly of Caucasian and non-Hispanic postmenopausal women (90%).

There are no significant differences in the baseline demographics and characteristics of the women participating in the two confirmatory phase 3 trials (Trials ERC-231 and ERC-238) submitted in support of an indication for the treatment of moderate to severe dyspareunia due to menopause. Non-Caucasians are underrepresented in both clinical trials.

***Disposition of Participating Women:***

The overall disposition of women in Trial ERC-238 is summarized in Table 10. A total of 558 women were enrolled in Trial ERC-238. However, seventy-two women did not meet the stated inclusion criteria on Day 1 (23 were randomized to the placebo vaginal insert treatment group; 49 were randomized to the 0.50% DHEA treatment group). Per the applicant, these women continued to receive their assigned trial medication (placebo or DHEA) as randomized in order to obtain additional exposure and safety data, but they were not part of the efficacy analysis due to their lack of compliance with the trial entry criteria on Day 1. Therefore, 482 women made up the ITT population after 4 women were excluded because they did not present any post-baseline data (2 in the placebo treatment group lost to follow-up, and 2 in the DHEA treatment group: one lost to follow-up and 1 withdrew consent). Four hundred and sixty-three (463) women completed Trial ERC-238. Nineteen (19) women discontinued prematurely.

Table 10: Disposition of Women in Trial ERC-238: ITT Population

	Placebo N = 157	0.50% DHEA N = 325	Total N = 482
Number Completed Trial	152 (96.8%)	311 (95.6)	463 (96.0%)
Total Discontinued	5 (3.1%)	14 (4.3%)	19 (3.9%)
Reason Discontinued			
- Adverse Event	3 (1.9%)	5 (1.5%)	8 (1.6%)
- Withdrew Consent	2 (1.2%)	7 (2.1%)	9 (1.8%)
- Lost to Follow-up	0 (0.0%)	2 (0.06%)	2 (0.04%)

Source: Adapted from NDA 208470, Trial ERC-238 Clinical Trial Report, Figure 8-1, page 81 of 601.

Definition: ITT = Intent-to-Treat

**Clinical Reviewer’s Comments:**

The percentage of women who completed the trial was similar across the two treatment groups. Likewise, the percentage of women discontinuing the trial was similar across treatment groups. The 0.50% DHEA treatment group presented with a slightly higher discontinuation rate than the placebo treatment group.

The most common reason for premature discontinuation overall in Trial ERC-238 was, “withdrew consent”.

See a discussion of adverse events in Subsection 7.3.3 of this review.

***Primary Efficacy Analyses:***

Five hundred fifty-eight (558) healthy postmenopausal women, with and without an intact uterus, 40 to 80 years of age [mean age 59.6 ± 0.29 years (mean ± SEM)], were enrolled in Trial ERC-238 (182 and 376 per treatment group for placebo and 0.50% DHEA, respectively). Four hundred eighty-two (482) women were included in the ITT population (157 and 325 per treatment group for placebo and 0.50% DHEA, respectively), which consists of all women who received at least one dose of trial drug (based on diary) with a baseline (Day 1) evaluation meeting the entry criteria.

Twenty-three (23) women enrolled in the placebo treatment group and 49 women enrolled in the 0.50% DHEA treatment group no longer met all inclusion criteria at Day 1 and were not included in the ITT population. However, these 72 women were retained in the safety population. Therefore, the safety population consists of 554 women (180 women in the placebo treatment group and 374 women in the 0.50% DHEA treatment group) which includes all women who received any amount of trial medication based on diary) and who had any safety data available. See Section 7 Summary of Safety.

Three hundred seventy-three (373) women were included in the PP population (119 women in the placebo treatment group and 254 women in the 0.50% DHEA treatment group) which is a subset of the ITT population that completed the trial with no major protocol violations considered to compromise efficacy data. The PP population is a supportive population for efficacy data analysis.

See Section 5.3.2.4 for a discussion of the co-primary endpoints in Trial ERC-238. Phase 3 Trial ERC-238 had the same 4 co-primary primary endpoints as in phase 3 Trial ERC-231.

The primary efficacy results obtained in the ITT population for Trial ERC-238 are shown in Table 11. These reported primary efficacy analyses are based on women who met all three of the baseline inclusion criteria: ≤ 5% superficial cells on a vaginal smear, a vaginal pH greater than 5.0, and dyspareunia self-identified as moderate to severe and most bothersome.

Table 11: Applicant-Reported Primary Efficacy Summary in Trial ERC-238: ITT Population

	Placebo N = 157	0.50% DHEA N = 325
<b>%Superficial Cells</b>		
- Baseline Mean (SD)	1.04 (1.40)	1.02 (1.44)
- Week 12 Mean (SD)	2.78 (3.37)	11.22 (10.18)
- Mean Change from Baseline (SD)	1.75 (3.33)	10.20 (10.35)
- P-value <sup>a</sup>	-	<0.0001
- P-value <sup>b</sup>	-	<0.0001
<b>% Parabasal Cells</b>		
- Baseline Mean (SD)	51.66 (37.60)	54.25 (38.64)
- Week 12 Mean (SD)	39.68 (33.57)	12.74 (18.44)

- Mean Change from Baseline (SD)	-11.98 (29.58)	-41.51 (36.26)
- P-value <sup>a</sup>	-	<0.0001
- P-value <sup>b</sup>	-	<0.0001
<b>Vaginal pH</b>		
- Baseline Mean (SD)	6.32 (0.66)	6.34 (0.65)
- Week 12 Mean (SD)	6.05 (0.89)	5.39 (0.94)
- Mean Change from Baseline (SD)	-0.27 (0.74)	-0.94 (0.94)
- P-value <sup>a</sup>	-	<0.0001
- P-value <sup>b</sup>	-	<0.0001
<b>Dyspareunia</b>		
- Baseline Mean (SD)	2.56 (0.50)	2.54 (0.50)
- Week 12 Mean (SD)	1.50 (1.05)	1.13 (0.98)
- Mean Change from Baseline (SD)	-1.06 (1.02)	-1.42 (1.00)
- P-value <sup>a</sup>	-	<0.0001
- P-value <sup>b</sup>	-	0.0002

Source: Adapted from NDA 208470, Trial ERC-238 Clinical Trial Report; Table 9-3 on page 95 of 601, Table 9-2 on page 93 of 601, Table 9-5 on page 98 of 601, and Table 9-7 on page 102 of 601.

Abbreviations: DHEA = dehydroepiandrosterone, SD = Standard Deviation

<sup>a</sup>P-value from a paired t-test (p-value versus baseline).

<sup>b</sup>ANCOVA test with treatment group as the main factor and baseline value as the covariate (p-value versus placebo).

### **Clinical Reviewer's Comments:**

From the data shown in Table 11, the 0.50% DHEA vaginal insert demonstrated significantly greater improvement over placebo at week 12 in the:

- Increase in the percentage of superficial epithelial cells (p<0.0001)
- Decrease in the percentage of parabasal epithelial cells (p<0.0001)
- Decrease in vaginal pH (p<0.0001)
- Decrease *in the severity of the MBS of dyspareunia* (p=0.0002)

The reader is encouraged to also review the Statistical Review of Dr. Dwyer, dated July 1, 2016.

Based on the inclusion criterion addressing sexual activity for Trial ERC-238 (women would have sexual activity at least once during the 12-week treatment and evaluation period), the applicant performed an additional analysis on a modified ITT (mITT) composed of women from the ITT population who had post-baseline sexual activity at least once before evaluation of dyspareunia at end-of-trial. However, only 14 women in the placebo treatment group (8.9%; 14 of 157 women) and 20 women in the 0.50% DHEA treatment group (6.1%; 20 of 325 women) did not engaged in sexual activity after Day 1. Data obtained from the mITT population analysis showed a dyspareunia severity score difference from placebo at Week 12 of -0.34 with a p-value of 0.0003. This finding is similar to the p-value for the ITT population (p=0.0002).

The applicant also performed additional analyses of co-primary endpoints and the MBS of dyspareunia for the cITT population removing those women who demonstrated a pattern of serum sex steroids at Week 12 typical of women taking estrogens. See page 48 of this review for a description of the cITT population. These cITT analyses produced similar p-values for the mean change at week 12 for superficial and parabasal epithelial cells and vaginal pH ( $p < 0.0001$  for each). The p-value for the mean change at week 12 for dyspareunia is reported as  $p = 0.0004$  for the 0.50% DHEA dose. The outcomes reported for the cITT population do not differ from the ITT Population.

**Secondary Efficacy Analyses:**

The secondary efficacy analyses in Trial ERC-238 are the same as stated above for Trial ERC-231 regarding the symptom score parameters of vaginal dryness and vulvovaginal irritation/itching, and the investigator observations of the vaginal mucosa and tolerance of administration of DHEA and placebo vaginal inserts. In Trial ERC-238, only the FSFI questionnaire was completed. Two additional secondary efficacy analyses conducted to investigate 1) a possible influence of treatment on the male partner and 2) to obtain information on the usability of the applicator used to insert the medication are more fully discussed in Subsections 7.3.5.3 and 7.3.5.4, respectively, of this review.

**Clinical Reviewer's Comments:**

EndoCeutics was advised that no secondary endpoints would be considered in evaluating the effectiveness of the DHEA vaginal insert to relieve moderate to severe dyspareunia due to menopause, and that the reported finding of secondary endpoints would not appear in product labeling.

**Safety Analyses:**

Refer to Section 7 for discussion.

5.3.3 Trial ERC-230:

5.3.3.1 Objectives

**Primary:**

The primary objective of Trial ERC-230 was to assess the long-term safety of 0.50% DHEA vaginal insert by collecting data from adverse events (AEs), hematology and coagulation, blood chemistry, urinalysis, lipid profiles, physical examination (including gynecological and vaginal examination), mammography, Pap smear, endometrial biopsy, and detailed serum steroid concentrations.

**Secondary:**

The secondary objectives were to:

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- Assess the long-term effects of DHEA vaginal insert on the symptoms and signs of vaginal atrophy by evaluating changes in the percentages of superficial and parabasal cells on a vaginal smear, vaginal pH and self-assessment of vaginal symptoms (questionnaire completed at baseline, Weeks 12, 26, 39, and 52).
- Assess the tolerance to DHEA vaginal insert.
- Assess the efficacy on arousal/lubrication, subjective arousal desire, pain at sexual activity, satisfaction and organism at screening, Day 1, Week 26, and Week 52 using the Female Sexual Function Index (FSFI) questionnaire.

### 5.3.3.2 Enrollment Criteria:

#### ***Inclusion Criteria***

Postmenopausal women were eligible for inclusion if they met the following inclusion criteria and none of the exclusion criteria:

1. Postmenopausal women (non-hysterectomized or hysterectomized), 40 to 75 years of age, must satisfy either a or b or c:
  - d) No menses for at least one year for non hysterectomized women, or
  - e) Follicle stimulating hormone (FSH) levels >40 IU/L or > postmenopausal value of the laboratory where the FSH assay is performed (a woman with previously measured elevated serum FSH meets the inclusion criteria) in women with no menses >6 months but <12 months, or in hysterectomized women who were premenopausal at the time of hysterectomy, or
  - f) Six months or more of Day 1 visit following bilateral oophorectomy with or without hysterectomy.
2. Have a normal mammogram within 9 months of trial start, normal breast examination, and normal Pap smear within the last 12 months (of Day 1).
3. Willing to participate in the trial and sign an informed consent.
4. Women who have self-identified at least one mild to severe of the following symptoms:
  - Vaginal dryness (none, mild, moderate or severe)
  - Vaginal and/or vulvar irritation/itching (none, mild, moderate or severe)
  - Vaginal pain associated with sexual activity (none, mild, moderate or severe)
5. Willing to have an endometrial biopsy at screening and end-of-trial.

#### ***Exclusion Criteria:***

1. Undiagnosed abnormal genital bleeding.
2. Previous diagnosis of cancer, except skin cancer (non-melanoma).
3. Active or history of thromboembolic disease.
4. Significant metabolic or endocrine disease.
5. Uncontrolled diabetes mellitus.

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6. Use of estrogen alone injectable drug therapy or progestin implant within 6 months prior to study entry (screening visit).
7. Use of estrogen pellet or progestin injectable drug within 6 months prior to study entry (screening visit).
8. Oral estrogen, progestin or DHEA exposure or intrauterine progestin therapy in the 8 weeks prior to baseline assessments (screening visit).
9. Vaginal hormonal products (rings, creams, gels or tablets) or transdermal estrogen alone or estrogen/progestin products in the 8 weeks prior to baseline assessment (screening visit).

Women can washout as follows, but the questionnaire on vaginal atrophy must be answered after the required washout period:

- At least an eight-week washout period for prior oral estrogen, DHEA and/or progestin therapy.
  - At least an eight-week washout period for prior transdermal hormone therapy.
  - At least an eight-week washout period for locally delivered hormone replacement therapy for vaginal dryness (rings, creams, gels or tablets).
  - At least 6 months for prior estrogen pellet therapy or progestin injectable drug therapy.
  - Eight weeks or longer for prior intrauterine progestin therapy.
  - Six months or longer for prior progestin implants and estrogen alone injectable drug therapy.
10. Cardiac failure or manifest coronary heart disease.
  11. Hypertension equal to or above 140/90 mm Hg or not controlled by standard therapy.
  12. Confirmed clinically significant depression or confirmed history of severe psychiatric disturbance.
  13. The administration of any investigational drug within 30 days of screening visit.
  14. Previous treatment with androgens or anabolic steroids within 3 months prior to screening visit.
  15. Clinically relevant abnormal serum biochemistry, urinalysis or hematology.
  16. Baseline cervical cytology showing low-grade squamous intraepithelial lesion (LGISIL) or worse.
  17. Palpable fibroids or Grade 2 uterine prolapse by gynecologic exam.
  18. Coagulation disorders or on anticoagulant drug therapy.
  19. Endometrial hyperplasia or cancer at biopsy performed at screening.
  20. Have vulvar lichen sclerosis.

### ***Allowed and Excluded Medications:***

Medications necessary for the woman's well-being were allowed during the trial with the exception of:

- Estrogen hormone therapy

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- Progestogen medication
- Natural oral "estrogenic" products
- Vaginal cream or gel
- Vaginal lubricant
- Vaginal douching

### 5.3.3.3 Trial Design and Conduct

Clinical Trial ERC-230 entitled, "Protocol ERC-230 - DHEA Against Vaginal Atrophy – Safety Study of 12 Months" was an open-label, multicenter (10 new recruiting sites in Canada and 31 new recruiting sites in the US), phase 3 trial of 530 non-hysterectomized postmenopausal women enrolled to receive 0.50% DHEA vaginal insert (6.5 mg of DHEA) for 12 months to examine long-term safety (435 completers). Per the protocol, non-hysterectomized women participating in Trial ERC-231 could elect to continue receiving DHEA at the 0.50% dose for a total of 12 months and thus be part of the safety population in Trial ERC-230. Non-hysterectomized women who were on 0.25% DHEA or placebo vaginal insert in Trial ERC-231 also could elect to receive treatment with 0.50% DHEA vaginal insert in Trial ERC-230. The first woman was enrolled on November 30, 2010, and the last woman completed the trial on July 16, 2012.

### 5.3.3.4 Assessment of Efficacy

Trial ERC-230 was not designed to provide primary efficacy information. Long-term effects of prasterone on the symptoms and signs of vaginal atrophy were assessed as secondary efficacy outcomes.

### 5.3.3.5 Assessment of Safety

Long-term safety of intravaginal prasterone was assessed as the primary objective.

#### **Adverse Events:**

Information was collected, throughout the trial, on serum steroid concentrations (DHEA and related metabolites), adverse events, clinical laboratory tests (hematology and coagulation, blood chemistry, urinalysis, and lipid profile), physical examination (including vital signs and gynecological examination), Pap smear, mammography, and endometrial biopsy.

All treatment-emergent AEs (TEAEs), serious adverse events (SAEs), and those events assessed as related to trial treatment were summarized and tabulated by SOC and preferred term, both overall and by severity. For tabulations by severity, only a woman's most severe event within the category was counted. The number and

percentage of women experiencing at least one Grade 3 (Severe) or Grade 4 (Life-threatening) or Grade 5 (Death) TEAE were summarized.

**Endometrial Assessment:**

See Subsection 7.3.5.1 in this review.

5.3.3.6 Statistical Methodology

Statistical analyses were performed at the two-sided significance level of 0.05 unless otherwise stated. Demographics and baseline characteristics were summarized and presented. The primary time point for analysis was the 52-week assessment, with additional presentations of the data at 12, 26, and 39 weeks. The safety population consists of a total of 521 women.

The Safety Population was defined as all women who received an administration of any amount of DHEA (based on diary card (valid data entry) or on drug accountability (if diary was not returned)), and who had any safety information available. The Safety Population was composed of 521 women and consisted mainly of White Caucasian non-Hispanic women (92%). Black or African American women were the second most represented race with 6% of the women. The average age of the women was 57.9 years with a median age of 58.0 and a range of 43 to 75 years. All analyses of safety parameters were based on this population. Data presentations were made separately for the following groups:

1. All women who received any amount of trial treatment.
2. All women who received 26 weeks or more of trial treatment up to 52 weeks.
3. All women who received 52 weeks of trial treatment.

5.3.3.7 Results:

**Demographics**

The demographics and baseline characteristics of the safety cohort of Trial ERC-230 are shown in Table 12.

Table 12: Demographics of Trial ERC-230: Safety Population

Parameters	0.50% DHEA
	N = 521
<b>Age (Years)</b>	
Mean	57.9
Median	58.0
Range (Min – Max)	43 – 75
<b>Anthropometric measurements (mean)</b>	
Body Mass Index	

(kg/m <sup>2</sup> )	26.3
Height (cm)	160.5
Weight (kg)	67.7
<b>Race (Number of Women, %)</b>	
Caucasian	478 (92%)
African American	31 (6%)
Asian	3 (1%)
Other	7 (2%)
<b>Ethnicity (Number of Women, %)</b>	
Not Hispanic or Latino	497 (95%)
Hispanic or Latino	24 (5%)

Source: Adapted from NDA 208470, Trial ERC-230 Clinical Trial Report, Table 8-3 Overview of demographics and baseline characteristics (Safety population), page 70 of 860.

**Clinical Reviewer’s Comments:**

The demographics and baseline characteristics of the women enrolled in Trial ERC-230 are similar to women enrolled in Trials ERC-231 and ERC-238. The trial population consisted mainly of Caucasian (92%) and non-Hispanic postmenopausal women (95%).

***Disposition of Participating Women:***

The overall disposition of women in Trial ERC-230 is summarized in Table 13. A total of 530 women were enrolled in Trial ERC-230, 435 women completed the trial, and 95 (18%) women discontinued prematurely.

Table 13: Disposition of Women in Trial ERC-231: ITT Population

	0.50% DHEA	
	N = 530	
Number Completed Trial	435 (82%)	
Total Discontinued N = 95 (18%)	Before Week 26 N = 71 (75%)	After Week 26 N = 24 (24%)
Reason Discontinued		
- Adverse event	20	9
- Non-compliance	1	3
- Lost to Follow-up	13	3
- Withdrew Consent	24	7
- Investigator’s Decision	2	1
- Other	11	1

Source: Adapted from NDA 208470, Trial ERC-238 Clinical Trial Report, Figure 8-1; Subject disposition chart, page 66 of 860.

**Clinical Reviewer’s Comments:**

While only 18% (95 of 530 treated women) of the women participating in 52-week Trial ERC-230 discontinued, this discontinuation rate exceeded 12-week Trials ERC-231 and ERC-238 (12.6% and 4.3%, respectively). The trial duration is a factor, however. Of interest in Trial ERC-230 is that the majority of discontinuations occurred before Week 26 (13.4%, 71 of 530 treated women)

versus 4.5% (24 of 530 women treated) between Weeks 26 to 52. Also of interest are the reasons for discontinuations before Week 26 including withdrew consent, adverse event and lost to follow-up which all decreased in the second 6 months of this 12-month trial.

### **Safety Analysis**

See Section 7 for discussion.

## 5.3.4 Supportive Clinical Trials:

### 5.3.4.1 Clinical Trial ERC-234:

Clinical Trial ERC-234 entitled, "DHEA Against Vaginal Dryness (Placebo-Controlled, Double-Blind and Randomized Phase III Study of 3-Month Intravaginal DHEA)" was a multicenter (10 trial sites in Canada and 21 trial sites in the US), randomized, double-blind, placebo-controlled, phase 3 trial conducted between June 21, 2011 (first woman, first visit) and April 12, 2013 (last woman, last visit) conducted to support the indication

(b) (4)

The primary objective of the trial was to confirm the efficacy of intravaginal DHEA on vaginal dryness, a symptom of vaginal atrophy. The trial enrolled postmenopausal women non hysterectomized or hysterectomized), 40 to 75 years of age, suffering from vaginal dryness, who self-identified at screening and baseline (Day 1) vaginal dryness as their most bothersome moderate to severe vaginal atrophy symptom.

The primary endpoints of Trial ERC-234 were:

- Evaluation of efficacy of DHEA compared to placebo from Day 1 to Week 12 for 0.25% and 0.50% DHEA
- Change in severity score of vaginal dryness as a co-primary objective as well as changes in % of parabasal cells, % of superficial cells, and vaginal pH.

Four hundred and fifty (450) postmenopausal women were randomized to receive one of the following regimens:

- 0.25% DHEA vaginal insert (3.25 mg DHEA; 148 women randomized; 128 completers)
- 0.50% DHEA vaginal insert (6.5 mg DHEA; 150 women randomized; 125 completers)
- Placebo vaginal insert (152 women randomized; 130 completers)

Additional details on the trial conduct and assessments are provided in Subsection 9.5.1 of this review.

**Clinical Reviewer's Comments:**

Clinical Trial ERC-234 was not considered in the efficacy evaluation of this NDA for the indication for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. (b) (4)

5.3.4.2 Clinical Trial ERC-210:

Clinical Trial ERC-210 entitled, "Topical DHEA Against vaginal atrophy (3-Months Placebo-Controlled Double-Blind Randomized Phase III Study)" was a randomized, double-blind, multicenter [2 centers in US (Jones Institute, Norfolk, VA and Women's Health Research Clinic, Cleveland, OH), 5 in Quebec, Canada, and 1 in Montreal, Canada], placebo-controlled trial conducted between June 28, 2007 (first subject enrolled) and May 23, 2008 (last subject completed trial).

The primary objective of Trial ERC-210 was to determine the dose-response (minimal concentration) of DHEA having a maximal effect on vaginal mucosa parameters. The local activity of DHEA was measured by changes in vaginal epithelial cell maturation (parabasal and superficial cells), and changes in vaginal pH. In addition, self-assessment was made of all three symptoms of vaginal atrophy (moderate to severe vaginal dryness, vaginal and/or vulvar irritation/itching, and vaginal pain associated with sexual activity) as composite symptoms.

Two hundred eighteen (218) postmenopausal women were randomized to receive a daily dose of:

- 0.25% (3.25 mg of DHEA vaginal insert)
- 0.50% (6.5 mg of DHEA vaginal insert)
- 1.0% (13 mg of DHEA vaginal insert)
- Placebo vaginal insert

Additional details on the trial conduct and assessments are provided in Subsection 9.5.2 of this review.

**Clinical Reviewer's Comments:**

Clinical Trial ERC-210 was not considered in the efficacy evaluation of this NDA for the indication for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Clinical Trial ERC-210 did not assess the mean change from baseline to Week 12 in the one

individual moderate to severe vulvar and vaginal atrophy symptom (for example, dyspareunia) self-identified by the women as being most bothersome to her. In the final study report for Trial ERC-210, the most bothersome symptom (MBS) calculation was based on a composite of all most bothersome symptom scores and was not adjusted for multiple comparisons.

## 6 Review of Efficacy

### **Efficacy Summary**

Prasterone (6.5 mg) vaginal insert, administered intravaginally once daily at bedtime, demonstrated statistically significant improvement over placebo in two confirmatory 12-week clinical trials (Trials ERC-231 and ERC-238). Approval of 6.5 mg prasterone for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy (b) (4), is fully supported by the available evidence of efficacy and safety.

#### 6.1 Indication

The proposed indication in the application reads, "Treatment of moderate to severe dyspareunia (b) (4) atrophy due to menopause."

#### **Medical Officer's Comments:**

The proposed indication in NDA 208470 is (b) (4) approved for the treatment of moderate to severe dyspareunia should read, "Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause." This is the indication that will be reflected in product labeling.

#### 6.1.1 Methods

The data presented in two 12-week, safety and efficacy phase 3 clinical trials (Trial ERC-231 and Trial ERC-238) were reviewed individually in their entirety. See Sections 5.3.1 and Sections 5.3.2.

#### 6.1.2 Demographics

See discussion of individual trial demographics for Trials ERC-231 and ERC-238 in Subsections 5.3.1.7 and Sections 5.3.2.7, respectively.

### 6.1.3 Subject Disposition

See discussion of disposition of women enrolled in Trials ERC-231 and ERC-238 in Subsections 5.3.1.7 and Sections 5.3.2.7, respectively.

### 6.1.4 Analysis of Primary Endpoint(s)

See discussion of the primary efficacy analyses of Trials ERC-231 and ERC-238 in Subsections 5.3.1.7 and Sections 5.3.2.7, respectively.

### 6.1.5 Analysis of Secondary Endpoints(s)

See discussion of the secondary efficacy analyses for Trials ERC-231 and ERC-237 in Subsections 5.3.1.7 and Sections 5.3.2.7, respectively.

### 6.1.6 Other Endpoints

No other endpoints for clinical Trial ERC-231 or clinical Trial ERC-238 will be discussed.

### 6.1.7 Subpopulations

As previously discussed in this review for Trial ERC-231, additional analyses were performed on a corrected ITT (cITT) population which did not include women for whom there was suspicion that they may have taken exogenous estrogens in addition to prasterone. Efficacy data obtained from these analyses are presented in this application for the four co-primary efficacy endpoints (percentage of parabasal and superficial cells, vaginal pH and severity score of dyspareunia).

In addition, steroid levels were also analyzed on a corrected safety population (cSafety). Data obtained from these analyses are also presented in the application.

#### **Clinical Reviewer's Comments:**

This reviewer and the Statistical Reviewer did not consider the cITT population in determining the effectiveness of 0.50% DHEA vaginal insert to relieve moderate

to severe dyspareunia due to menopause. All women in Trial ERC-231 are included in the safety analyses.

The applicant also presented additional analyses for Trial ERC-238 on the cITT population and cSafety population. The efficacy data from women suspected of having taken estrogens was removed from both of these subset analyses.

None of these subset analyses were considered in determining the effectiveness of 0.50% DHEA vaginal insert to relieve moderate to severe dyspareunia due to menopause. Likewise, all women in Trial ERC-238 are included in the safety analyses.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The reported differences in outcome analyses for the two DHEA vaginal insert doses (0.025% DHEA and 0.50% DHEA) used in Trial ERC231 can be found in subsection 5.3.1.7 in this review.

A single dosage, 0.50% DHEA, was evaluated in confirmatory Trial ERC-238.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy was evaluated in 12-week trials. Even through long-term safety extension Trial ERC-230 (52-week trial), collected efficacy information on the 0.50% DHEA vaginal insert, this information was not used to support efficacy as it was collected in an open label non-comparator trial.

### 6.1.10 Additional Efficacy Issues/Analyses

No additional primary efficacy analyses are considered in this review.

## 7 Review of Safety

### Safety Summary

The safety population in this NDA consists of 1542 healthy postmenopausal women, with or without a uterus, exposed to 0.25% prasterone (3.25 mg; N = 282), 0.50% prasterone (6.5 mg; N = 1196), 1.0% prasterone (13.0 mg; N = 64) or placebo (N = 474) in six clinical trials conducted during the prasterone (DHEA) development program. Eighty-nine percent (89%) of participating women (1365 of 1542 postmenopausal

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women) completed the six clinical trials; 11% (177 of 1542 postmenopausal women) discontinued. Five hundred twenty-one (521) of the participating postmenopausal women in the six clinical trials were treated up to 52-weeks with 0.50% prasterone (6.5 mg) vaginal inserts. EndoCeutics is requesting approval of 6.5 mg prasterone vaginal insert for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Although prasterone (DHEA) is not considered a new molecular entity (NME) by the Agency, it is a new chemical entity (NCE) for the proposed indication. Therefore, the Agency recommended, and EndoCeutics complied with, the ICH E 1 guidelines for premarket exposure for a drug product intended for chronic use.

In the prasterone (DHEA) development program, a total of 1196 healthy postmenopausal women were exposed to daily 0.50% DHEA (6.5 mg) vaginal insert with 521 women exposed up to 52 weeks. No deaths occurred in the six clinical trials. A total of 26 postmenopausal women experienced serious adverse events (SAEs) in the 0.50% prasterone (6.5 mg) treatment group (2.2%, 26 of 1196 women treated with 0.50% prasterone) compared with 5 postmenopausal women in the placebo treatment group (1%, 5 of 474 women treated with placebo). One SAE (invasive ductal breast carcinoma) in the 0.50% prasterone treatment group was considered possibly drug-related to prasterone by the investigator. One reported case of breast cancer does not raise safety concerns for the 6.5 mg prasterone vaginal insert.

The long-term general and endometrial safety of the 6.5 mg prasterone vaginal insert was investigated in a primary, 52-week safety clinical trial (Trial ERC-230). Four hundred twenty-two (422) non-hysterectomized women had an evaluable end-of-trial endometrial biopsy performed (97%, 422 of 435 women). The reported findings of the three independent, blinded pathologists support the absence of substantial endometrial effects for the 6.5 mg prasterone vaginal insert administered intravaginally daily over a 52-week duration. One reported case of disordered proliferative endometrium in 422 end-of-trial endometrial biopsies at 52-weeks does not raise safety concerns for the 6.5 mg vaginal insert. Likewise, one reported functional polyp also does not raise safety concerns for the 6.5 mg vaginal insert.

Overall, no major safety issues related, specifically to 0.50% DHEA (6.5 mg prasterone), were identified in this review in four 12-week, placebo-controlled clinical trials (ERC-210, ERC-231, ERC-234, and ERC-238), and one 12-month open-label clinical trial (ERC-230).

### 7.1 Methods

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

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The sNDA application contains an Integrated Summary of Safety (ISS). The safety population is defined as all women who received any amount of trial medication based on the woman’s diary and/or drug accountability, and who had any post-baseline safety information available. Safety data are provided for 1,542 women exposed to DHEA vaginal inserts [0.25% DHEA (3.25 mg), 0.50% DHEA (6.5 mg), and 1.0% DHEA (13.0 mg)], and 474 women exposed to placebo vaginal insert in the 6 clinical trials performed in the DHEA development program. See Table 14.

Table 14: Completed Clinical Trials with Prasterone (DHEA) Vaginal Insert

<b>Trial Number Type of Trial Trial Design</b>	<b>Single or Multi-Center/ Location</b>	<b>Trial Objectives Trial Population</b>	<b>No. of Women/ Doses/Duration of Treatment</b>	<b>Formulation/ Regimen</b>	<b>Age Mean (Age Range) Ethnicity Mean BMI</b>
ERC-213 phase 1/2 PK  Randomized, double-blind, placebo- controlled	Single center/ Quebec City Canada	Evaluation of the systemic bioavailability of DHEA and its metabolites and the pharmacokinetics of vaginal inserts at 4 different DHEA doses  Postmenopausal women with VVA	40 women enrolled/  Placebo, 0.50% DHEA, 1.0% DHEA, and 1.8% DHEA/  7 days	Vaginal insert/ Once daily	61 years (44-72 years)  99% White  Weight = 64 kg
ERC-210 phase 3 Safety and Efficacy/  Randomized, double-blind, placebo- controlled	Multi-center/ Canada US	To determine the dose-response of vaginal mucosa parameters to the local action of DHEA  Postmenopausal women with VVA	218 women enrolled/  Placebo, 0.25% DHEA, 0.50% DHEA, and 1.0% DHEA/  12 weeks	Vaginal insert/ Once daily	58 years (42-74 years)  100% White  BMI = 26
ERC-231 phase 3 Safety and Efficacy/  Randomized, double-blind, placebo- controlled	Multi-center Canada US	To confirm the efficacy of intravaginal DHEA on the symptoms of VVA  Postmenopausal women with dyspareunia as the most bothersome symptom	255 women enrolled/  Placebo, 0.25% DHEA, and 0.50% DHEA/  12 weeks	Vaginal insert/ Once daily	59 years (40-75 years)  92% White  BMI – 26.1
ERC-234	Multi-center	To confirm the	450 women	Vaginal insert	58 years

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phase 3 Safety and Efficacy/  Randomized, double-blind, placebo- controlled	Canada US	efficacy of intravaginal DHEA on vaginal dryness  Postmenopausal women with vaginal dryness as the most bothersome symptom	enrolled/  Placebo, 0.25% DHEA, and 0.50% DHEA/  12 weeks	Once daily for 2 weeks, then twice weekly for 10 weeks	(41-75 years)  90% White  BMI = 26.9
ERC-238 phase 3 Safety and Efficacy  Randomized, double-blind, placebo- controlled	Multi-center Canada US	To confirm the efficacy of intravaginal DHEA on dyspareunia  Postmenopausal women with dyspareunia as the most bothersome symptom	558 women enrolled/  Placebo and 0.50% DHEA/  12 weeks	Vaginal insert Once daily	59 years (40-80 years)  91% White  BMI = 26.4
ERC-230 phase 3 Safety  Open-label	Multi-center Canada US	To assess the long-term safety of intravaginal DHEA  Postmenopausal women who self- identified at least 1 mild to severe symptom of VVA	530 women enrolled/  0.50% DHEA/  12 months	Vaginal insert Once daily	58 years (43-75 years)  100% White  BMI = 26.3

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 1, pages 13-15 of 662.

**Reviewer's Comments:**

As shown in Table 14, the six clinical trials were performed on very similar populations of postmenopausal women with VVA. Five (5) of the six trials were performed using a daily dosing regimen. Trial ERC-234 used a reduced dosing regimen (daily for 2 weeks, then twice weekly for 10 weeks). Four (4) trials had the same trial design and the same 12-week trial duration (ERC-210, ERC-231, ERC-234, and ERC-238).

See Table 15 for the number and percentage of completers in the six clinical trials.

Table 15: Safety Population

Parameter	Placebo N (%)	0.25% DHEA (3.25 mg) N (%)	0.50 % DHEA (6.5 mg) N (%)	1.0% DHEA (13.0%) N (%)	Overall <sup>1</sup> N (%)
Safety					

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population <sup>2</sup>	474	282	1196	64	1542
Completed Trial					
- Yes	431 (91%)	250 (89%)	1054 (88%)	61 (95%)	1365 (89%)
- No	43 (9%)	32 (11%)	142 (12%)	3 (5%)	177 (11%)

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 3, page 17 of 662.

<sup>1</sup>Included data from Trials ERC-213, ERC-210, ERC-231, ERC-230, ERC-234, and ERC-238. Data from 10 women treated for 1 week with 1.8% DHEA in ERC-213 are not included.

<sup>2</sup>Women who received any amount of DHEA or placebo (based on diary card or medication count) and who had any post-baseline safety information available.

**Reviewer's Comments:**

Overall, 89% of postmenopausal women completed their participation in the DHEA development program. Only 11% discontinued their participation. Discontinuations are discussed in Subsection 7.3.3 Dropouts and/or Discontinuations of this review.

The application includes a summary of the demographics and other baseline characteristics of the safety population. As shown in Table 16, the six clinical trials completed had very similar populations of postmenopausal women with VVA. The safety population consisted mainly of White non-Hispanic women (92.2%; 1432 of 1542 women) followed by African American women (5.9%; 91 of 1452 women). Overall, the average age of the women enrolled in the safety population was 58.6 years with a median age of 58 and a range of 40 to 80 years. Similar age distributions are observed in all treatment groups. On average, the women measured 160.5 cm and weighed 68.2 kg with a BMI of 26.4.

Table 16: Demographic Profile of the Safety Population

Parameters	Placebo N = 474	0.25% DHEA (3.25 mg) N = 282	0.50% DHEA (6.5 mg) N = 1196	1.0% DHEA (13.0 mg) N = 64	Overall DHEA <sup>1</sup> N = 1542
<b>Race (Number of women %)</b>					
White Caucasian	427 (90.1%)	264 (93.6%)	1094 (91.5%)	63 (98.4%)	1421 (92.2%)
Black or African American	37 (7.8%)	14 (5.0%)	76 (6.4%)	1 (1.6%)	91 (5.9%)
Asian	1 (0.2%)	0 (0.0%)	9 (0.8%)	0 (0.0%)	10 (0.6%)
American Indian or Alaskan	0 (0.0%)	0 (0.0%)	4 (0.3%)	0 (0.0%)	4 (0.3%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	3 (0.3%)	0 (0.0%)	3 (0.2%)
Other	5 (1.1%)	3 (1.1%)	10 (0.8%)	0 (0.0%)	13 (0.8%)
<b>Ethnicity (Number of women, %)</b>					
Not Hispanic or Latino	450 (94.9%)	265 (94%)	1110 (92.8%)	62 (96.9%)	1437 (93.2%)
Hispanic or Latino	24 (5.1%)	17 (6.0%)	86 (7.2%)	2 (3.1%)	105 (6.8%)
<b>Age (years)<sup>2</sup></b>					
Mean	58.7	58.6	58.5	59.6	58.6
Median	58.0	58.0	58.0	59.0	58.0
Range (Min – Max)	41.0 - 75.0	40.0 – 75.0	40.0 – 80.0	46.0 – 69.0	40-0 – 80.0
<b>Anthropometric measurements (mean)</b>					
Height (cm)	161.0	160.9	160.7	158.0	160.6
Weight (kg)	68.5	68.5	68.2	66.3	68.2
Body Mass Index (kg.m <sup>2</sup> ) <sup>3</sup>	26.4	36.4	26.4	26.3	26.4
<b>Hysterectomy (Number of</b>	197 (41.6%)	131 (46.5%)	280 (23.4%)	25 (39.1)	436 (28.3%)

women, %					
<b>Ovariectomy (Number of women, %)</b>					
Any ovariectomy	135 (28.5%)	78 (27.7%)	210 (17.6%)	17 (26.6)	305 (19.8%)
Bilateral ovariectomy	94 (19.8%)	55 (19.5%)	131 (11.0%)	9 (14.1%)	195 (12.6%)

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 6, pages 21 and 22 of 662.

<sup>1</sup>Includes data for 0.25%, 0.50%, and 1.0% DHEA doses from Trials ERC-210, ERC-213, ERC-230, ERC-231, ERC-234, and ERC-238. Data for 10 women treated for 1 week with 1.8% DHEA in ERC-213 are not included.

<sup>2</sup>Age calculated from date of Day 1 and date of birth.

<sup>3</sup>BMI (Body Mass Index) = weight (kg) / height (m<sup>2</sup>).

### **Reviewer's Comments:**

The demographics and baseline characteristics of the women enrolled in the different DHEA treatment groups are similar. Caucasian women are over-represented in the safety population while significant (with respect to the percentage of the U.S. population) minority groups are underrepresented. Given that the applicant utilized a large number of geographically distinct clinical site in the DHEA development program, this underrepresentation of minority groups remains unexplained. Methods utilized to advertise and recruit women may be a contributing factor.

## 7.1.2 Categorization of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or a woman participating in a clinical investigation who administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment.

In the application, adverse events (AEs) include all and any medical experiences, regardless of their relationship to the trial drug, including, but not limited to: 1) a newly diagnosed disease, 2) pregnancy, 3) medication overdose, 4) injury, 5) surgery (scheduled or not), 6) apparent unrelated illnesses, 7) clinically significant changes in clinical pathology parameters (serum chemistry, hematology), symptomatology, and physical signs other than pre-existing conditions. A worsening in intensity and frequency of a pre-existing condition was also considered an AE. Treatment-emergent AEs (TEAEs) are defined as AEs that started or worsened after the first dose of trial drug through 30 days after the last dose of trial treatment. The ISS analysis only includes TEAEs.

Adverse events that were recorded at Baseline were not considered TEAEs unless they increased in severity after initiation of dosing of trial medication. Adverse events that were reported in relation with the pre-dose Day 1 assessment (for example, abnormal laboratory values, ASCUS (Atypical Squamous Cells of Undetermined Significance) on pre-dose Day 1 vaginal smear) were not considered TEAEs.

AEs were coded using different MedDRA versions in trials performed during the DHEA clinical development program. For the ISS analysis, all AEs were coded into system organ class (SOC) and preferred terms using MedDRA version 16.1.

The Common Terminology Criteria for Adverse Events (CTCAE) grading system was used for grading the observed intensity (severity) of an AE [Grade 1 (mild) through Grade 5 (death)].

A serious adverse event (SAE) is any untoward medical occurrence that:

- Results in death
- Is immediately (as opposed to potentially) life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability-incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that the Investigator considers serious

The causal relationship between an adverse event and the investigational product was assessed by the Investigator based on his medical judgment as: unrelated, possible, and related.

The Investigator or designee had to promptly report any SAE to EndoCeutics using the SAE report form. SAEs were also reported on the CRF of the woman. All non-SAEs were documented on the CRFs of the trial. AEs were monitored until 30 days after the completion of treatment (last dose). A phone call was made to women 30 days (30-37 days) after the last dose to inquire about AEs. The outcome of an adverse event was assessed by the investigator based on his/her medical judgment using the following definitions: recovered without sequelae, recovered with sequelae, ongoing, worsening.

In all trials included in the ISS analysis, AEs were recorded from the signature of the informed consent by the woman up to 30 days after the last dose of trial medication was taken. Therefore, for all trials in the DHEA clinical development program, TEAEs are those which occurred during a 4 month time-period, namely up to 12-weeks of treatment plus 30-day follow-up after the last dose was taken.

In order that TEAEs in open-label, 52-week Trial ERC-230 correspond approximately to the same time period of treatment in the other clinical trials for the ISS analysis, the applicant only includes those TEAEs in Trial ERC-230 that started after the first dose and were recorded up to 4 months (see the statistical analysis plan for the ISS dated June 23, 2015). However, long-term adverse events are available in the application for the 12-month daily administration of 0.50% DHEA vaginal insert in safety Trial ERC-230 divided in periods of 4 months in the ERC-230 final trial report.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

In the application, the following trials are pooled for the ISS analysis of TEAEs:

- Placebo: ERC-213, ERC-210, ERC-231, ERC-234 and ERC-238
- 0.25% DHEA: ERC-210, ERC-231 and ERC-234
- 0.50% DHEA: ERC-213, ERC-210, ERC-230 (up to Week 16), ERC-231, ERC-234 and ERC-238
- 1.0% DHEA: ERC-213 and ERC-210
- Overall: Combined data from 0.25%, 0.50% and 1.0% DHEA doses

For the evaluation of the laboratory parameters, namely hematology, chemistry, urinalysis, and steroids (DHEA and metabolites), the ISS analysis combined, as indicated below, the 12-week safety data from 5 out of 6 clinical trials, excluding from the ISS analysis, the laboratory data from the one-week phase 1 PK trial ERC-213. The following clinical trials were pooled for the ISS analysis of laboratory parameters:

- Placebo: ERC-210, ERC-231, ERC-234 and ERC-238
- 0.25% DHEA: ERC-210, ERC-231 and ERC-234
- 0.50% DHEA: ERC-210, ERC-230 (Week 12 data), ERC-231, ERC-234 and ERC-238
- Overall: Combined data from 0.25%, 0.50% and 1.0% DHEA doses

The laboratory data for 12-month Trial ERC-230 is discussed in Subsection 7.5.2 of this review.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the DHEA clinical development program, the extent of exposure was calculated as follows:

- The total number of days that each woman applied trial medication was calculated from the woman's diary card and trial drug accountability, and this total number of days was used in tabulations across the treatment groups to demonstrate any differences in total number of doses of medication used.
- The percentage of the total protocol-specified treatment amount at Week 12 was presented (defined as the number of applications performed (based on diary

data), divided by the number of expected applications during this time period as defined by the protocol.

- For the DHEA treatment groups, the total amount of DHEA received [number of applications (based on drug accountability) x 3.25 mg (0.25%), 6.5 mg (0.50%) or 13 mg (1.0%) DHEA/application] was calculated for each woman, and these data were summarized using descriptive statistics.

Total duration of treatment was calculated as the difference between the dates of last and first dose of trial medication plus one day.

The number (%) of women exposed to any dose of trial medication during the DHEA clinical development program is displayed in Table 17. During the DHEA development program, 50 postmenopausal women participated in more than one clinical trial. These women are counted in each individual trial.

Table 17: Number of Women Exposed to Various Doses of DHEA Vaginal Inserts (Safety Population)

Duration of Treatment	0.25% DHEA (3.25 mg) N = 282	0.50% DHEA (6.5 mg) N = 1196	1.0% DHEA (13 mg) N = 64	1.8% DHEA (23.4 mg) N = 10	Overall N = 1552
At least 1 day	282 (100%)	1196 (100%)	64 (100%)	10 (100%)	1552 (100%)
At least 10 weeks	251 (89.0%)	1116 (93.3%)	51 (79.7%)	0	1418 (91.4%)
At least 24 weeks	0	468 (39.1%)	0	0	468 (30.2%)
At least 50 weeks	0	435 (36.4%)	0	0	435 (28.0%)

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 5, page 19 of 662.

**Clinical Reviewer’s Comments:**

The exposures noted above at 10, 24, and 50 weeks are adequate for the chronic use of DHEA, a new chemical entity, for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

7.2.2 Explorations for Dose Response

Dose response was evaluated in three trials, ERC-210, ERC-231 and ERC-234.

7.2.2.1 Trial ERC-210

Clinical Trial ERC-210 entitled, “Topical DHEA Against vaginal atrophy (3-Months Placebo-Controlled Double-Blind Randomized Phase III Study)” was a randomized, double-blind, multicenter [2 centers in US (Jones Institute, Norfolk, VA and Women’s

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Health Research Clinic, Cleveland, OH), 5 in Quebec, Canada, and 1 in Montreal, Canada], placebo-controlled phase 3 dose-response trial conducted between June 28, 2007 (first woman enrolled) and May 23, 2008 (last woman completed trial).

The primary objective of the trial was to determine the dose-response (minimal concentration) of DHEA having a maximal effect on vaginal mucosa parameters. Local activity of DHEA was measured by changes in vaginal epithelial cell maturation (parabasal and superficial cells), and changes in vaginal pH. In addition, self-assessment was made of the three symptoms of vaginal atrophy (moderate to severe vaginal dryness, vaginal and/or vulvar irritation/itching, and vaginal pain associated with sexual activity).

The trial enrolled postmenopausal women (non-hysterectomized or hysterectomized), 40 to 75 years of age who self-identified at baseline, at least one moderate to severe symptom of vaginal dryness, vaginal and/or vulvar irritation/itching, or Vaginal pain associated with sexual activity (none, mild, moderate or severe),

Two hundred eighteen (218) postmenopausal women were randomized to receive a daily dose of:

- 0.25% (3.25 mg of DHEA vaginal insert dissolved in Whitepsol H-15 base),
- 0.50% (6.5 mg of DHEA vaginal insert dissolved in Whitepsol H-15 base),
- 1.0% (13 mg of DHEA vaginal insert dissolved in Whitepsol H-15 base), or
- Placebo vaginal insert (0 mg of DHEA dissolved in Whitepsol H-15 base).

Additional details on the design and conduct of this trial are provided in Subsection 9.5.2 in this review.

The applicant reports the following efficacy results for Clinical Trial ERC-210:

- Percentage of superficial epithelial cells: Statistically significant difference from placebo was observed for the 0.25% DHEA treatment group ( $p=0.009$ ), the 0.50% DHEA treatment group ( $p<0.0001$ ), and 1.0% DHEA treatment group ( $p=0.0002$ ).
- Percentage of parabasal epithelial cells: "All doses of DHEA are highly significantly different from placebo starting at 2 weeks and for all longer time intervals ( $p<0.0001$  for all)".
- Decrease in vaginal pH: Statistically significant difference from placebo was observed for the 0.25 % DHEA treatment group ( $p=0.008$ ), the 0.50% DHEA treatment group ( $=<0.0001$ ). and 1.0% DHEA treatment group ( $p<0.0001$ ).
- Severity score of a composite score of all most bothersome symptoms: "Statistically significant difference from placebo was observed at all DHEA ( $p=0.03$  to  $<0.0001$ )."

Safety findings in Trial ERC-210 are included in Subsection 9.5.2 of this review.

**Clinical Reviewer's Comments:**

Trial ERC-210 was not assessed by the Agency for efficacy. The trial did not assess the mean change from baseline to week 12 in the one individual moderate to severe vulvar and vaginal atrophy symptom (for example, dyspareunia) self-identified by the women as being most bothersome to her. In the final trial report for Trial ERC-210, the most bothersome symptom (MBS) calculation was based on a composite of all most bothersome symptom scores and was not adjusted for multiple comparisons.

In addition, Trial ERC-210 failed to enroll adequate numbers of women to test the MBS hypothesis, and failed to adjust for the three DHEA doses and placebo comparisons to control the overall type-1 error rate.

Trial ERC-210, submitted in this NDA application, is considered supportive of the efficacy and safety of the 0.50% DHEA vaginal insert.

7.2.2.2 Trial ERC-231

See discussion under Subsection 5.3.1 in this review.

**Clinical Reviewer's Comments:**

Results of Trial ERC-231 are confirmatory of the efficacy and supportive of the safety of the 0.50% DHEA vaginal insert.

7.2.2.3 Trial ERC-234

See discussion under Subsection 5.3.4 in this review. Safety findings are included in the integrative summary of safety (see Section 7).

**Clinical Reviewer's Comments:**

Results of Trial ERC-234 are supportive of the safety of the 0.50% DHEA vaginal insert.

7.2.2.4 Summary of Dose Exploration

An adequate exploration of dose response was conducted during the DHEA development program. DHEA doses ranged from 0.25% (3.25 mg) to 1.8% (23.4 mg). Overall results support the efficacy of the 0.50% DHEA vaginal insert alone.

### 7.2.3 Special Animal and/or In Vitro Testing

See the Pharmacology/Toxicology Review for a full discussion of special animal and *in vitro* testing of DHEA vaginal insert.

### 7.2.4 Routine Clinical Testing

The clinical evaluations conducted in the four 12-week, double-blind, placebo-controlled clinical trials and the single 52-week, open-label clinical trial met the recommended routine clinical standard for testing healthy postmenopausal women.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolites of DHEA were measured in rats and monkeys in the pharmacokinetic studies described in Section 3 of the application. See the Clinical Pharmacology Review of NDA 208470 for additional information.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

DHEA is not approved for any indication in the US.

## 7.3 Major Safety Results

### 7.3.1 Deaths

No deaths occurred during the conduct of the 6 clinical trials in the DHEA clinical development program.

### 7.3.2 Nonfatal Serious Adverse Events

Serious TEAEs are defined as any untoward medical occurrence at any dose which: 1) resulted in death, 2) was immediately (as opposed to potentially) life-threatening, 3) required inpatient hospitalization or prolongation of existing hospitalization, 4) resulted in persistent or significant disability-incapacity, 5) was a congenital anomaly/birth defect, 6) was an important medical event that the Investigator considered serious, regardless of causality.

The incidence of serious adverse events (SAEs) is displayed in Table 18, which includes data from Trials ERC-210, ERC-213 [except for 10 women treated with 1.8% (23.4 mg) DHEA], ERC-230 (up to Week 16), ERC-231, ERC-234, and ERC-238.

Table 18: Incidence of Serious Adverse Events: Safety Population; Integrated Summary of Safety

Primary System Organ Class\Preferred Term <sup>1</sup>	Placebo N = 474	0.25% DHEA (3.25 mg) N = 282	0.50% DHEA (6.5 mg) N = 1196	1.0% DHEA 13.0 mg) N = 64	Total DHEA N = 1542
<b>Number (%) of women with at least one SAE<sup>2</sup></b>	5 (1.1%)	5 (1.8%)	16 (1.3%)	0 (0.0%)	21 (1.4%)
<b>Gastrointestinal disorders</b>	3 (0.6%)	1 (0.4%)	2 (0.2%)	0 (0.0%)	3 (0.2%)
- Colitis ulcerative	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Gastritis erosive	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Gastrointestinal hemorrhage	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
- Pancreatitis	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Small intestine obstruction	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Hepatobiliary disorders</b>	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
- Cholecystitis acute	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
<b>Infections and infestations</b>	0 (0.0%)	1 (0.4%)	1 (0.1%)	0 (0.0%)	2 (0.1%)
- Bone abscess	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
- Cellulitis	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
<b>Injury, poisoning and procedural complications</b>	0 (0.0%)	1 (0.4%)	4 (0.3%)	0 (0.0%)	5 (0.3%)
- Laceration	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Muscle rupture	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Post-procedural complication	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Thoracic vertebral fracture	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
- Upper limb fracture	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
<b>Musculoskeletal and connective tissue disorders</b>	0 (0.0%)	1 (0.4%)	2 (0.2%)	0 (0.0%)	3 (0.2%)
- Kyphosis	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
- Osteoarthritis	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	2 (0.1%)
<b>Nervous system disorders</b>	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
- Movement disorders	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
<b>Psychiatric disorders</b>	1 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Stress	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Suicidal ideation	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
<b>Reproductive system and breast disorders</b>	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Uterine prolapse	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
<b>Respiratory, thoracic and mediastinal disorders</b>	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Pulmonary embolism	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
<b>Skin and subcutaneous tissue disorders</b>	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Angioedema	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
<b>Surgical and medical procedures</b>	0 (0.0%)	1 (0.4%)	4 (0.3%)	0 (0.0%)	5 (0.3%)
- Appendectomy	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Cholecystectomy	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
- Gastric bypass	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Hernia hiatus repair	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
- Knee arthroplasty	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
<b>Vascular disorders</b>	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)

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- Arteriovenous fistula	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)
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Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 21, pages 77-78 of 662.

<sup>1</sup>The worst severity per system organ class and preferred term per woman is counted.

<sup>2</sup>Any event that starts or worsens after start of treatment through 30 days after the last dose of trial treatment. (AEs coded with MedDRA version 16.1).

As shown in Table 18, a total of 21 women experienced SAEs in the DHEA clinical development program, per the NDA application. However, Table 18 only includes the first 16-weeks of the open-label, 52-week, Trial ERC-230.

For the data depicted in Table 18, 5 women were in the placebo treatment group, 5 women were in the 0.25% DHEA treatment group, 16 women were in the 0.50% DHEA treatment group, and none were in the 1.0% DHEA treatment group. Data from 10 women treated for 1 week with 1.8% DHEA in phase 1 PK Study ERC-213 is not included in this table because these women received trial drug for only one week. A total of 45 SAEs were reported among the treatment groups. Per the application, only one of the SAEs (occurring in woman number 230-02-061 in the 0.50% DHEA treatment group; invasive ductal breast carcinoma) was assessed as possibly drug-related to trial medication by the investigator.

**Clinical Reviewer’s Comments:**

As shown in Table 18, a small percentage of women in the DHEA development program experienced serious adverse events, less than 2% overall. Reported serious adverse events were similar between placebo and the 0.25 % and 0.50% DHEA treatment groups. The reported SAEs in Table 18 do not raise safety concerns for the 0.50% DHEA dose.

Overall, 14 women discontinued due to a SAE. More detailed information follows.

Five (5) women experienced SAEs in the placebo treatment groups. These women are identified as follows:

1. Number 234-10-004 - A woman 63 years of age, was seen in the emergency room for epigastric pain and nausea on Day 36. She was diagnosed with pancreatitis and hospitalized. She sustained a right rotator cuff injury during her hospitalization. She discontinued the clinical trial. The investigator assessed these SAEs as unrelated to trial medication.
2. Number 234-12-026 – A woman 56 years of age, with a history of progressive dyspnea (undeclared at Screening) was under the care of a pneumologist. She had a ventilation-perfusion scan of the lungs that revealed a pulmonary embolism of a superior segment of the inferior lobe of the right lung. She was hospitalized and received treatment. She was discontinued because this SAE violated the trial exclusion criteria. Her SAE was ongoing at discontinuation. The investigator assessed this SAE as unrelated to trial medication.

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3. Number 234-21-011 - A woman 56 years of age, was seen in the emergency room with abdominal pain on Day 25. A CT scan of the abdomen revealed a partial small bowel obstruction. She was hospitalized and received treatment. She recovered without sequelae and completed the clinical trial. The investigator assessed this SAE as unrelated to trial medication.
4. Number 234-50-001 - A woman 56 years of age, was seen in the emergency room with abdominal pain and nausea on Day 29. An esophagogastroduodenoscopy showed a hiatal hernia and small gastric erosion in the hernia. She was hospitalized and received treatment. She recovered without sequelae and completed the clinical trial. The investigator assessed this SAE as unrelated to trial medication.
5. Number 234-50-014 - A woman 64 years of age, reported stress and was admitted to the hospital via the emergency room on Day 30 for bizarre behavior and seizure-like activity that had evolved over a period of 2 months. Her brain CT, MRI and EEG were reported as normal. She was seen as an outpatient by a psychiatrist. She recovered without sequelae and completed the clinical trial. The investigator assessed this SAE as unrelated to trial medication.

### **Clinical Reviewer's Comments:**

This reviewer agrees with the Investigator's assessments for these 5 women assigned to the placebo treatment group in the DHEA clinical development program.

Five (5) women experienced SAEs in the 0.25% DHEA treatment groups in Trial ERC-210, ERC-231, and ERC-234. These women are identified as follows:

1. Number 210-02-035 - A woman 62 years of age, was seen in the emergency room on Day 11 with abdominal pain. She was hospitalized for symptomatic cholelithiasis and underwent an endocholecystectomy. She recovered without sequelae and completed the clinical trial. The investigator assessed this SAE as unrelated to 0.25% DHEA vaginal insert.
2. Number 231-11-014 - A woman 64 years of age, noticed redness on her left hip on Day 34. She was seen in the emergency room and underwent an ultrasound of the left hip that showed a collection of fluid compatible with an abscess of the lateral face of the left major trochanter. She underwent treatment, recovered without sequelae, and completed the clinical trial. The investigator assessed this SAE as unrelated to trial medication.
3. Number 231-26-001 - A woman 65 years of age, was involved in a boating accident and sustained multiple injuries including T2-T4 thoracic vertebral fracture. She underwent back surgery and was placed in a back brace. She discontinued the clinical trial. The investigator assessed this SAE as unrelated to trial medication.
4. Number 231-30-017 - A woman 52 years of age, was seen in the emergency room on Day 31 complaining of bright red blood in her stools. She underwent

colonoscopy which revealed severe proctitis, a small hemorrhoid, and a polyp at 65 cm of the anal margin. On Day 60, she was again seen in the emergency room for intermittent right upper quadrant abdominal pain. An ultrasound showed cholelithiasis with thickening of the gallbladder wall consistent with acute cholecystitis. She underwent a laparoscopic cholecystectomy. She recovered without sequelae and completed the clinical trial. The investigator assessed these SAEs as unrelated to trial medication.

5. Number 234-66-012 - A woman 53 years of age, experienced muscle stiffness and spasms on Day 80 and was hospitalized. She was unwilling to disclose her medical records. Her lumbar puncture, CT scan, MRI of the brain, and EEG were all reported as normal. No further information is provided. Her SAEs are reported as ongoing. She completed the clinical trial. The investigator assessed this SAE as unrelated to trail medication.

**Clinical Reviewer's Comments:**

This reviewer agrees with the Investigators' assessments of these 5 women.

Twenty-six women experienced 33 SAEs in the 0.50% DHEA treatment group. These 26 women include women who participated beyond Week 16 in 52-week Trial ERC-230. Five (5) of these 26 women experienced more than one SAE. Overall, 14 of these 26 women discontinued trial participation. These women are identified as follows:

1. Number 210-05-012 - A woman 64 years of age, presented to the emergency room on Day 4 with a several-day history of anorexia, nausea, and right lower quadrant abdominal pain. She was diagnosed with appendicitis and underwent an appendectomy. She recovered without sequelae and completed the clinical trial. The investigator assessed this SAE as unrelated to 0.50% DHEA vaginal insert.
2. Number 230-01-028 - A woman 66 years of age, was seen in the emergency room for abdominal pain and rectal bleeding on Day 183 (b) (6), evening of her Week 26 visit). A colonoscopy performed on (b) (6), revealed ischemic colitis of the splenic flexure. The woman was managed conservatively. She took her last dose of trial medication on August 25, 2011. The investigator elected to discontinue this woman. The investigator assessed this SAE as unrelated to trial medication. A control colonoscopy, performed on (b) (6), showed no signs of colitis.
3. Number 230-01-036 - A woman 58 years of age, reported pulsatile tinnitus in her right ear on Day 8 (March 25, 2011). A cerebral magnetic resonance angiogram, performed on (b) (6) revealed a dural arteriovenous fistula of the right mastoid with probable chronic thrombosis of the right transverse sinus. The woman was discontinued on June 12, 2011 (Day 88). The fistula was occluded by endovascular embolization on (b) (6). The investigator assessed this SAE as unrelated to trial medication.

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4. Number 230-01-038 - A woman 62 years of age, with a medical history of dyspepsia, gastroesophageal reflux disease, anxiety, insomnia, essential hypertension, and hypothyroidism. She was seen in the emergency room with epigastric pain, nausea, and diarrhea on [REDACTED] (b) (6) (Day 183). Her gastroscopy was normal. She was hospitalized and treated (adjustment of her proton pump inhibitor medication), recovered without sequelae, and completed the clinical trial. The investigator assessed these SAEs and unrelated to trial medication.
5. Number 230-02-011 - A woman 66 years of age, with a history of hypertension, was seen in the emergency room with abdominal pain, nausea, vomiting and constipation on [REDACTED] (b) (6) (first dose of trial medication on January 8, 2011). A duodenoscopy revealed a narrowing of the fourth segment of the duodenum compatible with Crohn's disease. She underwent a partial resection of the duodenum on [REDACTED] (b) (6). The woman elected to discontinue the trial. The investigator assessed this SAE as unrelated to trial medication.
6. Number 230-02-049 - A woman 61 years of age, was seen in the emergency room with abdominal pain and nausea on [REDACTED] (b) (6). An abdominal and pelvic CT showed signs of appendicular peritonitis. She underwent a laparoscopic appendectomy, and recovered without sequelae. She completed the clinical trial. The investigator assessed this SAE as unrelated to trial medication.
7. Number 230-02-061 - A woman 55 years of age, with a history of a stereotactic biopsy of the right breast for microcalcifications (September 2005), had a pre-trial mammogram considered normal based on the absence of changes compared to the previous exam (December 2010). This woman reported a history of not taking hormone therapy. She took her first dose of trial medication on March 12, 2011; her last dose on February 29, 2012. Her Week 52 breast examination was normal. Her post-trial mammogram on Day 357 revealed a new cluster of polymorphic microcalcifications in the left breast, confirmed by a second exam performed at higher magnification. Following a stereotactic biopsy performed on [REDACTED] (b) (6), she had a segmental mastectomy [REDACTED] (b) (6) with a final histologic diagnosis of infiltrating carcinoma positive for estrogen and progesterone receptors. The investigator assessed this SAE as possibly drug-related to 0.50% DHEA vaginal inserts. The applicant disagrees "since breast tumors evolve over a much longer time period before reaching such stage. Moreover, DHEA inhibits breast tumor growth in numerous breast cancer models, including human breast cancer cells in vitro and tumors in vivo (Labrie, El-Alfy et al. 2003)." In addition, "this woman's serum steroid concentrations did not vary significantly and remained well within the normal postmenopausal range during the trial, including estrone sulfate, parameter of total estrogen activity which was lower at 52-weeks compared to baseline."

The results of evaluation of serum steroid concentrations in this woman are as follows:

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- DHEA Day 1 = 1388 pg/mL; Week 52 = 3825 pg/mL (normal range = 560 - 3900 taken from Labrie, Cusan et al, 2008 in the application)
  - Androstenedione Day 1 = 351 pg/mL; Week 52 = 508 pg/mL (normal range = 170 - 710 taken from Labrie, Cusan et al, 2008 in the application)
  - Testosterone Day 1 = 103 pg/mL; Week 52 = 144 pg/mL (normal range = 60 - 260 taken from Labrie, Cusan et al, 2008 in the application)
  - DHT Day 1 = 30.5 pg/mL; Week 52 = 69.7 pg/mL (normal range = 10 - 70 taken from Labrie, Cusan et al, 2008 in the application)
  - Estradiol Day 1 = 4.4 pg/mL; Week 52 = 5.0 pg/mL (normal range = 1.0 – 9.3 taken from Labrie, Cusan et al, 2008 in the application)
  - Estrone Day 1 = 18.3 pg/mL; Week 52 = 17.9 pg/mL (normal range = 7.6 – 34.8 taken from Labrie, Cusan et al, 2008 in the application)
  - Estrone-sulfate Day 1 = 254 pg/mL; Week 52 = 200 pg/mL (normal range = 40 - 590 taken from Labrie, Cusan et al, 2008 in the application)
8. Number 230-02-091 - A woman 64 years of age, underwent a lumbar-sacral laminectomy in 2010. She took her first dose of trial medication on April 19, 2011. She reported thoracic pain and dyspnea on Day 252 (b) (6) and was hospitalized. She reported an episode of right calf pain and edema in October 2011 following a long car ride, but did not seek medical attention at that time. A ventilation/perfusion scan of the lungs revealed bilateral small subsegmental pulmonary emboli. Tests performed indicated no deficiency in anticoagulation factors (Protein C, Protein S, antithrombin III) or mutations associated with hypercoagulability disorders (Factor V Leiden, prothrombin, G20210A). She received low molecular weight heparin and was discharged on (b) (6). The woman elected to discontinue her participation in the clinical trial. The investigator assessed this SAE as unrelated to trial medication.

The results of evaluation of serum steroid concentrations in this woman are as follows:

- DHEA Day 1 = 1087 pg/mL; Week 52 = 1043 pg/mL (normal range = 560 - 3900 taken from Labrie, Cusan et al, 2008 in the application)
- Androstenedione Day 1 = 155 pg/mL; Week 52 = 208 pg/mL (normal range = 170 - 710 taken from Labrie, Cusan et al, 2008 in the application)
- Testosterone Day 1 = 113 pg/mL; Week 52 = 127 pg/mL (normal range = 60 - 260 taken from Labrie, Cusan et al, 2008 in the application)
- DHT Day 1 = 28.2 pg/mL; Week 52 = 24.2 pg/mL (normal range = 10 - 70 taken from Labrie, Cusan et al, 2008 in the application)
- Estradiol Day 1 = 2.6 pg/mL; Week 52 = 2.8 pg/mL (normal range = 1.0 – 9.3 taken from Labrie, Cusan et al, 2008 in the application)
- Estrone Day 1 = 10.9 pg/mL; Week 52 = 8.9 pg/mL (normal range = 7.6 – 34.8 taken from Labrie, Cusan et al, 2008 in the application)

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- Estrone-sulfate Day 1 = 95.6 pg/mL; Week 52 = 73.2 pg/mL (normal range = 40 - 590 taken from Labrie, Cusan et al, 2008 in the application)
9. Number 230-05-036 A woman 59 years of age, with a history of osteoarthritis in the right knee and a prior knee replacement surgery, reported an exacerbation of her right knee osteoarthritis. She was hospitalized and underwent right knee replacement surgery. Medical records were not provided. She was lost to follow-up. The investigator assessed this SAE as unrelated to trial medication.
  10. Number 230-07-001 - A woman 59 years of age, was hit by a car and suffered a fractured femur on Day 274 (January 2012). She was temporarily discontinued, hospitalized, and treated. She recovered without sequelae and completed the trial. The investigator assessed this SAE as unrelated to trial medication.
  11. Number 230-10-007 - A woman 56 years of age, with a history of osteoarthritis and arthroscopic surgery of the left knee, was diagnosed with a tear of the right posterior tibial tendon (no other information provided). She underwent a surgical repair on (b) (6), and completed the clinical trial on April 3, 2012. The investigator assessed this SAE as unrelated to trial medication.
  12. Number 230-15-004 - A woman 63 years of age reported worsening of her right hip pain on Day 162. She underwent a right total hip arthroplasty. Postoperatively, she developed a staphylococcal infection considered life threatening. The Investigator discontinued her from the trial and assessed this SAE as unrelated to trial medication.
  13. Number 230-16-003 - A woman 47 years of age, with a past medical history for hypothyroidism, multiple sclerosis, depression, insomnia, migraines, asthma, and intermittent abdominal pain, took her first dose of trial medication on April 18, 2011. At Week 52 (April 16, 2016), she weighed 67.2 kg (compared to 76.4 kg at Screening). She had an ovarian mass found on ultrasound on (b) (6) (Day 393). She then had an exploratory laparotomy on (b) (6) with removal of her uterus, adnexa, omentum, and a portion of her rectum. The final histologic diagnosis was stage IIIC ovarian serous and clear cell carcinoma. The notes from her multidisciplinary gynecologic oncology committee indicate a family history of breast and ovarian cancer, and a BRCA1 mutation. The investigator assessed this SAE as unrelated to trial medication.

The results of evaluation of serum steroid concentrations in this woman are as follows:

- DHEA Day 1 = 6919 pg/mL; Week 52 = 1869 pg/mL (normal range = 560 - 3900 taken from Labrie, Cusan et al, 2008 in the application)
- Androstenedione Day 1 = 786 pg/mL; Week 52 = 309 pg/mL (normal range = 170 - 710 taken from Labrie, Cusan et al, 2008 in the application)
- Testosterone Day 1 = 183 pg/mL; Week 52 = 199 pg/mL (normal range = 60 - 260 taken from Labrie, Cusan et al, 2008 in the application)
- DHT Day 1 = 92 pg/mL; Week 52 = 132 pg/mL (normal range = 10 - 70 taken from Labrie, Cusan et al, 2008 in the application)

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- Estradiol Day 1 = 12.5 pg/mL; Week 52 = 4.1 pg/mL (normal range = 1.0 – 9.3 taken from Labrie, Cusan et al, 2008 in the application)
  - Estrone Day 1 = 17.3 pg/mL; Week 52 = 21.7 pg/mL (normal range = 7.6 – 34.8 taken from Labrie, Cusan et al, 2008 in the application)
  - Estrone-sulfate Day 1 = 108 pg/mL; Week 52 = 132 pg/mL (normal range = 40 - 590 taken from Labrie, Cusan et al, 2008 in the application)
14. Number 230-18-018 - A woman 57 years of age, lacerated both of her thumbs in a work-related accident on June 4, 2011. She had reconstructive surgery and discontinued the clinical trial. No further information is provided. The investigator assessed this SAE as unrelated to trial medication.
  15. Number 230-22-003 - A woman 55 years of age, with a medical history of hypertension and arthritis, reported swelling of the lips (angioedema) on Day 15 and was seen in the emergency room. She was taking lisinopril (40 mg) and was told she was allergic to it. She presented one week later with similar symptoms because she did not discontinue her Lisinopril. She discontinued trial participation. The investigator assessed this SAE as unrelated to trial medication.
  16. Number 230-24-023 - A woman 69 years of age, reported worsening of known osteoarthritis in her left knee on Day 16 (first dose of trial medication on March 9, 2011). She underwent a left total knee replacement (b) (6). On Day 216, her MRI showed spinal stenosis and she had back surgery (b) (6) with resulting pain in her upper left leg. She had a left hip total arthroplasty on (b) (6). She completed the trial. The investigator assessed these SAEs as unrelated to trial medication.
  17. Number 230-24-042 - A woman 62 years of age, reported worsening of her frequency/urgency symptoms due to her prolapsed uterus at Week 12. At Week 26, she underwent a hysterectomy, and discontinued trial participation. The investigator assessed this SAE as unrelated to trial medication.
  18. Number 230-30-013 - A woman 54 years of age, had a history of prolapsed bladder, cystocele and rectocele. She took her first dose of trial medication on April 13, 2011. During the trial, she elected to have a vaginal hysterectomy with cystocele and rectocele repair. She elected to discontinue trial participation (last dose of trial medication on October 10, 2011). The investigator assessed these SAEs as unrelated to trail medication.
  19. Number 230-44-004 - A woman 51 years of age, with a history of hypothyroidism and depression, was hospitalized for pancreatitis on Day 86 (b) (6) based on an elevated blood lipase value (134 U/L versus a normal range of 15-60). She was temporarily discontinued, and then returned to complete trial participation. The investigator assessed this SAE as unrelated to trial medication.
  20. Number 231-30-001 - A woman 51 years of age had a medical history of depression. On Day 29 she presented with signs of suicidal ideation and was hospitalized for a three-day observation period (subsequently she remained for

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12 days). She discontinued trial medication for this life threatening SAE. The investigator assessed this SAE as unrelated to trial medication.

21. Number 234-39-015 - A woman 67 years of age, with type 2 diabetes, obesity, chronic bronchitis, hypertension, and hypercholesterolemia, was seen in the emergency room on Day 17 with swelling, redness, and pain of the left side of her face after she squeezed a pimple. A CT scan revealed cellulitis. She was admitted, received intravenous antibiotics, and underwent surgical incision of her facial abscess. She elected to discontinue trial medication. The investigator assessed this SAE as unrelated to trial medication.
22. Number 238-21-044 - A woman 56 years of age, with a history of hiatal hernia, was admitted to the hospital for an elective hiatal hernia repair on (b) (6) (first dose of trial medication on September 9, 2014). She was temporarily discontinued, but returned to complete the trial. The investigator assessed this SAE as unrelated to trial medication.
23. Number 238-78-003 - A woman 68 years of age, with a history of bilateral knee osteoarthritis, was admitted to the hospital for an elective total left knee arthroplasty on (b) (6) (first dose of trial medication on April 7, 2014). She was temporarily discontinued, but returned to complete the trial. The investigator assessed this SAE as unrelated to trial medication.
24. Number 238-79-009 - A woman 50 years of age, with a history of type 2 DM, dyslipidemia, hypertension, and depression, was admitted to the hospital for elective gastric bypass surgery on (b) (6) (first dose of trial medication on July 25, 2014). Following discharge, she was readmitted for post gastric bypass surgery complications. She was terminated early for the reason of lost to follow-up. The investigator assessed these SAEs as unrelated to trial medication.
25. Number 238-80-057 - A woman 65 years of age, with a history of ulcerative colitis, was admitted to the hospital for an ulcerative colitis flare on Day 84 (b) (6); first dose of trial medication on September 26, 2014). During hospitalization she developed anemia requiring blood transfusions. She recovered with sequelae, and returned to complete the clinical trial. The investigator assessed this SAE as unrelated to trial medication.
26. Number 238-85-020 - A woman 66 years of age, with hypertension, fell and sustained a left humerus fracture. She was admitted to the hospital on Day 27 (b) (6) for left arm surgery. The investigator discontinued her from the trial because she was unable to perform trial-related activities due to arm pain. The investigator assessed this SAE as unrelated to trial medication.

### **Clinical Reviewer's Comments:**

This reviewer agrees with the investigators' assessments for these 26 women who received treatment up to 52-weeks in a 0.50% DHEA treatment arm in the trials for prasterone.

Additional comment is warranted for participating woman Number 230-02-061, who was diagnosed with infiltrating carcinoma of the left breast. As stated

above, the investigator considered this SAE as ‘possibly-related’ to 0.50% DHEA vaginal insert. Although her 2005 history of microcalcifications in her left breast (no malignant changes identified) places her at increased risk, her baseline mammogram was reported as normal based on the absence of changes compared to her previous mammogram on December 2010. Therefore, it is not possible to completely rule out the 52-weeks of 0.50% DHEA vaginal insert exposure as a contributing factor to the May 2012 diagnosis of infiltrating carcinoma. It is interesting to note, however, that this woman had an increase in serum DHEA concentration at Week 52 (3825 pg/mL at Week 52 versus 1388 pg/mL on Day 1), but no appreciable increase in her serum estradiol concentration at Week 52 (5.0 pg/mL at Week 52 versus 4.4 pg/ml on Day 1).

Overall, the reported SAEs in 1196 women exposed to 0.50% DHEA vaginal insert up to 52-weeks do not raise concerns for the safety of the 0.50% DHEA vaginal insert for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

### 7.3.3 Dropouts and/or Discontinuations

In the ISS, the applicant presented discontinuations for participating women in the safety population in the 6 clinical trials conducted under the DHEA clinical development program. The safety population consists of 1,542 women exposed to DHEA and 474 women exposed to placebo. Discontinuations of women are based on the reason for discontinuation reported on the woman’s case report form. Table 19 includes the reported findings from these 6 clinical trials.

Table 19: Overall Profile of Participating Women Who Discontinued Trial Drug: Safety Population

Parameters	Placebo N = 474	0.25% DHEA N = 282	0.50% DHEA N = 1196	1.0% DHEA N = 64	Overall N = 1542 <sup>1</sup>
<b>Completed Trial N (%)</b>					
- Yes	431 (91%)	250 (89%)	1054 (88%)	61 (95%)	1365 (89%)
- No	43 (9%)	32 (11%)	142 (12%)	3 (5%)	177 (11%)
<b>Reason for Discontinuation N (%)</b>					
- Adverse event	10 (23%)	11 (34%)	40 (28%)	1 (33%)	52 (29%)
- Non-compliant	2 (5%)	0 (0%)	5 (4%)	0 (0%)	5 (3%)
- Lost to follow-up	1 (2%)	0 (0%)	14 (10%)	0 (0%)	14 (8%)
- Withdrew consent	14 (33%)	3 (9%)	42 (30%)	1 (33%)	46 (26%)
- Investigator’s decision	1 (2%)	1 (3%)	5 (4%)	0 (0%)	6 (3%)
- Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

- Other	15 (35%)	17 (53%)	36 (25%)	1 (33%)	54 (31%)
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Source: NDA 208470, Integrated Summary of Safety, Table 10, page 34 of 662.

<sup>1</sup>Includes data for 0.25%, 0.50%, and 1.0% DHEA doses for Trials ERC-210, ERC-213, ERC-230, ERC-231, ERC-234, and ERC-238. Data for 10 women treated for 1 week with 1.8% DHEA in Trial ERC-213 are not included.

**Clinical Reviewer’s Comments:**

As shown in Table 19, the percentage of women who discontinued from the three DHEA treatment groups and the placebo treatment group are similar. The largest percentage of discontinuations occurred in the 0.50% DHEA treatment group, the largest represented treatment group in the DHEA clinical development program. “Subject withdrew consent” accounted for the largest number of discontinuations in the 0.50% DHEA treatment group, followed by adverse events, and “Other”.

Overall, the most common reason for discontinuations in all DHEA treatment groups in the DHEA clinical development program was “Other”, followed by adverse events. However, the discontinuation for “Other” was higher in the placebo treatment group (35%) than in the 0.50% DHEA treatment group (25%) and in the overall combined DHEA treatment groups (31%).

“Other” included violations of trial inclusion/exclusion criteria, mostly involving the proportion of superficial cells on a vaginal smear collected on Day 1 not meeting the protocol criterion for the percentage of superficial cells, and investigator’s decision. See a discussion of the corrected Safety (cSafety) population under 5.3.1.6 Statistical Methodology.

The following information pertains to the 10 women who discontinued due to TEAEs in the placebo treatment group:

1. Number 210-01-065 - A woman 64 years of age discontinued due to a Low grade Squamous Intraepithelial Lesion (LSIL) (MedDRA Preferred Term “cervical dysplasia”) reported on the Week 4 vaginal smear. The investigator assessed this AE as mild in intensity and unrelated to the trial medication.
2. Number 210-03-017 - A woman 63 years of age, discontinued due to traumatic injuries to both hands, right hip, both feet and right hip suffered during a robbery. The investigator assessed this adverse event as moderate in intensity and unrelated to trial medication.
3. Number 231-04-009 - A woman 59 years of age, discontinued due to symptoms of moderate vaginal burning sensation and moderate vaginal tingling. The investigator assessed these symptoms as possibly related to the trial medication. The applicant considers these AEs as unrelated to trial drug because the insert vehicle (Witepsol) is non-irritating.

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4. Number 234-10-004 - A woman 63 years of age discontinued due to a moderate tear in her right rotator cuff while hospitalized for an SAE. The investigator assessed this AE as unrelated to trial medication.
5. Number 234-15-004 - A woman 59 years of age discontinued due to symptoms of moderate abdominal bloating accompanied by intermittent diarrhea and abdominal cramping. The investigator assessed this AE as unrelated to trial medication.
6. Number 238-21-003 - A woman 61 years of age discontinued due to symptoms of a facial rash, oily skin, bumps (acne) on the face, thinning hair and increased facial hair. The investigator assessed these symptoms as mild and unrelated to trial medication.
7. Number 238-36-015 - A woman 63 years of age discontinued due to symptoms of moderate vaginal itching. The investigator assessed this AE as unrelated to trial medication.
8. Number 238-45-012 - A woman 53 years of age discontinued due to symptoms of nausea, pelvic pain, back spasm, emotional (weepy), migraine and bloated. The investigator assessed all symptoms as mild and possibly-related to trial medication.
9. Number 238-54-001 - A woman 60 years of age discontinued due to moderate mood changes and moderate aggressiveness. The investigator assessed these symptoms as possibly-related to the trial medication.
10. Number 238-54-020 - A woman 54 years of age discontinued due to moderate insomnia, moderate anxiety, mild nausea, and mild chest palpitations. The investigator assessed these AEs as possibly-related to trial medication.

In addition, Number 234-12-026, in the placebo treatment group, discontinued Trial ERC-234 due to a serious TEAE. This woman was being evaluated by a pneumologist for a history of progressive dyspnea which predated her participation in the trial. She did not declare this condition at Screening. She had a pre-scheduled ventilation/perfusion scan of the lungs that showed an embolism of a segment of the right inferior lobe (MedDRA preferred term, pulmonary embolism). This adverse event was reported as a serious TEAE. The woman was discontinued because this serious adverse event (SAE) violated the exclusion criteria for the trial. The investigator and applicant agreed that this adverse event was unrelated to the trial drug.

### **Clinical Reviewer's Comments:**

This reviewer agrees with the individual investigator's assessments regarding these TEAEs in the placebo treatment group with the following exceptions:

- Nausea, pelvic pain, back pain, weepy, migraine, and bloating in Number 238-45-012; possibly-related
- Mood change in Number 238-54-012, possibly related
- Insomnia, anxiety, nausea, and chest palpitations in Number 238-54-001; possibly-related

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The following information pertains to the 11 women who discontinued due to TEAEs in the 0.25% DHEA treatment group:

1. Number 210-02-041 - A woman 62 years of age discontinued due to breast discomfort with a mild intensity, and mucous in her stool for 1 day. These AEs resolved spontaneously without medical treatment. The investigator assessed the breast discomfort as possibly-related, and stool mucous as unrelated to trial medication.
2. Number 210-02-050 - A woman 58 years of age discontinued due to mild chin hairiness (hirsutism) and mild pimples (acne) on her chin. The investigator assessed these AEs as possibly-related to trial medication. The applicant disagrees because it is inconsistent with the known pharmacologic properties of DHEA. Medical history = hypertension and lumbar pain; concomitant medications = angiotensin-converting enzyme inhibitor (Quinapril) and a calcium channel blocker (Amlodipine); first dose = 1/28/08; hirsutism = 3/1/08; acne = 3/3/08; last dose = 3/25/08, Investigator was unable to confirm AEs at end-of-trial exam.
3. Number 210-03-020 - A woman 58 years of age discontinued due to finding of a 5 mm nodular density in her right breast on mammogram. She took her first dose of trial medication on 2/25/08. Her abnormal mammogram was reported on 3/10/08. Follow-up exams were normal. The investigator assessed this AE as unrelated to trial medication.
4. Number 210-05-046 - A woman 53 years of age discontinued due to mild vaginal itching (vulvovaginal pruritus). She reported mild vaginal itching on Day 1, no vaginal itching on Day 14, and moderate vaginal itching at Week 4 after which she discontinued. The investigator assessed this AE as possibly-related to trial medication. The applicant disagrees because "it is inconsistent with the known pharmacologic properties of DHEA."
5. Number 210-02-003 - A woman 70 years of age discontinued due to symptoms of palpitations, dysgeusia (minty taste), and mild hot flashes. The investigator assessed these AEs as unrelated to trial medication.
6. Number 231-05-050 - A woman 60 years of age discontinued following the discovery of LSIL on a vaginal smear at Day 1. The investigator assessed this AE as mild and unrelated to trial medication.
7. Number 231-13-001 - A woman 52 years of age discontinued due to moderate application site discharge. The investigator assessed this AE as related to trial medication.
8. Number 234-11-005 - A woman 64 years of age discontinued because she had Atypical Squamous Cells of Undetermined Significance (ASCUS) on her Week 2 vaginal smear, a low-grade squamous intraepithelial lesion (LSIL) on her Week 6 vaginal smear, and a positive Human Papilloma Virus (HPV) test. She underwent a colposcopic examination which did not reveal any abnormal findings. The investigator assessed this AE as moderate in intensity and unrelated to trial medication

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9. Number 234-50-004 - A woman 54 years of age discontinued due to a moderate lack of energy (asthenia) and moderate irritability after 5 doses of trial medication. The investigator assessed these AEs as unrelated to trial medication.
10. Number 234-60-021 - A woman 70 years of age discontinued due to mild urticaria. The investigator assessed this AE as unrelated to trial medication.
11. Number 231-26-001 - A woman 65 years of age was involved in a boating accident in which she sustained multiple injuries including a severe fracture of the T2-T4 thoracic vertebrae (MedDRA preferred term, thoracic vertebral fracture). She underwent back surgery and was placed in a back brace. The woman also reported severe thoracic kyphosis (MedDRA preferred term, kyphosis). These adverse events were reported as serious TEAEs. She discontinued the trial because she was unable to perform trial related activities. The investigator assessed these adverse events as unrelated to intravaginal DHEA.

### **Clinical Reviewer's Comments:**

This reviewer agrees with the individual investigator's (and not necessarily the applicant's) assessments regarding these TEAEs. Specifically, this reviewer agrees with the following TEAEs as possibly drug-related:

- Hirsutism: Participating woman Number 210-02-050
- Acne: Participating woman Number 210-02-050
- Vaginal itching: Participating woman Number 210-05-046

Although DHEA was discovered in the early 1930s and is sold as a dietary supplement in the US, long-term effects of its use is largely unknown. However, oral DHEA is reported to be associated with acne, facial hair on women, irritability, restlessness, hair thinning or hair loss, heart palpitations or rhythm disturbances, among other side effects.

Eight of the 40 women, who discontinued due to TEAEs in the 0.50% DHEA treatment group, had TEAEs that were considered drug-related by the investigator:

- Number 230-02-001 - A woman 55 years of age, experienced moderate application site discharge beginning on Day 1, January 7, 2011, and discontinued Trial ERC-230 on April 5, 2011. The investigator assessed this AE as drug-related to trial medication.
- Number 230-02-026 - A woman 58 years of age, reported moderate vulvar burning beginning on Day 1, February 14, 2011, and discontinued Trial ERC-230 on May 6, 2011. The investigator assessed this AE as drug-related to trial medication.
- Number 230-02-029 - A woman 62 years of age, experienced mild application site discharge (unknown date of start) and discontinued Trial ERC-230 on

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September 29, 2011. The investigator assessed this AE as drug-related to trial medication.

- Number 230-18-005 - A woman 61 years of age, reported moderate application site discharge on Day 67, April 29, 2011, and mild vulvar redness on Day 75, May 6, 2011, that lasted for 1 day. She discontinued Trial ERC-230 on May 10, 2011. The investigator assessed the application site discharge as drug-related, and the vulvar redness as possibly-related to trial medication.
- Number 230-28-003 - A woman 61 years of age, reported moderate application site discharge beginning on Day 1, May 5, 2011, and discontinued Trial ERC-230 on September 15, 2011. The investigator assessed this AE as drug-related to trial medication.
- Number 238-02-003 - A woman 60 years of age, reported moderate application site discharge beginning on Day 6, April 30, 2014, and discontinued Trial ERC-238 on June 27, 2014. The investigator assessed this AE as drug-related to trial medication.
- Number 238-21-015 - A woman 58 years of age, reported mild vaginal irritation and mild application site discharge beginning on Day 3, April 24, 2014, and discontinued Trial ERC-238 on June 3, 2014. The investigator assessed these AEs as drug-related to trial medication. The applicant disagreed with the Investigator's assessment for vaginal irritation as this AE "cannot be attributed to the trial drug because neither DHEA nor the vehicle Witepsol is irritating."

### **Reviewer's Comments:**

This reviewer agrees with the investigators' assessments of these TEAEs as drug-related. Witepsol H15 is the only excipient in Intrarosa.

Eleven (11) of the 54 reported TEAEs in the 40 women who discontinued because of a TEAE, were considered possibly-drug related by the investigator:

- Number 230-02-024 - A woman 58 years of age, reported a mild burning sensation on the posterior aspects of her thighs beginning on Day 15, February 7, 2011, and discontinued Trial ERC-230 on May 2, 2011. The investigator assessed this AE as possibly-related to trial medication. The applicant disagrees.
- Number 230-02-041 - A woman 63 years of age, reported vaginal discharge on February 3, 2011 and moderate increase in libido on May 17, 2011, and discontinued Trial ERC-230 on April 27, 2011. She did not have a sexual partner at the time and found this AE disturbing. The investigator assessed this AE as possibly-related to trial medication.
- Number 230-03-021 - A woman 54 years of age, reported mild breast tenderness beginning on Day 3, January 27, 2011, and mild nausea beginning on Day 12. She discontinued Trial ERC-230 on July 6, 2011. The breast examination conducted upon her discontinuation was reported as normal. The investigator assessed these AEs as possibly-related to trial medication.

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- Number 230-05-024 - A woman 55 years of age, reported moderate vaginal irritation (vulvovaginal discomfort) beginning on Day 274, January 17, 2012, and discontinued Trial ERC-230 on March 1, 2012. The investigator assessed this AE as possibly-related to trial medication. The applicant disagrees because “neither DHEA nor the vehicle Witepsol is irritating.”
- Number 230-13-009 - A woman 56 years of age, reported mild arthralgia on Day 41, June 7, 2011, and discontinued Trial ERC-230 on October 25, 2011. The investigator assessed this AE as possibly-related to trial medication.
- Number 230-18-005 - A woman 61 years of age, reported moderate application site discharge beginning on Day 68, April 29, 2011, and mild vulvar redness (vulvovaginal erythema) on Day 75, May 10, 2011. She discontinued Trial ERC-238 on May 10, 2011. The investigator assessed these AEs as possibly-related to trial medication. The applicant agrees with the Investigator’s assessment for applicant site discharge. The applicant disagrees with the Investigator’s assessment for vulvar redness.
- Number 230-22-003 - A woman 55 years of age, reported a mild vaginal odor beginning on Day 1 and discontinued Trial ERC-230 on July 27, 2011. The investigator assessed this AE as possibly-related to trial medication. The applicant disagrees because “the drug is odorless.”
- Number 230-38-005 - A woman 83 years of age, reported nephrolithiasis on Day 116 (September 13, 2011) and discontinued Trial ERC-230 on November 16, 2011. The investigator assessed this AE as possibly-related to trial medication. The applicant disagrees because “it is inconsistent with the pharmacological effects of DHEA.”
- Number 230-41-004 - A woman 55 years of age, reported mild lower abdominal pain on Day 100 (June 16, 2011) and discontinued Trial ERC-230 on October 12, 2011. The investigator assessed this AE as possibly-related to trial medication. The applicant disagrees because “it is inconsistent with the pharmacological effects of DHEA.”
- Number 238-81-013 - A woman 62 years of age, reported moderate vaginal bleeding on Day 4, May 12, 2014. A pelvic transabdominal and endocervical ultrasound reported the presence of multiple uterine fibroids. Her bleeding stopped spontaneously. She discontinued Trial ERC-238 on June 30, 2014. The investigator assessed this AE as possibly-related to trial medication. The applicant disagrees since the presence of multiple uterine fibroids is known to cause this type of symptomatology.

In addition, although not included in the above listing but available in the case report form, participating woman Number 230-28-003 experienced acne and increased facial hair on June 20, 2011 prior to her discontinuation on September 15, 2011. The investigator assessed these two AEs as possibly drug-related to 0.05% DHEA vaginal insert.

### **Clinical Reviewer’s Comments:**

This reviewer agrees with the individual investigator's assessments regarding these reported TEAEs as possibly-related to 0.50% DHEA vaginal insert. One exception is participating woman Number 238-81-013 in Trial ERC-238. Uterine fibroids are known to cause vaginal bleeding. Vaginal bleeding in this woman began shortly after first use of 0.50% DHEA vaginal insert.

Thirty-five (35) of the 54 reported TEAEs that led to discontinuation in these 40 women in the 0.50% DHEA treatment group were considered unrelated by the investigator:

- Number 210-01-504 - A woman 62 years of age, was diagnosed with moderate Low grade Squamous Intraepithelial Lesion (LSIL; MedDRA Preferred term "cervical dysplasia") on a vaginal smear on Day 60 (March 17, 2008) and discontinued Trial ERC-210 on March 31, 2008. The investigator assessed this AE as unrelated to trial medication.
- Number 210-03-014 - A woman 59 years of age, reported worsening migraine headaches on Day 10, and discontinued Trial ERC-210 on April 16, 2008. The investigator assessed this AE as unrelated to trial medication.
- Number 230-01-015 - A woman 56 years of age, reported moderate depression on Day 29, March 25, 2011. She was discontinued from Trial ERC-230 on April 6, 2011 due to non-compliance. The investigator assessed this AE as unrelated to trial medication. She also experienced pain in both breast on February 15, 2011, ophthalmic migraine on March 25, 2011, urinary tract infection on April 1, 2011, extreme fatigue and abundant leucorrhea during her follow-up telephone call on July 7, 2011. These AEs were also assessed as unrelated to trial medication.
- Number 230-01-028 - A woman 66 years of age, was seen in the emergency room on Day 183 with abdominal pain and rectal bleeding. A colonoscopy on (b) (6) revealed severe ischemic colitis. She discontinued Trial ERC-230 on September 2, 2011. The investigator assessed this AE as unrelated to trial medication. Additional information in the CRF indicates inflammatory colon polyp and tubular adenoma without high grade dysplasia on December 15, 2011, both assessed and unrelated by the investigator.
- Number 230-01-036 - A woman 58 years of age, underwent a cerebral magnetic resonance angiogram on Day 8 (b) (6) which revealed a severe arteriovenous fistula in the right mastoid. She had reported insomnia on March 25, 2011. The investigator discontinued her from Trial ERC-230 on June 13, 2011 and assessed this AE as unrelated to trial medication.
- Number 230-02-011 - A woman 66 years of age, reported vomiting on July 27, 2011, headache on August 12, 2011, nausea on December 16, 2011, insomnia on December 17, 2011, and anxiety on December 19, 2011, all assessed as unrelated. She underwent a duodenoscopy which revealed severe duodenal stenosis on Day 343 (b) (6). She had a partial surgical resection of the duodenum (b) (6) and discontinued Trial ERC-230 on

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January 17, 2012. The investigator assessed the duodenal stenosis as unrelated to trial medication.

- Number 230-02-056 - A woman 59 years of age, with a history of removal of fibroadenoma in the left breast in 2009, had a normal mammogram at Screening dated November 10, 2010 (Day 1 on [REDACTED] (b) (6)). She had a breast ultrasound, bilateral mammogram, and a diagnostic mammogram on Day 296 [REDACTED] (b) (6) which showed suspicious microcalcifications. Breast ultrasound demonstrated Breast Imaging-Reporting and Data System (BIRADS) category 4 (suspicious abnormality) of the right breast. A stereotactic biopsy was performed reporting right breast atypical ductal hyperplasia. She underwent a partial mastectomy. The final histological diagnosis was atypical intraductal epithelial hyperplasia with micropapillary architecture (MedDRA Preferred Term "breast hyperplasia"). There were no malignant changes and the surgical margins were negative. The investigator discontinued her from Trial ERC-238 on December 14, 2011. The investigator assessed this AE as unrelated to trial medication.

Evaluations of serum steroid concentrations in this woman are as follows:

- DHEA Day 1 = 2827 pg/mL; Week 26 (Day 185) = 4444 pg/mL; Discontinuation ( Day 3P) = 2017 pg/mL (normal range = 560 - 3900 taken from Labrie, Cusan et al, 2008 in the application)
- Androstenedione Day 1 = 381 pg/mL; Week 26 (Day 185) = 509 pg/mL; Discontinuation = 289 pg/mL (normal range = 170 - 710 taken from Labrie, Cusan et al, 2008 in the application)
- Testosterone Day 1 = 122 pg/mL; Week 26 (Day 185) = 224 pg/mL; Discontinuation = 133 pg/mL (normal range = 60 - 260 taken from Labrie, Cusan et al, 2008 in the application)
- DHT Day 1 = 31 pg/mL; Week 26 (Day 185) = 69 pg/mL; Discontinuation = 47 pg/mL (normal range = 10 - 70 taken from Labrie, Cusan et al, 2008 in the application)
- Estradiol Day 1 = 1.4 pg/mL; Week 26 (Day 185) = 1.7 pg/mL; Discontinuation = 1.2 pg/mL (normal range = 1.0 – 9.3 taken from Labrie, Cusan et al, 2008 in the application)
- Estrone Day 1 = 8.0 pg/mL; Week 26 (Day 185) = 8.5 pg/mL; Discontinuation = 6.8 pg/mL (normal range = 7.6 – 34.8 taken from Labrie, Cusan et al, 2008 in the application)
- Number 230-02-091 - A woman 64 years of age, experienced severe thoracic pain and dyspnea and underwent a ventilation/perfusion scan of the lungs which revealed bilateral small subsegmental pulmonary emboli (MedDRA Preferred Term "pulmonary embolism") on Day 252 ([REDACTED] (b) (6)), and she discontinued Trial ERC-230 on March 5, 2012. Additional AEs reported included insomnia on December 26, 2011, bronchitis, probable vasovagal syncope, and

diarrhea on February 13, 2012. The investigator assessed all of these AEs as unrelated to trial medication.

Evaluations of serum steroid concentrations in this woman are as follows:

- DHEA Day 1 = 1087 pg/mL; Week 26 (Day 190) = 1288 pg/mL; Discontinuation = 1043 pg/mL (normal range = 560 - 3900 taken from Labrie, Cusan et al, 2008 in the application)
- Androstenedione Day 1 = 155 pg/mL; Week 26 (Day 190) = 191 pg/mL; Discontinuation = 208 pg/mL (normal range = 170 - 710 taken from Labrie, Cusan et al, 2008 in the application)
- Testosterone Day 1 = 113 pg/mL; Week 26 (Day 190) = 122 pg/mL; Discontinuation = 127 pg/mL (normal range = 60 - 260 taken from Labrie, Cusan et al, 2008 in the application)
- DHT Day 1 = 28 pg/mL; Week 26 (Day 190) = 29 pg/mL; Discontinuation = 24 pg/mL (normal range = 10 - 70 taken from Labrie, Cusan et al, 2008 in the application)
- Estradiol Day 1 = 2.6 pg/mL; Week 26 (Day 190) = 2.6 pg/mL; Discontinuation = 2.8 pg/mL (normal range = 1.0 – 9.3 taken from Labrie, Cusan et al, 2008 in the application)
- Estrone Day 1 = 10.8 pg/mL; Week 26 (Day 190) = 10.4 pg/mL; Discontinuation = 8.9 pg/mL (normal range = 7.6 – 34.8 taken from Labrie, Cusan et al, 2008 in the application)
- Number 230-11-031 - A woman 56 years of age, with a vulvovaginal exam at Screening (February 9, 2011) that demonstrated atrophy had an AE on May 8, 2011 reported as “genital lesion”. She was diagnosed with mild lichen sclerosus et atrophicus on Day 242 (January 17, 2012), and discontinued Trial ERC-230. The investigator assessed this AE as unrelated to trial medication.
- Number 230-11-040 - A woman 59 years of age, with a past history of cervical dysplasia (2006 and 2009) and ASCUS on Day 1 (March 21, 2011), had a positive human papilloma virus (HPV) test and LSIL on Day 64, (June 2, 2011) and discontinued Trial ERC-230 on June 20, 2011. The investigator assessed this AE as unrelated to trial medication.
- Number 230-15-004 - A woman 56 years of age, reported worsening pain in her left hip (arthralgia) on Day 162 (August 1, 2011), and underwent a right total hip arthroplasty (b) (6). During her post-operative recovery, she was diagnosed with a staphylococcal infection (MRSA) on Day 345 (b) (6). She discontinued Trial ERC-230 on January 12, 2012. The investigator assessed this AE as unrelated to trial medication.
- Number 230-15-012 - A woman 54 years of age, with a normal PAP smear at Screening (February 21, 2011) was diagnosed with Ectropion of the cervix on Day 106 (July 5, 2011) and cervicitis on Day 119 (July 18, 2011). She

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discontinued Trial ERC-230 on August 1, 2011. The investigator assessed this AE as unrelated to trial medication.

- Number 230-15-014 - A woman 58 years of age, with a history of first degree uterine prolapse, was diagnosed with moderate cystocele and uterine prolapse on Day 28 (May 1, 2011). She discontinued Trial ERC-230 on August 4, 2011. The investigator assessed this AE as unrelated to trial medication.
- Number 230-15-020 – A woman 68 years of age, reported moderate uterine cramping on Day 28 (December 28, 2012) and right lower quadrant abdominal pain on January 4, 2012, and discontinued Trial ERC-230 on January 16, 2012. The investigator assessed this AE as unrelated to trial medication.
- Number 230-18-018 - A woman 57 years of age, reported anxiety on Day 4, insomnia on Day 8, hot flashes on Day 8, and sustained a laceration to both thumbs on Day 96 (June 4, 2011). She discontinued Trial ERC-230 on June 15, 2011. The investigator assessed this AE as unrelated to trial medication.
- Number 230-21-009 – A woman 58 years of age, without a history of migraines experienced a moderate migraine on Day 43 (May 28, 2011) and again on June 14, 2011. She discontinued Trial ERC-230 on June 28, 2011. The investigator assessed this AE as unrelated to trial medication.
- Number 230-24-042 - A woman 62 years of age, with a history of prolapsed uterus had a worsening of her uterine prolapse (stage IV) on May 1, 2011 and discontinued Trial ERC-230 on November 18, 2011. She had surgery on (b) (6). The investigator assessed this AE as unrelated to trial medication.
- Number 230-30-013 - A woman 54 years of age, with a history of cystocele, rectocele, and prolapsed bladder, underwent an elective cystocele and rectocele repair, and hysterectomy on Day 185 (b) (6) and discontinued Trial ERC-230 the same day. The investigator assessed this AE as unrelated to trial medication.
- Number 231-15-013 - A woman 65 years of age, reported moderate arthralgia beginning on Day 24 (April 2, 2011) and discontinued Trial ERC-231 on April 18, 2011. The investigator assessed this AE as unrelated to trial medication.
- Number 231-30-001 - A woman 51 years of age, had a medical history of depression, and presented signs of worsening anxiety/depression and life-threatening suicidal ideation on Day 29 (March 23, 2011). She was hospitalized and treated. She stopped taking the trial drug and discontinued on April 12, 2011. The investigator assessed this AE as unrelated to trial medication.
- Number 234-04-006 - A woman 54 years of age, with moderate increase in her fibromyalgia on Day 61 (November 28, 2011) discontinued Trial ERC-234 on December 14, 2011. The investigator assessed this AE as unrelated to trial medication.
- Number 234-36-024 - A woman 59 years of age, had a positive HPV test collected during Screening and discontinued Trial ERC-234 on November 15,

2011 (no longer met exclusion criterion number 16). The investigator assessed this AE as unrelated to trial medication.

- Number 234-39-015 - A woman 67 years of age, presented in the ER with swelling, redness and pain of the left side of her face on Day 17 [REDACTED] (b) (6). A CT scan revealed cellulitis of her right cheek. She discontinued Trial ERC-234 on December 13, 2011. The investigator assessed this AE as unrelated to trial medication.
- Number 238-79-009 - A woman 50 years of age, had an elective gastric bypass performed (date unknown) and developed a severe post-procedural complication (October 2014). She discontinued Trial ERC-239 on November 24, 2014. The investigator assessed this AE as unrelated to trial medication.
- Number 238-85-020 - A woman 66 years of age, fell on a rock and sustained a broken left shoulder (upper limb fracture) on Day 27 (August 11, 2014). The investigator discontinued her from Trial ERC-238 on September 4, 2014 because she was unable to perform trial-related activities. The investigator assessed this AE as unrelated to trial medication.

**Clinical Reviewer's Comments:**

Overall, this reviewer agrees with the investigators' assessments of the above reported AEs as unrelated to trial medication. The majority of discontinuations in the 0.50% DHEA treatment group occurred in 52-week Trial 230.

Participating woman Number 230-02-091 (bilateral small subsegmental pulmonary emboli) has been previously discussed under Subheading 7.3.2 Nonfatal Serious Adverse Events.

Atypical ductal hyperplasia (preferred term "breast hyperplasia") found in participating woman Number 230-02-056 is not a form of breast cancer. Rather, it is a marker for women who may have a risk for developing breast cancer in the future. Her treatment management appears appropriate.

One (1) woman discontinued due to TEAEs in the 1.0%% DHEA treatment group. Participating woman Number 210-05-026 in Trial ERC-210 developed moderate vaginal burning on Day 30 (January 3, 2008). She discontinued Trial ERC-210 the same day. The investigator assessed this AE as possibly-related to trial medication.

#### 7.3.4 Significant Adverse Events

The applicant includes a classification of "significant TEAEs" as those TEAEs that were graded as severe in intensity (severity) by the investigator, but did not meet the definition of a serious AE.

Six (6) women in the placebo treatment group, experienced severe AEs, but completed their participation in the DHEA development program. These women were classified as experiencing significant TEAEs:

1. Number 210-11-006 - A woman 57 years of age, reported severe dysuria on Day 18 of treatment. No action was taken, and she recovered without sequelae and completed the trial. The investigator assessed the severe AE as unrelated to trial medication.
2. Number 210-11-042 - A woman 59 years of age, reported severe vomiting on Day 5 of treatment. No action was taken and she recovered without sequelae and completed the trial. The investigator assessed the severe AE as unrelated to trial medication.
3. Number 234-21-011 - A woman 64 years of age, reported severe dehydration and transitory severe hyperglycemia on Day 25. She was hospitalized and treated for a partial small bowel obstruction not requiring surgery. She returned to complete the trial. The investigator assessed the severe AE as unrelated to trial medication.
4. Number 234-63-011 - A woman 51 years of age, reported severe worsening of her known right knee osteoarthritis which was ongoing. She completed the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.
5. Number 238-12-009 - A woman 60 years of age, reported a severe right foot fracture on Day 97 that did not require hospitalization. No information is available regarding action taken. She completed the trial. The investigator assessed the severe AE as unrelated to trial medication.
6. Number 238-55-021 - A woman 57 years of age, reported a severe right ankle fracture on Day 38 that did not require hospitalization. No information is available regarding action taken. She completed the trial. The investigator assessed the severe AE as unrelated to trial medication.

**Clinical Reviewer's Comments:**

This reviewer agrees with the trial investigators that the reported severe AEs are significant, but not related to the placebo trial drug.

Three (3) women experienced severe AEs, but continued the trial in the 0.25% DHEA treatment group:

1. Number 210-02-023 – A woman 65 years of age, reported a single episode of a severe headache on Day 3. Drug treatment was provided and the subject recovered without sequelae. The investigator assessed the AE as possibly-related to trial medication. The applicant disagrees because the severe AE “is inconsistent with the known pharmacologic properties of DHEA.”
2. Number 210-02-035 – A woman 62 years of age, was diagnosed with severe symptomatic cholelithiasis on Day 10. She was hospitalized and underwent an

endocholecystectomy. She returned to complete the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.

3. Number 234-30-015 – A woman 59 years of age, reported severe worsening of her left leg pain (medical history of left leg deep vein thrombosis), and severe worsening of left iliac vein stenosis on an unknown date. She was diagnosed with a severe post phlebitis syndrome and treated. She returned to complete the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.

**Clinical Reviewer's Comments:**

This reviewer generally agrees with the investigators' assessments regarding all three of these women exposed to 0.25% DHEA. That said, while there are many factors that may precipitate a severe headache, it is not possible to completely rule out the 0.25% DHEA vaginal insert as the cause of this adverse event in participating woman Number 210-02-023.

Eleven (11) women experienced severe AEs, eight of these 11 women completed the trial in the 0.50% DHEA treatment group:

1. Number 210-02-020 – A woman 65 years of age, reported severe hot flashes (medical history of hot flashes) on Day 2 for 1 day. No action was taken, and she recovered without sequelae. She completed the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.
2. Number 210-02-048 – A woman 59 years of age, reported a severe cough on Day 77 that resolved without treatment on Day 81. She completed the clinical trial. The investigator assessed the AE as unrelated to trial medication.
3. Number 230-02-025 – A woman 62 years of age, with a medical history of anemia had a transitional leucopenia. No action was taken. Her condition resolved without sequelae. She completed the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.
4. Number 230-11-010 – A woman 54 years of age had one episode of loss of consciousness on Day 30. No action was taken. She recovered without sequelae, but discontinued trial medication due to insufficient response to trial medication. The investigator assessed the severe AE as unrelated to trial medication.
5. Number 230-11-031 – A woman 56 years of age, presented with a syncopal episode following her endometrial biopsy procedure performed on Day 306 at early withdrawal due to mild lichen sclerosis. The investigator assessed the AE as unrelated to trial medication.
6. Number 230-30-010 – A woman 54 years of age, reported severe common cold symptoms on Day 274 that resolved with treatment on Day 299. She completed the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.

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7. Number 238-60-029 – A woman 58 years of age, underwent a right foot bunionectomy on Day 38. She recovered without sequelae and completed the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.
8. Number 238-68-005 – A woman 54 years of age, had an increased alanine aminotransferase on Day 82. No action was taken. She completed the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.
9. Number 238-73-031 – A woman 48 years of age, with known Type 2 Diabetes Mellitus developed inadequate control on Day 101 since she stopped taking her diabetes medications. She had completed the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.
10. Number 238-79-009 – A woman 50 years of age, suffered a severe dislocation of the 1<sup>st</sup> toe of her right foot and a severe fracture of her 5<sup>th</sup> left toe on Day 16. She received treatment. She was terminated early because she was lost to follow-up. The investigator assessed the severe AE as unrelated to trial medication.
11. Number 238-85-022 – A woman 62 years of age, reported a flare-up of her known Crohn's disease on Day 10. She received treatment, and completed the trial without sequelae. The investigator assessed the severe AE as unrelated to trial medication.

### **Clinical Reviewer's Comments:**

This reviewer agrees with the investigators' assessments for these 11 women in the 0.50% DHEA treatment group.

Seven (7) women experienced severe AEs, but continued the trial in the 1.0% DHEA treatment group:

1. Number 210-02-007 – A woman 62 years of age, reported severe back pain and urinary infection on Day 52. She was treated with antibiotics and recovered without sequelae. She completed the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.
2. Number 210-02-013 – A woman 62 years of age, reported severe diarrhea on Day 49. She received treatment and completed the clinical trial. The investigator assessed the severe AE as unrelated to trial medication.
3. Number 210-02-019 – A woman 54 years of age, reported severe nausea and dizziness on Day 24 that resolved without treatment on Day 26. She also reported severe sinusitis on Day 46 that resolved without sequelae with treatment. She completed the clinical trial. The investigator assessed these severe AEs as unrelated to trial medication.
4. Number 210-02-037 – A woman 69 years of age, reported severe coccyx pain on Day 30 that resolved with treatment on Day 40 without sequelae. She also developed severe neck pain on Day 83 that resolved the same day with

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treatment. She completed the clinical trial. The investigator assessed these severe AEs as unrelated to trial medication.

5. Number 210-08-012 – A woman 59 years of age, reported severe generalized abdominal pain on Day 52 that resolved with treatment. She completed the clinical trial. The investigator assessed the SAE as unrelated to trial medication.
6. Number 210-11-017 – A woman 54 years of age, reported severe vaginal burning and itching on Day 37 of treatment unresolved until Day 59. She completed the 12-week clinical trial. The investigator assessed these severe AEs as unrelated to trial medication.
7. Number 210-11-040 – A woman 58 years of age, reported severe left leg pain associated with sciatic nerve pain on Day 68. She reported a medical history of lumbar hernia. She completed the clinical trial. Her severe AE was ongoing. The investigator assessed this severe AE as unrelated to trial medication.

### **Clinical Reviewer's Comments:**

This reviewer generally agrees with the investigators' assessments for these 7 women. Participating woman Number 210-11-017 is a possible exception. It is uncertain whether her burning and itching were due to 1.0% DHEA vaginal insert in spite of the applicant's insistence that neither DHEA nor the vehicle Witepsol is irritating. The applicant is not seeking approval of the 1.0% DHEA dose for the intended indication, however.

One (1) woman in 7-Day Trial ERC-213, experienced dizziness and hypotension on Day 2 of treatment with 1.8% DHEA. Per the application, no action was taken and the woman recovered without sequelae. These severe AEs were assessed, by the Investigator as unrelated to trial medication.

### **Clinical Reviewer's Comments:**

This reviewer agrees with the assessment by the investigator discussed above.

Overall, significant severe TEAEs (TEAEs graded as severe in intensity but not meeting the definition of a SAE) observed in the DHEA clinical development program occurred at a low frequency and appear to be unrelated to trial medication. Of the total 28 women reporting severe TEAEs, only participating woman Number 210-02-023 (severe headache) was considered possibly-related to 0.25% DHEA vaginal insert. Only 3 women discontinued the trial due to a severe TEAE (Numbers 230-11-010, 230-11-031, and 238-79-009).

## 7.3.5 Submission Specific Primary Safety Concerns

### 7.3.5.1 Endometrial Safety

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A major concern with the use of hormonal therapy (estrogen and progestogen) for the treatment of symptoms due to menopause is the risk of endometrial hyperplasia/cancer. Although DHEA is neither an estrogen nor a progestogen, it can be converted to androstenedione, which in turn is interconverted to estrone, or to androstenediol, which can be converted to testosterone and then estradiol.

Endometrial safety was monitored in phase 3, 12-week placebo-controlled Trials ERC-210, ERC-231, ERC-234, and 52-week open-label Trial ERC-230. In each of these trials an endometrial biopsy was performed at baseline and at end-of-trial to evaluate endometrial histology. Phase 3 Trial ERC-238 conducted an endometrial biopsy at baseline only to prevent enrollment of a woman with abnormal endometrial histology in this 12-week trial.

Assessment of the histology from endometrial biopsy specimens was to be performed in accordance with the Agency's 2003 draft clinical evaluation Guidance for Industry as follows:

- The endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the trial, and at the end-of-trial will be processed in the same manner by a central laboratory.
- A single pathologist reader (any one of the three blinded pathologists) will initially assess the slides from the endometrial biopsies obtained at screening (or because of participant bleeding) for a safety determination as to whether a woman should participate in the trial.
- Women found to have endometrial hyperplasia or adenocarcinoma of the endometrium must be excluded from initial or further drug treatment (if discovered during trial drug treatment period) and referred for *standard of care* clinical management and followed to complete resolution, and the report of any medical or surgical procedures and the resultant pathology be provided to the Agency.
- If hyperplasia is diagnosed by the single safety reader for a woman who has bled while on trial drug, the slides become part of the slide set given to the two other pathologists for reading.
- Three independent expert pathologists, blinded to treatment group and to each other's readings should determine the final histologic diagnosis of slides from endometrial biopsy specimens obtained during the conduct of the trial for any woman who has an end-of-trial biopsy or a for cause biopsy because of bleeding while on trial drug.
- The slide set distributed to each of the three pathologists for the end-of-trial pathology review incorporate control slides representing a randomly selected 10 percent of the screening normal slides and all slides from women excluded for the diagnosis of hyperplasia or cancer to insure quality control.
- For the evaluation, the concurrence of two of the three pathologists will be accepted as the final diagnosis. If there is no agreement among the three

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pathologists, the most severe pathologic diagnosis (i.e., atypical hyperplasia > complex hyperplasia > simple hyperplasia > benign endometrium) would be used as the final diagnosis.

- All slides and reports will be maintained by the sponsor and be made available upon the Agency's request.
- Curricula vitae for participating pathologists should be provided to the Agency and should document expertise in gynecologic pathology.
- Participating expert pathologists should be from different institutions with independent fiduciary and organizational reporting, and these pathologists should not meet to review slides before or during the conduct of the clinical trial.
- Standardized criteria as provided in Blaustein's pathology text (Pathology of the Female Genital Tract) should be used for the diagnosis of endometrial hyperplasia.
- Endometrial biopsies, and not uterine ultrasounds, were to be used for the evaluation of endometrial hyperplasia.
- Endometrial polyps were to be fully characterized as to the glandular proliferation and atypia.
- Histologic description was according to the Agency's 2003 draft Guidance for Industry, histologic descriptions as follows:
  - No sample obtained because of administrative or technical reason.
  - Insufficient sample for histology assessment because of insufficient (strophic) endometrial tissue
  - Atrophic
  - Inactive (non-secretory)
  - Proliferative
    - Weakly proliferative
    - Active proliferative
    - Disordered proliferative
  - Secretory
    - Cyclic type
    - Progestational type (including stromal decidualization)
  - Menstrual type
  - Simple hyperplasia without atypia
  - Simple hyperplasia with atypia
  - Complex hyperplasia without atypia
  - Complex hyperplasia with atypia
  - Carcinoma (specify type)

Additional histologic characteristics included:

- Polyps:
  - Functional
  - Atrophic
  - Hyperplastic without atypia
  - Hyperplastic with atypia

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- Carcinomatous
- Other (type must be specified)
- Stromal tissue:
  - Smooth muscle tissue, normal
  - Features suggestive of adenomyoma
  - Features suggestive of stromal nodule
  - Sarcoma (type must be specified)
    - Metaplasia:
      - Squamous
      - Papillary
      - Eosinophilic
      - Ciliated
      - Mucinous
      - Syncitial
      - Other (type must be specified)
- Cervical tissue:
  - Fragments of negative cervical epithelium
  - Endocervical polyp
  - Atypical endocervical glandular epithelium
  - Atypical squamous metaplasia
  - Squamous dysplasia
  - Cervical carcinoma

Overall, 628 women, exposed to DHEA during the course of the clinical trials, underwent an endometrial biopsy at Screening and 291 women of these women had a post-baseline endometrial biopsy obtained up to 12-weeks in Trials ERC-210, ERC-231, and ERC-234. Overall, 521 women were exposed to DHEA up to 52-weeks in Trial ERC-230 and 456 had a post-baseline endometrial biopsy.

In total, 1149 women, exposed to DHEA during the course of the clinical trials, underwent an endometrial biopsy at Screening and 747 women had a post-baseline endometrial biopsy obtained up to 52 weeks in 12-week Trials ERC-210, ERC-231, ERC-234, and 52-week Trial ERC-230.

Table 20 shows histology results, as reported in the October 16, 2015 application submission (single pathologists <sup>(b) (4)</sup>), from endometrial biopsies in women with treatment up to 12-weeks in Trials ERC-210, ERC-231, and ERC-234. The findings of the three independent, blinded pathologists are presented in Table 23.

Table 20: Endometrial Biopsy Results Up to Week 12 in Trials ERC-210, ERC-231, and ERC-234; Safety Population

<b>Endometrial Biopsy</b> Number of women with endometrial biopsy post-baseline	<b>Placebo</b> <b>N = 137</b>	<b>0.25% DHEA</b> <b>N = 130</b>	<b>0.50% DHEA</b> <b>N = 135</b>	<b>1.0% DHEA</b> <b>N = 33</b>	<b>Total DHEA<sup>1</sup></b> <b>N = 298</b>
<b>Histologic Characteristics N (%)<sup>2</sup></b> - No tissue	9 (7%)	9 (7%)	14 (10%)	2 (6%)	25 (8%)

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- Tissue insufficient for diagnosis	5 (4%)	2 (2%)	1 (1%)	0 (0%)	3 (1%)
- Atrophic	119 (87%)	119 (92%)	120 (89%)	30 (91%)	269 (90%)
- Inactive	1 (1%)	0 (0%)	0 (0%)	1 (3%)	1 (0%)
- Weakly proliferative	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Active proliferative	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Disordered proliferative	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Secretory type	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Menstrual type	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Simple hyperplasia without atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Simple hyperplasia with atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Complex hyperplasia without atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Complex hyperplasia with atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Polyp N (%)<sup>2</sup></b>					
- None	137 (100%)	129 (99%)	135 (100%)	33 (100%)	292 (100%)
- Functional	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Hyperplastic with atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Atrophic	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (0%)
- Carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Hyperplastic without atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Stromal Tissue N (%)<sup>2</sup></b>					
- None	136 (99%)	130 (100%)	135 (100%)	33 (100%)	298 (100%)
-Smooth muscle tissue normal	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Metaplasia N (%)<sup>2</sup></b>					
- None	136 (99%)	130 (100%)	135 (100%)	33 (100%)	298 (100%)
- Ciliated	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Cervical Tissue N (%)<sup>2</sup></b>					
- None	85 (62%)	95 (73%)	98 (73%)	23 (70%)	216 (70%)
- Fragments of negative cervical epithelium	52 (38%)	34 (26%)	36 (27%)	10 (30%)	80 (27%)
- Atypical endocervical glandular epithelium	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Squamous dysplasia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Endocervical polyp	0 (0%)	1 (1%)	1 (1%)	0 (0%)	2 (1%)
- Atypical squamous metaplasia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Cervical carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 14.3.6, pages 653 through 655 of 662 (as reported by single pathologists (b) (4)).

<sup>1</sup>Includes data of 0.25% DHEA, 0.50% DHEA, and 1.0% DHEA doses in Trials ERC-210, ERC-231, and ERC-234.

<sup>2</sup>Percentages are based on the number of women with post-baseline endometrial biopsy.

In 52-weeks Trial ERC-230 only, an endometrial biopsy was performed at Screening and at Week 52 or at time of discontinuation for those women who were treated for 12 weeks or more. An end-of-trial endometrial biopsy was performed on 422 (97%) of 435 women treated with daily 0.50% DHEA vaginal insert for 52 weeks (and 15 (79%) of the 19 women who discontinued between weeks 26 and 52). Of these 422 women treated with daily 0.50% DHEA vagina insert, 389 (92%) had sufficient tissue for diagnosis. See Table 21 for report of histology.

Table 21: Overview of Endometrial Biopsy and Transvaginal Ultrasound finding in 52-Week Trial ERC-230

Parameter	Weeks on 0.50% DHEA Vaginal Insert		
	≥ 26 Weeks	52 Weeks	All <sup>1</sup>
Number of women in treatment interval	19	435	484
Number of women who did not have an end-			

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of-trial endometrial biopsy	4	13	27
Number of women who had an end-of-trial endometrial biopsy	15	422	457
Number of evaluable women <sup>2</sup>	15	389	
Histologic characteristics N (%)			
- No tissue	0	27	28
- Insufficient tissue for diagnosis	0	6	8
- Atrophic	15	385	417
- Inactive	0	4	4
Other findings			
- Polyp (atrophic)	0	1	1
- Endocervical polyp	0	3	3
Number of women who had a transvaginal ultrasound			43
- Endometrial thickness < 4 mm	-	-	38
- Endometrial thickness 5-6 mm	-	-	5
- Mean endometrial thickness, mm (SD)	-	-	2.2 (1.4)

Source: Adapted from NDA 208470, Clinical Trial Report for Trial ERC-230, Table 10-78: Overview of endometrial biopsy and transvaginal ultrasound findings, page 238 of 860 (as reported by single pathologists (b) (4)).

<sup>1</sup>Used intravaginal DHEA inserts for at least 3 months.

<sup>2</sup>Evaluable women who had sufficient tissue for diagnosis

The endometrium was reported as atrophic in 385 women (99%, 385 of 389 evaluable women), and inactive in 4 women (1%).

Table 22 shows histology results, as reported in the October 16, 2015 application submission, from endometrial biopsies in women with treatment up to 52-weeks, including 12-week Trials ERC-210, ERC-231, ERC-234, and 52-week Trial ERC-230.

Table 22: Endometrial Biopsy Results Up to Week 52; Safety Population

Endometrial Biopsy	Placebo N = 474	0.25% DHEA N = 282	0.50% DHEA N = 1196	1.0% DHEA N = 64	Total DHEA <sup>1</sup> N = 1542
Number of women with endometrial biopsy post-baseline	137	130	589	33	752
<b>Histologic Characteristics N (%)<sup>2</sup></b>					
- No tissue	9 (7%)	9 (7%)	42 (7%)	2 (6%)	53 (7%)
- Tissue insufficient for diagnosis	5 (4%)	2 (2%)	9 (2%)	0 (0%)	11 (1%)
- Atrophic	118 (87% <sup>1</sup> )	119 (92%)	534 (91%)	30 (91%)	683 (91%)
- Inactive	1 (1%)	0 (0%)	4 (1%)	1 (3%)	5 (1%)
- Weakly proliferative	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Active proliferative	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Simple hyperplasia without atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Simple hyperplasia with atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Complex hyperplasia without Atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Complex hyperplasia with atypia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Polyp N (%)<sup>2</sup></b>					
- None	137 (100%)	129 (99%)	588 (100%)	33 (100%)	750 (100%)
- Atrophic	0 (0%)	1 (1%)	1 (0%)	0 (0%)	2 (0%)
- Carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Metaplasia N (%)<sup>2</sup></b>					
- None	136 (99%)	130 (100%)	589 (100%)	33 (100%)	752 (100%)
<b>Cervical Tissue N (%)<sup>2</sup></b>					
- None	85 (62%)	95 (73%)	451 (77%)	23 (70%)	752 (100%)
- Atypical squamous metaplasia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
- Fragments of negative cervical					

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epithelium	52 (36%)	34 (26%)	130 (22%)	10 (30%)	174 (23%)
- Endocervical polyp	0 (0%)	1 (1%)	4 (1%)	0 (0%)	5 (1%)
- Cervical carcinoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 37, page 123 of 662  
(as reported by single pathologists (b) (4)).

<sup>1</sup>Includes data of 0.25% DHEA, 0.50% DHEA, and 1.0% DHEA doses in Trials ERC-210, ERC-230, ERC-231, and ERC-234.

<sup>2</sup>Percentages are based on the number of women with post-baseline endometrial biopsy.

Per the original application submission, 100% of women with a post-baseline biopsy, who received DHEA up to 52 weeks, had no tissue (7%), insufficient tissue (1) atrophic (91%) or inactive (1%) without any clinically significant histologic findings.

**Clinical Reviewer’s Comments:**

In the Agency’s Filing Communication Letter, dated December 28, 2015, the Division requested that EndoCeutics provide:

“For each evaluable subject in 12-week Trial ERC-231 and 52-week Trial ERC-230, provide a copy of both the baseline and the end-of-trial (or early termination) endometrial biopsy reports. The end-of trial reports should be provided for each of the three independent, blinded pathologists participating in Trial ERC-231 and Trial ERC-238. If the actual endometrial biopsy reports have already been included in the NDA, advise us as to their location.”

The applicant replied on February 12, 2016 and provided endometrial biopsy reports for clinical Trials ERC-231 and ERC-230 generated by a single pathologist, (b) (4), with the following explanation:

*“The Sponsor acknowledges that the information provided in trial protocols ERC-231 and ERC-230 regarding the evaluation of endometrial biopsies was not correct since the text from the 2003 guidance was copied in both protocols but the beginning of the sentence “For the efficacy evaluation, ...” was removed by error, thus giving the impression that all end-of-trial biopsies would be read by three independent pathologists as would have been required for efficacy evaluation. When the error was noted in protocols, a note-to-file (NTF) has been prepared and included in the Trial Master File of both studies. The NTFs explaining that situation were annexed to clinical trial reports. Refer to Appendix 16.1.9 of ERC-230 and Appendix 16.1.9 of ERC-231 t reports to access these NTFs.”*

*“The Sponsor considers that the evaluation of endometrial biopsies by a single pathologist is in agreement with the FDA 2003 guidance and recommendations from the Agency taking into account that the endometrial biopsy was performed as a safety assessment throughout the clinical development program.”*

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The clinical team does not agree with the applicant regarding evaluation of endometrial biopsies by a single pathologist. Per the agreed-to protocols for 12-week Trials ERC-210, ERC-231, ERC-234, and 52-week Trial ERC-230 and per the Agency's 2003 draft clinical evaluation Guidance for Industry, three independent pathologists were to provide final histologic diagnoses from endometrial biopsies obtained in these trials

On March 29, 2016, the Agency sent an Information Request (IR) letter advising EndoCeutics that the endometrial assessment by endometrial biopsies conducted for participating women at Week 12 for Trials ERC-210, ERC-231, and ERC-234 and Week 52 for Trial ERC-230 were not conducted according to the Agency's 2003 draft clinical evaluation Guidance for Industry. The IR letter stated:

- “Specifically you did not have three independent pathologists evaluate and provide an adequate endometrial histological diagnosis. With one exception, a single pathologist, (b) (4), made the histological diagnosis for all endometrial samples obtained in the above trials as well as trial ERC-238. The exception involved the read of some of the baseline endometrial biopsies from ERC-210. (b) (4) read these slides.”
- “Failure to have three independent and blinded pathologists read the end-of-trial endometrial biopsies constitutes inadequate and insufficient endometrial assessment for your product.”
- “To remedy the above situation, each endometrial biopsy for which endometrial tissue was obtained will need to be re-read by two additional independent and blinded pathologists.”
- “These pathologists should be located at different institutions and have no common fiduciary or reporting responsibilities.”

The IR letter further provided EndoCeutics directions regarding the conduct of the re-read of endometrial biopsies, including a recut of the original endometrial biopsy specimen or a re-read of the original endometrial biopsy slide if a recut of the specimen was not possible.

The applicant was also requested to provide the Agency with a safety protocol for the conduct of the re-read of each endometrial biopsy for which endometrial tissue was obtained, and a time frame for completion of the re-read of endometrial biopsy slides. In addition, the Agency advised EndoCeutics that failure to adequately assess endometrial safety is an approvability issue.

On April 6, 2016, EndoCeutics posed two questions in follow-up to the Agency's March 29, 2016 IR letter. The Agency responded on April 8, 2015. EndoCeutics' questions and the Agency's responses are presented as follows:

1. *“Does the Agency agree that the re-read of all endometrial biopsies be performed on the original set of slides while ensuring that slides do not contain any markings from the previous read?”*

**FDA Response:**

“No. We have the following clarification of specific comments from our March 29, 2016, Information Request letter:

- For each sample recut the block of tissue at the same level as that for the previous evaluation to obtain a new slide for a re-read.
- For any given sample if a recut is not possible because of insufficient tissue, the original slide for that sample may be re-used provided there are no markings from the previous read by (b) (4) [redacted] if relevant). Your written report of the endometrial histology reassessment must identify any sample for which a recut could not be performed because of insufficient tissue.
- A re-read of the original slides should take place only under the circumstance where you have verified that there is insufficient tissue to make a recut of the sample.

With the exception of the comments noted in the three bullets above, all other comments in the March 29, 2016, Information Request letter, remain the same.”

2. *“Does the Agency agree that all slides of endometrial biopsies be evaluated by one additional expert pathologist while for biopsies with a diagnosis different from “inactive” or “atrophic”, two additional pathologists would provide their diagnosis?”*

**FDA Response:**

“No, we do not agree with your proposed evaluation of 50% of all slides by one additional blinded pathologist. We recommend that 100% of all end-of-trial or discontinuation endometrial biopsy samples be evaluated by two additional, independent, blinded pathologists. Consistent with the Agency’s 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”, the concurrence of two of the three pathologists, including (b) (4) [redacted] if relevant), would be accepted as the final diagnosis. If there is disagreement of diagnosis between the three independent, blinded pathologists, then the most severe histology finding would be the final diagnosis.”

On May 6, 2016, EndoCeutics submitted a clinical amendment to the NDA with a protocol for ERC-237 entitled “Protocol for Second and Third Readings of End-of-Study Endometrial Biopsies from Postmenopausal Women with Vulvovaginal

(b) (4)

Per the protocol submitted for ERC-237, the final data and report for the second and third readings of endometrial biopsy evaluations will be submitted to the Agency by June 30, 2016.

Comments regarding the safety protocol for Trial ERC-237 were sent to EndoCeutics in an IR letter dated May 16, 2016:

1. “With one exception, we generally concur with your proposal to conduct a re-read of the end-of trial endometrial biopsies specifically for 12-Week Trials ERC-210, ERC-231, and ERC-234 and 52-Week Trial ERC-230, as outlined in the above protocol.”

“We do not agree with the selection of five pathologists (b) (4) to participate as the “third reader” for the re-read of the slide set. Designate a single pathologist with expertise in gynecologic pathology to participate as the “third reader.” Additionally, provide the actual endometrial biopsy reports from each of the three independent pathologists as well as the individual subject data listings.”

On June 1, 2016, EndoCeutics submitted a clinical amendment to the NDA designating (b) (4) as the third independent reader, and an updated protocol for ERC-237. DBRUP concurred with the selection of (b) (4) as the third independent reader on June 15, 2016, and requested that EndoCeutics “provide actual endometrial biopsy reports from each of the three independent pathologists (b) (4) as well as the individual subject data listings.”

On June 30, 2016, DBRUP received individual pathologist’s endometrial biopsy pathology reports and summary tables for endometrial histology re-evaluation ERC-237. On July 12, 2016, EndoCeutics submitted a final Clinical Study Report for ERC-237 entitled, “Clinical Study Report for Second and Third Readings on End-of-Study Endometrial Biopsies from Postmenopausal women with Vulvovaginal Atrophy (VVA) for Studies ERC-210, ERC-230, ERC-231 and ERC-234.”

Table 23 shows histology results, as reported in the July 12, 2016 amendment submission for endometrial histology re-evaluation ERC-237, from endometrial biopsies in women with treatment up to 12-weeks in Trials ERC-210, ERC-231, and ERC-234.

Table 23: Overview of End-of-Trial Endometrial Biopsy Data from 12-Week Trials ERC-210, ERC-231 and ERC-234 – Final Diagnosis from Three Independent Pathologists

Parameters	Treatment Groups				
	Placebo N=284	0.25% DHEA N=283	0.50% DHEA N=291	1.0% DHEA N=54	Total N=912
<b>Total Number of Women At Week-12 (%)</b>	250 (88%)	250 (88%)	252 (86%)	51 (94%)	803 (88%)
Women with end-of-trial endometrial biopsy	135 (54%)	128 (51%)	131 (52%)	32 (63%)	426 (53%)
Women who refused biopsy	2 (0.8%)	3 (1.2%)	7 (2.8%)	0 (0.0%)	12 (2.8%)
Hysterectomized women	113 (45%)	119 (48%)	114 (45%)	19 (37%)	365 (45%)
<b>Final Diagnosis Histologic Characteristics (N, % of women with biopsy)</b>					
No tissue	7 (5.2%)	3 (2.3%)	6 (4.6%)	2 (6.2%)	18 (4.2%)
Tissue Insufficient	2 (1.5%)	4 (3.1%)	5 (3.8%)	0 (0.0%)	11 (2.6%)
Atrophic	123 (91%)	121 (94%)	120 (92%)	29 (91%)	393 (92%)
Weakly proliferative	2 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
Disordered proliferative	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.1%) <sup>1</sup>	1 (0.2%)
Complex hyperplasia with atypia <sup>2</sup>	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
<b>Other Findings</b>					
Polyps					
- Atrophic	2 (1.5%)	3 (2.3%)	1 (0.7%)	1 (3.1%)	7 (1.6%)

Source: Adapted from NDA 208470, NDA Amendment dated July 12, 2016, Clinical Trial Report for ERC-237, Section 8 Results, Table 3 for Trial ERC-210 on page 18 of 81, Table 5 for Trial ERC-231 on page 20 of 81, and Table 6 for ERC-234 on page 21 of 81.

<sup>1</sup>Woman identified by applicant as having an estrogen signature.

<sup>2</sup>Trial participant Number 234-30-040 in Trial ERC-234 (b) (4), first reader, did not provide the histologic characteristics on biopsy specimen and recommended follow-up. This woman underwent an endometrial curettage which reported fragments of benign endometrium with reactive changes consistent with effects of an intrauterine device.

**Clinical Reviewer’s Comments:**

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The reported findings of the three independent, blinded pathologists in these three clinical trials support the absence of substantial endometrial effects for the 0.50% DHEA vaginal insert administered intravaginally daily over a 12-week duration. The finding of 2 cases of weakly proliferative endometrium and one case of complex hyperplasia with atypia in the placebo vaginal insert treatment group does not raise safety concerns. The finding of one case of disordered proliferative endometrium at the 1.0% DHEA dose also does not raise safety concerns. The applicant is not requesting approval of this dose for the stated indication.

Of interest however, are the following results of evaluation of serum steroid concentrations in the one case of disordered proliferative endometrium (trial participant Number 210-01-360):

- DHEA Day 1 = 3.33 ng/mL; Day 14 = 5.51 ng/mL; Week 12 = 3.86 ng/mL
- Testosterone Day 1 = 0.19 ng/mL; Day 14 = 0.34 ng/mL; Week 52--12 = 0.28 ng/mL
- DHT Day 1 = 0.03 ng/mL; Day 14 = 0.08 ng/mL; Week 12 = 0.05 ng/mL
- ADT-G Day 1 = 21.56 ng/mL; Day 14 = 42.36 ng/mL; Week 12 = 26.83 ng/mL
- Estradiol Day 1 = 8.8 pg/mL; Day 14 = 90.17 pg/mL; Week 12 = 27.85 pg/mL (normal range = 1.0 – 9.3 taken from Labrie, Cusan et al, 2008 in the application)
- Estrone Day 1 = 17.82 pg/mL; Day 14 = 75.96 pg/mL; Week 12 = 34.4 pg/mL (normal range = 7.6 – 34.8 taken from Labrie, Cusan et al, 2008 in the application)
- Estrone-sulfate Day 1 = 128 pg/mL; Day 14 = 896 pg/mL; Week 12 = 297 pg/mL (normal range = 40 - 590 taken from Labrie, Cusan et al, 2008 in the application)

The applicant views this case as evidence of exogenous estrogen use. This reviewer agrees that the Week 12 serum estrogen levels are elevated above Day 1 while the Week 12 DHEA levels remain essentially the same as Day 1. The highly elevated estrogen levels and slightly elevated DHEA level at Day 14 remain unexplained, however.

Table 24 shows histology results, as reported in the July 12, 2016 amendment submission for ERC-237, from endometrial biopsies in women with treatment up to 52-weeks in Trial ERC-230.

Table 24: Overview of End-of-Trial Endometrial Biopsy Data from 52-Weeks Trial ERC-230 – Final Diagnosis of Three Independent Pathologists

Parameters	Weeks on 0.50% (6.5 mg) DHEA		
	52 Weeks	26 - < 52 Weeks	All <sup>1</sup>

	N = 435	N = 24	N = 521
<b>Total Number of Women in Treatment Interval (%)</b>	435 (100%)	19 (79%)	483 (93%)
Women who had an end-of-trial biopsy	422 (97%)	15 (79%)	456 (94%)
Women who did not have end-of-trial biopsy	13 (3%)	4 (21%)	27 (6%)
<b>Final Diagnosis Histologic Characteristics (N, % of women with biopsy)</b>			
No tissue	11 (3%)	0 (0.0%)	11 (2%)
Tissue Insufficient for Diagnosis	17 (4%)	0 (0.0%)	20 (4%)
Atrophic	393 (93%)	15 (100%)	424 (93%)
Disordered proliferative	1 (0.2%) <sup>2</sup>	0 (0.0%)	1 (0.2%) <sup>2</sup>
<b>Other Findings</b>			
Polyps			
- Atrophic	7 (2%)	0 (0.0%)	7 (2%)
- Functional	0 (0.0%)	1 (7%) <sup>2</sup>	1 (0%)

Source: Adapted from NDA 208470, NDA Amendment dated July 12, 2016, Clinical Trial Report for ERC-237, Section 8 Results, Table 4, page 19 of 81.

<sup>1</sup>Includes women who discontinued after 12 weeks but before 26 weeks.

<sup>2</sup>Woman identified by applicant as having an estrogen signature.

### **Clinical Reviewer's Comments:**

The reported findings of the three independent, blinded pathologists in clinical Trial ERC-230 support the absence of substantial endometrial effects for the 0.50% DHEA vaginal insert administered intravaginally daily over a 52-week duration. One reported case of disordered proliferative endometrium in 422 end-of-trial endometrial biopsies at 52-weeks does not raise safety concerns for the 0.50% DHEA vaginal insert. Likewise, one reported functional polyp also does not raise safety concerns for the 0.50% DHEA vaginal insert. These findings do, however, demonstrate a known effect of estrogen on the endometrium.

Per the applicant, trial participant Number 230-02-028 (endometrial biopsy diagnosis of proliferative endometrium) and trial participant Number 230-15-020 (endometrial biopsy diagnosis of functional polyp) both had “an estrogen signatures typical of a subject who took estrogens”, per the applicant.

The results of evaluation of serum DHEA, estradiol, and estrone concentrations in trial participant Number 230-02-028 are as follows:

- DHEA Day 1 = 2267.72 pg/mL; Week 12 = 2325.31 pg/mL; Week 26 = 1566.75 pg/mL; Week 52 = 2830.11 pg/mL
- Estradiol Day 1 = 51.75 pg/mL; Week 12 = 10.33 pg/mL; Week 26 = 10.87 pg/mL; Week 52 = 90.46 pg/mL
- Estrone Day 1 = 48.47 pg/mL; Week 12 = 22 pg/mL; Week 26 = 24.79 pg/mL; Week 52 = 76.56

The results of evaluation of serum DHEA, estradiol, and estrone concentrations in trial participant Number 230-15-020 are as follows:

- DHEA Day 1 = 1945.46 pg/mL; Week 12 = 2795.08 pg/mL; Week 26 = 3580.97 pg/mL; Week 52 = 3493.64 pg/mL
- Estradiol Day 1 = 18.98 pg/mL; Week 12 = 24.39 pg/mL; Week 26 = 27.02 pg/mL; Week 52 = 26.72 pg/mL
- Estrone Day 1 = 36.54 pg/mL; Week 12 = 45.81 pg/mL; Week 26 = 50.31 pg/mL; Week 52 = 46.23

Throughout this application, the applicant asserts that “some women had taken exogenous estrogens (an excluded concomitant medication) as indicated by finding marked elevations of serum estrogens (estradiol, estrone, estrone-sulfate) without parallel changes in serum DHEA as well as ADT-G, the mail androgen metabolite.”

For trial participants 230-02-028 and 230-15-020, their reported DHEA levels were higher at Week 52 than at Day 1. Likewise, their reported estradiol and estrone levels were also higher at Week 52 than at Day 1. These two cases represent an increase in DHEA and a correlated increase in estradiol and estrone. These reported outcomes refute the applicant insertion that these two women had an estrogen signature typical of a woman who took estrogen.

In spite of the limited occurrence of these events, consideration should be given to including these reported effects on the endometrium in product labeling.

Table 25 shows the overall final diagnoses of the three independent pathologists for combined 12-week Trials ERC-210, ERC-231, and ERC-234, and 52-week Trial ERC-230.

Table 25: Overview of End-of-Trial Endometrial Biopsy Data from Combined 12-Week Trials ERC-210, ERC-231 and ERC-234, and 52-Week Trial ERC-230 – Final Diagnosis from Three Independent Pathologists

Parameters	Treatment Groups				
	Placebo N=284	0.25% (3.25 mg) DHEA N=283	0.50% (6.5 mg) DHEA N=812	1.0% (13 mg) DHEA N=54	Total (DHEA + Placebo N=1433
<b>Total Number of Women At Week-12 up to Week 52 (N, %)</b>	250 (88%)	250 (88%)	735 (90%)	51 (94%)	1286 (90%)
Women with end-of-trial endometrial biopsy	135 (54%)	128 (51%)	587 (80%)	32 (63%)	882 (69%)
Women who refused biopsy	2 (0.8%)	3 (1.2%)	34 (5%)	0 (0%)	39 (3%)
Hysterectomized Women	113 (45%)	119 (48%)	114 (15%)	19 (37%)	365 (28%)

<b>Final Diagnosis Histologic Characteristics (N, % of women with biopsy)</b>					
No tissue	7 (5%)	3 (2%)	17 (3%)	2 (6%)	29 (3%)
Tissue insufficient	2 (1%)	4 (3%)	25 (4%)	0 (0%)	31 (3%)
Atrophic	123 (91%)	121 (94%)	544 (93%)	29 (91%)	817 (93%)
Weakly proliferative	2 (1%) <sup>1</sup>	0 (0%)	0 (0%)	0 (0%)	2 (0.2%)
Disordered proliferative	0 (0%)	0 (0%)	1 (0.2%) <sup>1</sup>	1 (3%) <sup>1</sup>	2 (0.2%)
Complex hyperplasia with atypia	1 (0.7%) <sup>2</sup>	0 (0%)	0 (0%)	0 (0%)	1 (0.1%)
<b>Other Findings</b>					
Polyps					
- Atrophic	2 (1.2%)	3 (2.3%)	8 (1.4%)	0 (0%)	13 (1.5%)
- Functional	0 (0%)	0 (0%)	1 (0.2%) <sup>1</sup>	0 (0%)	1 (0.1%)

Source: Adapted from NDA 208470, NDA Amendment received July 12, 2016, Clinical Trial Report for ERC-237, Section 8 results, Table 7, page 22 of 81.

<sup>1</sup>Woman identified by applicant as having an estrogen signature

<sup>2</sup>Trial participant Number 234-30-040 in Trial ERC-234. (b) (4) first reader, did not provide the histologic characteristics on biopsy specimen and recommended follow-up. This woman underwent an endometrial curettage which reported fragments of benign endometrium with reactive changes consistent with effects of an intrauterine device.

### **Clinical Reviewer's Comments:**

No safety concerns arise from the data presented in Table 25 for the 0.50% DHEA vaginal insert administered intravaginally daily.

The Clinical Study Report for ERC-237 also provides summary data of end-of-trial endometrial biopsy listings of the final histologic characteristics reported following the reading of biopsy slides by each of the three independent pathologists.

The three independent pathologists were consistent in their diagnosis of the histological characteristics of the endometrial biopsy specimen in 807 (91.5%) of the 882 endometrial biopsy specimens examined for Trials ERC-210, ERC-230, ERC-231, and ERC-234. For examples, all three independent pathologists agreed that the endometrial biopsy specimen histologic characteristics showed an atrophic endometrium, or all three pathologists agreed that no endometrial tissue for diagnosis was found on the specimen slide.

For **75 specimen slides examined (8.5%)**, the three pathologists did not reach a consensus diagnosis on the histological characteristics of the biopsy specimen. This reviewer examined the reported histologic findings reached by the three independent pathologists, and the final diagnosis reported in the Clinical Trial Report for ERC-237, to determine consistency with the protocol submitted and reviewed for ERC-237.

Table 26 shows the final diagnosis reported by the applicant following reading of slides by the three independent pathologists.

Table 26: Summary Data of End-of-Trial Endometrial Biopsies Following Reading of Slides by Three Independent Pathologists and Final Diagnosis of 12-Week Trials ERC-210, ERC-231 and ERC-234, and 52-Week ERC-230

Trial ERC-210 – 12 Weeks		Histologic Characteristic of the Endometrium			
Trial Participant Number	Dose Group	(b) (4)			Final
210-11-042	Placebo	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
210-01-132	0.25% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
210-02-075	0.25% DHEA	No tissue	Atrophic	Tissue insufficient for diagnosis	Atrophic
210-05-053	0.25% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
210-01-063	0.50% DHEA	No tissue	Atrophic	Atrophic	Atrophic
210-02-001	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
210-05-012	0.50% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
210-05-022	0.50% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
210-01-360	1.0% DHEA	Inactive	Weakly proliferative	Disordered proliferative	Disordered proliferative
210-11-009	1.0% DHEA	Atrophic	Atrophic	Disordered proliferative	Atrophic
<b>Trial ERC-231 – 12-Weeks</b>					
231-14-005	Placebo	Tissue insufficient for diagnosis	Atrophic	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
231-05-026	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
231-14-009	0.50% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
231-30-030	0.50% DHEA	Tissue insufficient for diagnosis	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
<b>Trial ERC-234 – 12-Weeks</b>					
234-03-023	Placebo	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
234-04-027	Placebo	No tissue	Atrophic	Tissue insufficient for diagnosis	Atrophic
234-11-012	Placebo	Tissue insufficient for diagnosis	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
234-12-010	Placebo	Tissue insufficient for diagnosis	No tissue	Atrophic	Atrophic
234-12-019	Placebo	Tissue insufficient for diagnosis	Atrophic	Atrophic	Atrophic
234-30-007	Placebo	Weakly proliferative	Weakly proliferative	Disordered proliferative	Disordered proliferative
234-30-023	Placebo	Weakly proliferative	Weakly proliferative	Disordered Proliferative	Weakly proliferative
234-30-040	Placebo	- <sup>1</sup>	Atrophic	Complex hyperplasia with atypia	Complex hyperplasia with atypia
234-55-012	Placebo	Tissue insufficient for diagnosis	Atrophic	Atrophic	Atrophic
234-55-027	Placebo	No tissue	Atrophic	Tissue insufficient for diagnosis	Atrophic

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234-03-016	0.25% DHEA	No tissue	Atrophic	Tissue insufficient for diagnosis	Atrophic
234-06-004	0.25% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
234-12-004	0.25% DHEA	Tissue insufficient for diagnosis	Atrophic	Atrophic	Atrophic
234-21-022	0.25% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
234-12-026	0.25% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis 234-30-054
234.30-054	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
234-36-001	0.50% DHEA	Atrophic	Atrophic	Inactive	Atrophic
234-50-008	0.50% DHEA	No tissue	Atrophic	Tissue insufficient for diagnosis	Atrophic
234-60-027	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
<b>Trial ERC-230 – 52-Weeks</b>					
230-01-006	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-01-043	0.50% DHEA	Atrophic	No tissue	Atrophic	Atrophic
230-02-028	0.50% DHEA	Inactive	Weakly proliferative	Disordered proliferative	Disordered proliferative
230-02-034	0.50% DHEA	No tissue	Atrophic	Atrophic	Atrophic
230-02-046	0.50% DHEA	No tissue	Atrophic	No tissue	Atrophic
230-02-070	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-02-096	0.50% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
230-04-005	0.50% DHEA	Atrophic	Complex hyperplasia without atypia	Atrophic	Atrophic
230-04-011	0.50% DHEA	Atrophic	No tissue	Tissue insufficient for diagnosis	Atrophic
230-05-007	0.50% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
230-05-016	0.50% DHEA	Tissue insufficient for diagnosis	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-05-017	0.50% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
230-05-018	0.50% DHEA	Atrophic	No tissue	Atrophic	Atrophic
230-05-022	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-05-039	0.50% DHEA	Tissue insufficient for diagnosis	Atrophic	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-06-002	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-08-005	0.50% DHEA	Atrophic	No tissue	No tissue/Atrophic	Atrophic
230-08-006	0.50% DHEA	Atrophic	No tissue	Tissue insufficient for diagnosis/Atrophic	Atrophic
230-08-027	0.50% DHEA	No tissue	Atrophic	No tissue/Atrophic	Atrophic
230-08-034	0.50% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
230-08-036	0.50% DHEA	Tissue insufficient for diagnosis	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-11-009	0.50% DHEA	Tissue insufficient for diagnosis	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-11-022	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-11-023	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-11-026	0.50% DHEA	Atrophic	No tissue	Atrophic	Atrophic

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230-11-047	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-11-052	0.50% DHEA	Atrophic	No tissue	Atrophic	Atrophic
230-11-053	0.50% DHEA	Inactive	Atrophic	Atrophic	Atrophic
230-11-059	0.50% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
230-12-023	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-13-003	0.50% DHEA	No tissue	Atrophic	Atrophic	Atrophic
230-14-007	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-16-003	0.50% DHEA	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
230-23-006	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-30-009	0.50% DHEA	Tissue insufficient for diagnosis	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-31-004	0.50% DHEA	Tissue insufficient for diagnosis	No tissue	No tissue	Tissue insufficient for diagnosis
230-33-006	0.50% DHEA	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-44-001	0.50% DHEA	No tissue	Atrophic	Tissue insufficient for diagnosis	Atrophic
230-02-024	Discontinuation	Atrophic	Atrophic	Tissue insufficient for diagnosis	Atrophic
230-04-006	Discontinuation	No tissue	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-11-010	Discontinuation	Tissue insufficient for diagnosis	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis
230-13-009	Discontinuation	Tissue insufficient for diagnosis	No tissue	Tissue insufficient for diagnosis	Tissue insufficient for diagnosis

Source: Adapted from NDA 208470, NDA Amendment dated July 12, 2016, Clinical trial Report for ERC-237, Section 11.4 Histologic Characteristics of the Endometrium from 3 Independent Pathologists – Side-by-Side Comparison, pages 47 to 77 of 81.

**Clinical Reviewer’s Comments:**

The final diagnoses reported in the table above are consistent with the protocol submitted and reviewed for ERC-237.

**7.3.5.2 Cervical Cytology Evaluation:**

Papanicolaou (Pap) smears were conducted at baseline [unless obtained within 9 months of Day 1 of the trial (with confirmatory written documentation)] for 12-Week, phase 3, placebo-controlled Trials ERC-210, ERC-231, ERC-234 and ERC-238, and at baseline and end-of-trial for 52-Week open-label Trial ERC-230.

Cytological findings were categorized as follows using the Bethesda system<sup>6</sup> for reporting cervical and vaginal cytologic diagnoses:

- Atypical squamous cells
  - Atypical squamous cells of undetermined significance (ASC-US)

<sup>6</sup> Wilbur DC, Nayar R. Bethesda 2014: improving on a paradigm shift. Cytopathology. 2015 Dec;26(^):339-42.

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- Atypical squamous cells – cannot exclude HSIL (ASC-H)
  - Low grade squamous intraepithelial lesion (LGSIL or LSIL)
  - High grade squamous intraepithelial lesion (HGSIL or HSIL)
  - Squamous cell carcinoma
  - Atypical Glandular Cells not otherwise specified (AGC-NOS)
  - Atypical Glandular Cells, suspicious of AIS or cancer (AGC-neoplastic)
  - Adenocarcinoma *in situ* (AIS)

For inclusion in the DHEA clinical trials, women had to have a normal Pap smear (which includes inflammatory changes) at Baseline or within the last 12 months. Women with Baseline cervical cytology showing atypia of squamous cells of undetermined significance (ASCUS) or worse were excluded for trial participation. However, a woman was eligible for participation in the clinical trial if she had a Pap smear with a diagnosis of ASCUS at Baseline without a history of abnormal Pap smears within the last 2 years and a negative Human papillomavirus (HPV) test. Participating women also had an end-of-trial Pap smear performed in 52-Week Trial ERC-230.

Per the applicant, abnormal cytological findings (for example, ASCUS or LSIL), observed on vaginal smears, collected to determine the percentage of superficial and parabasal cells, performed after Day 1 or later were documented as TEAEs in all clinical trials conducted. The Preferred MedDRA term for these TEAEs is “cervical dysplasia”. The applicant cautions, however, that “atrophic vaginal cells can be reported as ASCUS”.

Treatment-emergent cervical dysplasia was reported in 6 women in the placebo treatment group (1.3%, 6 of 474 placebo-treated women) in 12-week clinical Trials ERC-210, ERC-231, and ERC-234. See Table 27.

Table 27: Women with Treatment-Emergent Adverse Event “Cervical Dysplasia” in the Placebo Treatment Group in 12-Week Clinical Trials ERC-210, ERC-231, and ERC-234

Subject	Treatment	Hysterectomy	Finding <sup>1</sup>	Visit <sup>2</sup>	HPV Test	Comments
<b>Trial ERC-210 – 12-Weeks</b>						
210-01-065	Placebo	No	LSIL reported on vaginal smear, Screening Pap smear normal	Day 29	Not performed	Discontinued clinical trial, colposcopy not performed
210-01-461	Placebo	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Day 57	Not performed	Normal vaginal smear at Week 12, colposcopy not performed
<b>Trial ERC-231 – 12 Weeks</b>						

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231-01-018	Placebo	Yes	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Positive	Normal vaginal smear at Week 12, colposcopy not performed
231-05-005	Placebo	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Not performed	Normal vaginal smear at Week 12, colposcopy not performed
<b>Trial ERC-234 – 12 weeks</b>						
234-06-025	Placebo	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Negative	ASCUS reported on vaginal smear at Week 12, colposcopy not performed
234-54-010	Placebo	No	LSIL reported on vaginal smear, Screening Pap smear normal	Week 12	Positive	2 <sup>nd</sup> Pap result reported as normal, colposcopy not performed

Source: Adapted from NDA 208470, Clinical Trial Report for Trial ERC-210, 16.2.6 Listing of Adverse Events; Clinical Trial Report for ERC-231, Table 10-37, page 223 of 591; Clinical Trial Report for ERC-234, Table 10-28, page 262 of 750.

<sup>1</sup> Findings: ASCUS = Atypical Squamous Cells of Unknown Significance (including atrophic cells); CIN = Cervical intraepithelial Neoplasia; LSIL Low grade Squamous Intraepithelial Lesion; HSIL = High grade Squamous Intraepithelial Lesion

<sup>2</sup> Visit at which treatment-emergent adverse event was found.

**Clinical Reviewer’s Comments:**

All six of the placebo-treated women listed above had an abnormal finding reported on a vaginal wall smear (ASCUS or LSIL) and a normal Baseline Pap smear. Two of these six women had a positive HPV test; one had a negative HPV test.

ASCUS on a vagina wall smear or a Pap smear does not indicate a “cervical dysplasia”.<sup>7</sup> In this case, however, the applicant complied with the Preferred MedDRA term.

In the DHEA development program, HPV test were performed when indicated, although inconsistently, as noted in Table 27. Human Papilloma Virus (HPV) is a common sexually transmitted virus that causes cervical dysplasia. There are

<sup>7</sup> McGrath CM. ASCUS in Papanicolaou smears. Problems, controversies, and potential future directions. Am J Clin Pathol 2002 Jun;117 Suppl:S62-75.

hundreds of types of HPV virus. Some are low-risk causing genital warts. HPV types 6 or 11 are commonly found at time of detection of genital warts. HPV 16, 18, 31, 33, and 35 are found occasionally as coinfection with HPV 6 or 11 in genital warts.

Others types of HPV virus are high-risk and can cause cell changes that can turn into cervical dysplasia or cancer. HPV types 16 and 18 are responsible for most HPV-caused cancers (cervical, anal, oropharyngeal, and rarer cancers). This application reports HPV testing as negative or positive, without regards to the type of HPV virus found.

Participating woman Number 234-54-010, with a positive HPV test, had low-grade squamous intraepithelial lesion (LSIL) reported on a vaginal wall smear. LSIL indicates cellular tissue damage or dysplasia. The viral etiology of true cervical dysplasia, such as LSIL, is well established.

Treatment-emergent cervical dysplasia was reported in 8 women in the 0.25% DHEA treatment group (2.8%, 8 of 282 women treated with 0.25% DHEA) in 12-week clinical Trials ERC-231, and ERC-234. See Table 28.

Table 28: Women with Treatment-Emergent Adverse Event “Cervical Dysplasia” in the 0.25% DHEA Treatment Groups in 12-Week Clinical Trials ERC-231 and ERC-234

Subject	Treatment	Hysterectomy	Finding <sup>1</sup>	Visit <sup>2</sup>	HPV Test	Comments
<b>Trial ERC-231 – 12-Weeks</b>						
231-05-050	0.25% DHEA	Yes	LSIL reported on vaginal smear, Screening Pap smear normal	Day 1	Not performed	Discontinued for inclusion criterion violation
<b>Trial ERC-234</b>						
234-06-010	0.25% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 2	Negative	Normal vaginal smear at Week 12, colposcopy not performed
234-11-005	0.25% DHEA	Yes	ASCUS LSIL reported on vaginal smear, Screening Pap smear normal	Week 2 Week 6	Positive	Normal colposcopy, ASCUS on vaginal smear at discontinuation
234-18-019	0.25% DHEA	No	ASCUS reported on vaginal	Week 2	Negative	Normal vaginal smear at Weeks 6 and

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			smear, Screening Pap smear normal			12, colposcopy not performed
234-21-022	0.25% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 2	Negative	Normal vaginal smear reported at Weeks 6 and 12
234-36-027	0.25% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Screening	Negative	Discontinued, ASCUS on vaginal smear
234-36-037	0.25% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 2	Negative	Normal vaginal smear reported at Weeks 6 and 12
234-59-003	0.25% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Negative	Normal vaginal smear reported at Week 12

Source: Adapted from NDA 208470, Clinical Trial Report for ERC-231, Table 10-37, page 223 of 591;  
Clinical Trial Report for ERC-234, Table 10-28, page 262 of 750.

<sup>1</sup> Findings: ASCUS = Atypical Squamous Cells of Unknown Significance (including atrophic cells); CIN = Cervical intraepithelial Neoplasia; LSIL Low grade Squamous Intraepithelial Lesion; HSIL = High grade Squamous Intraepithelial Lesion

<sup>2</sup> Visit at which treatment-emergent adverse event was found.

**Clinical Reviewer's Comments:**

All eight of these participating women had normal Pap smears reported at Baseline with abnormal cells reported on the vaginal wall smear (ASCUS or LSIL). Six of these 8 women had negative HPV tests. Participating woman Number 234-11-005 had a positive HPV test and a normal colposcopy at discontinuation. The one reported case of LSIL was reported on Day 1 resulting in discontinuation.

Treatment-emergent cervical dysplasia was reported in a total of 41 women in the 0.50% DHEA treatment group (3%, 41 of 1196 women treated with 0.50% DHEA) in 12-week clinical Trials ERC-210, ERC-231, ERC-234, and ERC-238, and 52-week clinical Trial ERC-230. See Table 29.

Table 29: Women with Treatment-Emergent Adverse Event “Cervical Dysplasia” in the 0.50% DHEA Treatment Group in 12-Week Clinical Trials ERC-210, ERC-231, ERC-234, ERC-238, and 52-Week Clinical Trial ERC-230

Subject	Treatment	Hysterectomy	Finding <sup>1</sup>	Visit <sup>2</sup>	HPV Test	Comments
<b>Trial ERC-210 – 12-Weeks</b>						
210-01-103	0.50% DHEA	No	LSIL reported on vaginal smear at Week 12, Screening Pap smear normal	Week 12	Not performed	Colposcopy not performed
210-01-504	0.50% DHEA	Yes	LSIL reported on vaginal smear, Screening Pap smear normal	Day 60	Not performed	Discontinued, normal vaginal smear reported
<b>Trial ERC-231 - 12 Weeks</b>						
231-01-024	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 12	Not performed	Colposcopy not performed
231-15-007	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Day 1	Not performed	Discontinued for inclusion criterion violation
231-21-008	0.50% DHEA	Yes	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Not performed	Normal vaginal smear at Week 12
<b>ERC-234 – 12 Weeks</b>						
234-04-008	0.50% DHEA	No	LSIL reported on Screening <b>Pap</b> smear	Screening	Not performed	HSIL at colposcopy
234-04-020	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 2	Positive	Normal colposcopy, normal vaginal smear at Weeks 6 and 12
234-05-012	0.50% DHEA	No	ASCUS reported on vaginal	Week 12	Not performed	Colposcopy not performed

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			smear, Screening Pap smear normal			
234-36-024	0.50% DHEA	Yes	LSIL reported on vaginal smear, Screening Pap smear normal	Week 2	Positive	Discontinued, exclusion criteria #16 not met
234-39-020	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Positive	ASCUS on vaginal smear at Week 12, CIN I-II at colposcopy
234-47-008	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Negative	ASCUS reported on vaginal smear at Week 12, colposcopy not performed
234-60-016	0.50% DHEA	Yes	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 2	Not performed	Discontinued trial, follow-up with primary care physician
234-65-013	0.50% DHEA	Yes	ASCUS reported on vaginal smear, Screening Pap smear normal	Day 1	Not performed	Normal vaginal smear at Weeks 2, 6, and 12
<b>Trial ERC-238 – 12 Weeks</b>						
238-12-015	0.50% DHEA	Yes	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Negative	Normal vaginal smear reported at Week 12
238-15-001	0.50% DHEA	Yes	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Negative	Normal vaginal smear reported at Week 12
238-30-046	0.50% DHEA	No	ASCUS reported on vaginal smear,	Week 12	Not performed	Referred to primary care physician for follow-up

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			Screening Pap smear normal			
238-54-014	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 12	Negative	Colposcopy not performed, no additional comments
238-60-029	0.50% DHEA	No	LSIL reported on vaginal smear, Screening Pap smear normal	Week 6	Not performed	Normal vaginal smear at Week 12, normal colposcopy
238-75-011	0.50% DHEA	No	LSIL reported on vaginal smear, Screening Pap smear normal	Week 6	Not performed	LSIL on vaginal smear at Week 12, abnormal colposcopy, chronic cervicitis
238-84-022	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 6	Negative	Normal vaginal smear reported at Week 12
<b>Trial ERC-230 – 52 Weeks</b>						
230-01-041	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 26	Negative	Normal vaginal smear at Week 52, normal Pap smear at Week 52
230-02-039	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 52	Negative	Normal Pap smear reported at Week 52
230-02-046	0.50% DHEA	No	ASCUS reported on Pap smear, Screening Pap smear normal	Week 52	Negative	No comments
230-02-078	0.50% DHEA	No	LSIL reported on vaginal smear, Screening Pap smear	Week 52	Not performed	Normal Pap smear at Week 52, normal colposcopy

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230-08-001	0.50% DHEA	No	normal ASCUS reported on <b>Pap</b> smear, Screening Pap smear normal	Week 52	Positive	Normal colposcopy
230-08-007	0.50% DHEA	No	ASCUS reported on <b>Pap</b> smear, Screening Pap smear normal	Week 52	Negative	No comments
230-08-023	0.50% DHEA	No	ASCUS reported on <b>Pap</b> smear, Screening Pap smear normal	Week 52	Negative	Cervical biopsy reported as normal
230-11-037	0.50% DHEA	No	LSIL reported on <b>Pap</b> smear, Screening Pap smear normal	Week 52	Not performed	Normal colposcopy
230-11-040	0.50% DHEA	No	LSIL reported on vaginal smear, Screening Pap smear normal	Discontinued	Positive	LSIL on vaginal smear at discontinuation, normal Pap smear, normal colposcopy
230-12-013	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 52	Negative	Normal Pap smear at Week 52
230-13-004	0.50% DHEA	No	ASCUS reported on <b>Pap</b> smear, Screening Pap smear normal	Week 52	Negative	No comments
230-18-012	0.50% DHEA	No	ASCUS reported on <b>Pap</b> smear, Screening Pap smear normal	Week 52	Positive	Normal colposcopy
230-22-002	0.50% DHEA	No	ASCUS reported on <b>Pap</b> smear, Screening Pap smear normal	Week 52	Negative	No comments
230-24-025	0.50% DHEA	No	ASCUS	Week 52	Not	Normal

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			(possible HSIL) reported on <b>Pap</b> smear, Screening Pap smear normal		performed	colposcopy, normal cervical biopsy
230-30-001	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	< 26 Weeks	Not performed	Discontinued, Pap smear reported as normal
230-30-006	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 52	Negative	Normal Pap smear at Week 52
230-31-007	0.50% DHEA	No	ASCUS reported on vaginal smear, normal Screening Pap smear	Week 52	Not performed	Normal Pap smear reported at Week 52
230-35-006	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	Week 52	Not performed	Normal Pap smear at Week 52
230-36-026	0.50% DHEA	No	ASCUS reported on vaginal smear, Screening Pap smear normal	< 26 Weeks	Positive	Discontinued, no additional comments
230-38-004	0.50% DHEA	No	ASCUS reported on <b>Pap</b> smear, Screening Pap smear normal	Week 52	Negative	No comments
230-39-002	0.50% DHEA	No	ASCUS reported on <b>Pap</b> smear, Screening Pap smear normal	Week 52	Negative	No comments

Source: NDA 208470, Clinical Trial Report for Trial ERC-210, 16.2.6 Listing of Adverse Events; Clinical Trial ERC-231, Table 10-37, page 223 of 591; Clinical Trial Report for ERC-234, Table 10-28, page 262 of 750; Clinical Trial Report for ERC-238, Table 10-43, page 232 of

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601; Clinical Trial Report for ERC-230, Table 10-8, page 146 of 860 and Table 10-80, page 241 of 860.

<sup>1</sup> Findings: ASCUS = Atypical Squamous Cells of Unknown Significance (including atrophic cells); CIN = Cervical intraepithelial Neoplasia; LSIL = Low grade Squamous Intraepithelial Lesion; HSIL = High grade Squamous Intraepithelial Lesion

<sup>2</sup> Visit at which treatment-emergent adverse event was found.

### **Clinical Reviewer's Comments:**

Table 29 presents a total of 41 women diagnosed with "treatment-emergent cervical dysplasia" by Preferred MedDRA term in the 0.50% DHEA treatment group. Twenty (20) cases, of the total 41 cases, of "treatment-emergent cervical dysplasia" were diagnosed in 12-week, placebo-controlled clinical Trials ERC-210, ERC-231, ERC-234, and ERC-238. Twenty-one (21) cases, of the total 41 cases, of "treatment-emergent cervical dysplasia" were diagnosed in 52-week, open-label clinical Trial ERC-230.

As shown in Table 29, in 12-week placebo-controlled clinical Trials ERC-210, ERC-231, ERC-234, and ERC-238, 14 women were diagnosed with ASCUS on a lateral wall vaginal smear that had a normal Pap smear at Screening. Two (2) of these 14 women had a positive HPV test (Number 234-04-020 and Number 234-39-020; HPV type not identified), five of these 14 women had a negative HPV test, and no HPV testing was performed or reported for 7 of these 14 women.

In these same placebo-controlled clinical trials, five women were diagnosed with LSIL on a lateral wall vaginal smear that had a normal Pap smear at Screening. One (1) of these 5 women had a positive HPV test (Number 234-36-024; HPV type not identified), and four of these 5 women had no HPV test performed or recorded. Only one woman (Number 234-08-008) in the placebo-controlled trials had LSIL reported on a Screening Pap smear. She was discontinued for not meeting the inclusion criteria. Her colposcopy showed HSIL. A HPV test was not performed or recorded for this woman.

Eight (8) of the 41 women shown in Table 29, in 52-week Trial ERC-230, had ASCUS diagnosed on a lateral wall vaginal smear at Week 52 or discontinuation that had a normal Pap smear at Screening. One (1) of these 8 women has a positive HPV test (Number 230-36-026; HPV type not identified). Four (4) of these 8 women had a negative HPV test; the remaining 3 of these 8 women had no HPV test performed or recorded.

Two (2) women in Trial ERC-230 had LSIL diagnosed on a lateral wall vaginal smear at Week 52 that had a normal Pap smear at Screening. One (1) of these 2 women had a positive HPV test (Number 230-11-040; HPV type not identified), the other women did not have an HPV test performed or recorded.

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Eleven women in Trial ERC-230 had an abnormal Pap smear recorded at Week 52. Ten (10) of these eleven women had ASCUS diagnosed on a Pap smear at Week 52; one (1) woman had LSIL diagnosed on her Pap smear at Week 52 (Number 230-11-037). All of these 11 women had a normal Pap smear at Screening. Two (2) of these 11 women had a positive HPV test (Numbers 230-08-001 and 230-18-012; HPV type not identified). Both of these women had a normal colposcopy at Week 52. Seven (7) of these 11 women had negative HPV test; two (2) women did not have an HPV test performed or recorded.

As previously stated, ASCUS on a vagina wall smear or a Pap smear does not always indicate a "cervical dysplasia". Overall, few women discontinued because of reported findings of ASCUS or LSIL on a vaginal smear [one in the placebo treatment group (0.2%, 1 of 474 placebo treatment group), and 7 in the 0.50% DHEA treatment group (0.6%, 7 of 1196 women)]. None of these abnormal vaginal wall smears, or Pap smears, were considered related to the trial drug or placebo in the application.

This reviewer notes an association with DHEA and treatment-emergent abnormal Pap smears consisting of ASCUS or LSIL. These abnormal Pap smear results should be included in labeling.

### 7.3.5.3 Usability of the Applicator:

No formal use study of the to-be-marketed applicator was performed in the clinical development of prasterone.

In the conduct of Trial ERC-238, a questionnaire was given to participating women and their partners to assess some usability information on the DHEA vaginal insert.

A total of 373 women in the PP population responded to the usability questionnaire for both treatment groups (119 women in the placebo treatment group and 254 women in the 0.50% treatment group).

The questionnaire eliciting responses to seven individual questions is presented as follows:

1. Did you have difficulties to load the applicator?  No  Yes  
If yes, how difficult was it? Very little difficulty → Very difficult; scale of 1 to 5
2. Did you have difficulties in performing an application?  No  Yes  
If yes, how difficult was it? Very little difficulty → Very difficult; scale of 1 to 5
3. Did you feel pain, when inserting the applicator?  No  Yes  
If yes, how painful was it? Very little pain → Very painful; scale of 1 to 5.
4. Did you feel pain, when withdrawing the applicator after the application:  No  Yes

- If yes, how painful was it? Very little pain → Very painful; scale of 1 to 5
5. Did you have any trouble in understanding the instructions how to administer the (b) (4)  No  Yes
- If yes, how difficult was it? Very little difficulty → Very difficult; scale of 1 to 5
6. Overall, what do you like about this applicator device? What do you dislike about it? Is there anything you would change about it? Space provided for response.
7. How confident are you that you can perform an application with the applicator of (b) (4) successfully in the future? Very confident → Not confident at all; scale of 1 to 5.

Participant response to the Use Questionnaire is presented in Table 30.

Table 30: Usability of the Applicator (Question 6) – Summary of Principal Like/Recommended Improvement about the Applicator (PP Population)

Comments	Placebo N = 119 N (%)	0.50% DHEA N = 254 N (%)	Overall <sup>1</sup> N = 373 N (%)
<b>Liked Applicator</b>			
- Applicator was easy to use	37 (31%)	62 (24%)	99 (27%)
- Applicator works fine	20 (17%)	49 (19%)	69 (18%)
- Would not change anything	30 (25%)	52 (20%)	82 (22%)
- Good size (compact/small/diameter/thinness)	3 (3%)	8 (3%)	11 (3%)
- Comfortable (soft and smooth material)	1 (1%)	8 (3%)	9 (2%)
- Good packaging (disposable/hygienic)	2 (2%)	5 (2%)	7 (2%)
- Painless	2 (2%)	5 (2%)	7 (2%)
- No Comment	33 (28%)	81 (32%)	114 (31%)
<b>Recommended Improvement</b>			
- Insert fell out from applicator	4 (3%)	11 (4%)	15 (4%)
- Prefer reusable applicator	5 (4%)	6 (2%)	11 (3%)
- Make applicator rounder/softer/smaller	2 (2%)	5 (2%)	7 (2%)
- Preload applicator with insert	0 (0%)	5 (2%)	5 (1%)
- Lubricate applicator	1 (1%)	1 (0%)	2 (1%)
- Other Comments	4 (3%)	8 (3%)	12 (3%)

Source: NDA 208470, Trial ERC-238 clinical Trial Report, Table 11-2, page 235 of 601.

<sup>1</sup>A woman may be counted more than once in each category.

**Clinical Reviewer’s Comments:**

Questions number 1 through number 5 assessed whether the woman had difficulty in loading the applicator; difficulties understanding the applicator use instructions or pain with insertion and removal of the combination drug-device

Per the Trial ERC-238 protocol, the applicator would be evaluated as suitable if at least 80% of women reported a global score  $\leq 2$  units for questions 1 to 5. Per the Clinical Trial Report, 94% to 100% of women had a score  $\leq 2$  units in these 5 questions in both the placebo and DHEA treatment groups, respectively, thus indicating a high degree of satisfaction with the use of the applicator.

Question 6 allowed the subject to state her likes/dislikes regarding the applicator and any recommended changes to be made to the applicator. Refer to the table for findings. It is interesting to note, however, that 31% of trial participants (who completed the applicator questionnaire had no comments.

Spontaneous comments regarding the insert itself included:

- Difficulty in unwrapping the insert (98 comments)
- Insert too small for the applicator (3 comments)
- Insert too oily (4 comments)

Question 7 in the questionnaire assessed the woman's confidence in future use of the applicator. Overall, 92.5% indicated that they were very confident that they could perform an application with the applicator in the future. This suggests that the instructions for use of the combination drug-device are adequate.

Overall, 31% (114 of 373 women) of the participating women in Trial ERC-238 failed to provide any comments on the applicator use questionnaire. The remaining women (59%, 259 of 373 women) "liked" and successfully used the applicator.

It should be noted, however, that although similar, the to-be-marketed applicator is not the same as the applicator used in the clinical trials. EndoCeutics will be requested to provide specific focused pharmacovigilance information in the NDA Annual Report regarding the to-be-marketed applicator, particularly for issues regarding difficulty of insertion and/or removal of the applicator, and subsequent vaginal abrasion and/or laceration of the vaginal wall with use of the applicator.

#### 7.3.5.4 Possible Influence of Treatment on the Male Partner:

The potential influence of DHEA on the woman's male partner (related to intercourse) was evaluated, as a secondary objective in Trial ERC-238. Male partners self-completed a questionnaire, on a voluntary basis, at Screening and at Week 12. The Screening and Week 12 questionnaires had 5 similar questions pertaining to penile irritation, pain, redness, and duration of redness. The Week 12 questionnaire had 1 additional question (question 6) assessing the "situation" at Screening and comparing the difference at Week 12. The male partner questionnaire was as follows:

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1. Did you feel the vaginal dryness of your partner during intercourse:
  - Almost never or never (scored as 0)
  - A few times (less than half the time) (scored as 1)
  - Sometimes (about half the time) (scored as 2)
  - Most times (more than half the time) (scored as 3)
  - Almost always or always (scored as 4)
2. Did you feel irritation or pain on your penis at intercourse? Same responses as above for question 1. Same scoring system was used for this question as used for question 1.
3. How do you rate the irritation or pain on your penis at intercourse?
  - None (no irritation or pain) (scored as 0)
  - Mild (scored as 1)
  - Moderate (scored as 2)
  - Severe (scored as 3)
  - Very severe (scored as 4)
4. Did you have redness on your penis following intercourse? Same responses as above for question 3. Same scoring system was used for this question as used for question 3.
5. How long did the redness on your penis last following intercourse:
  - No redness (scored as 0)
  - Up to 5 minutes (scored as 1)
  - 5 to 60 minutes (scored as 2)
  - One to 6 hours (scored as 3)
  - More than 6 hours (scored as 4)

The Week 12 questionnaire included 1 additional question (question 6):

6. Which difference do you find comparing the situation before starting treatment of your partner?
  - Very improved (scored as 2)
  - Improved (scored as 1)
  - No change (scored as 0)
  - Worse (scored as -1)
  - Much worse (scored as -2)

Per the protocol for Trial ERC-238 participating women were given a letter addressed to her stable male partner containing a brief explanation of the expected role of the male partner, a consent form, and a questionnaire in a self-addressed returned envelope. A phone call to the male partner was made during Screening and at Week 12, by the clinic staff, to provide information concerning the consent form and the short questionnaire, and to remind him to return the consent form and questionnaire if he agreed to participate.

Based on the answers provided on the Week 12 questionnaire, the clinic site Investigator (or his designee) called the male partner to get additional information if “worse” or “much worse” was answered for question 6 on the questionnaire and to report adverse event(s), if applicable. The Investigator at each site determined if the male partner needed to be seen in the clinic for reported adverse events.

A total of 100 male partners answered the Male Partner Exposure Questionnaire (34 male partners of trial participants in the placebo treatment group, and 66 male partners of trial participants in the 0.50% DHEA treatment group).

Analysis of the data from the male partner questionnaire was performed on the male partners of women who were part of the PP population and who have filled the male partner questionnaire at both baseline and Week 12. Paired t-tests were performed to determine the statistical significance for the changes from baseline to Week 12.

Data at Screening and Week 12 as well as changes from baseline to Week 12 are summarized individually for each question for Questions 1 through 5 by treatment group (placebo and DHEA separately) in Table 31.

Table 31: Male Partner Questionnaire Results (Questions 1 to 5)

<b>Question Visit Parameter</b>	<b>Placebo N = 34</b>	<b>0.50% DHEA N = 66</b>
Question 1 <sup>1</sup>		
Screening		
- Mean (SEM)	2.76 (0.24)	2.88 (0.16)
Week 12		
- Mean (SEM)	1.82 (0.27)	1.18 (0.17)
- Change from Baseline (SEM)	-0.94 (0.30)	-1.70 (0.20)
- Score ≤ 1	97	98
- Difference from Placebo <sup>2</sup>	-	-0.76
- P-value	-	0.0347
Question 2 <sup>3</sup>		
Screening		
- Mean (SEM)	1.62 (0.25)	1.73 (0.20)
Week 12		
- Mean (SEM)	0.74 (0.23)	0.41 (0.11)
- Change from Baseline (SEM)	-0.88 (0.29)	-1.32 (0.20)
- Score ≤ 1	94	97
- Difference from Placebo	-	-0.44
- P-value	-	0.2164
Question 3 <sup>4</sup>		
Screening		
- Mean (SEM)	1.38 (0.18)	1.21 (0.13)
Week 12		
- Mean (SEM)	0.62 (0.17)	0.38 (0.08)
- Change from Baseline (SEM)	-0.76 (0.20)	-0.83 (0.14)
- Score ≤ 1	97	98

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- Difference from Placebo	-	-0.07
- P-value	-	0.7760
Question 4 <sup>5</sup>		
Screening		
- Mean (SEM)	0.91 (0.16)	0.82 (0.12)
Week 12		
- Mean (SEM)	0.41 (0.11)	0.21 (0.06)
- Change from Baseline (SEM)	-0.50 (0.15)	-0.61 (0.11)
- Score ≤ 1	100	100
- Difference from Placebo	-	-0.11
- P-value	-	0.5547
Question 5 <sup>6</sup>		
Screening		
- Mean (SEM)	1.18 (0.22)	1.02 (0.15)
Week 12		
- Mean (SEM)	0.47 (0.13)	0.27 (0.08)
- Change from Baseline (SEM)	-0.71 (0.22)	-0.74 (0.14)
- Score ≤ 1	100	100
- Difference from Placebo	-	-0.04
- P-value <sup>1</sup>	-	0.8833

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 25, pages 96 and 97 of 662.

<sup>1</sup>Did you feel the vaginal dryness of your partner during intercourse?

<sup>2</sup>Difference from placebo: DHEA (Week 12 – baseline mean) – Placebo (Week 12 mean – baseline mean).

<sup>3</sup>Did you feel irritation or pain on your penis at intercourse?

<sup>4</sup>How do you rate the irritation or pain on your penis at intercourse?

<sup>5</sup>Did you have redness on your penis following intercourse?

<sup>6</sup>How long did the redness on your penis last following intercourse?

Per the applicant, the administration of intravaginal DHEA to women was considered to have no significant negative effect on the male partner if at least 80% of male partners from the DHEA-treated group had a global score ≤ 1 for changes from baseline to Week 12.

**Clinical Reviewer’s Comments:**

The data demonstrated in Table 31 does not present a clear picture regarding the safety of the exposed male partner. Four (4) of the 5 questions included in a self-administered questionnaire of male partners failed to demonstrate improvement at Week 12 for the 0.50% DHEA vaginal insert compared to the placebo vaginal insert.

Only question number 1, “Did you feel the vaginal dryness of your partner during intercourse?” showed a statistically significant difference versus placebo at Week 12 (p=0.0347). The remaining 4 questions did not.

The severity score for penile irritation or pain at intercourse (question number 2) did not show a statistically significant decrease vs. placebo for the 0.50% DHEA

treatment group. Likewise, the severity score for penile redness following intercourse (question number 4) did not show a statistically significant decrease vs. placebo for the 0.50% DHEA treatment group. It should be pointed out, however, that these male responders reported less than mild redness (scored as 1) at baseline in both treatment groups.

Tables 32 and 33 show the response to question number 6, “Which difference do you find comparing to the situation before starting treatment of your partner?” completed only at Week 12. Question 6 was evaluated on a 5-point Likert scale: very improved = 2; improved = 1; no change = 0; worse = (-) 1; much worse = (-) 2.

Table 32: Male Partner Questionnaire: Number of Responses by Category to Question 6

Category of Response	Placebo N = 34	0.50% DHEA N = 66
Very Improved	6 (18%)	24 (36%)
Improved	14 (41%)	24 (36%)
No Change	14 (41%)	18 (27%)
Worse	0	0
Much Worse	0	0

Source: Adapted from NDA 208470, Trial ERC-238 Clinical Trial Report, Table 11-6, page 241 of 601.

Table 33: Male Partner Questionnaire (Question 6: Week 12)

Visit Parameter	Placebo N = 34	0.50% DHEA N = 66
Week 12		
- Mean (SEM)	0.76 (0.13)	1.09 (0.10)
- Difference from Placebo	-	0.33
- P-value <sup>1</sup>	-	0.0503

Source: Adapted from NDA 208470, Trial ERC-238 Clinical Trial Report, Table 11-7, page 241 of 601.

<sup>1</sup>T-test comparison.

**Clinical Reviewer’s Comments:**

As shown in Table 33, a statistically significant (p-value of 0.0503 utilizing a 2-sample t-test comparison) improvement was demonstrated in the 0.50% DHEA treatment group vs. placebo.

No adverse reactions were reported by male partners of women treated with DHEA or placebo vaginal inserts in Trial ERC-238.

Although self-administered, the Male Partner Questionnaire provides limited information due to the directed nature of the questions regarding applicant-

selected adverse outcomes. More open-ended questions regarding adverse events may have been more informative.

The results of the Male Partner Questionnaire, collected as a secondary endpoint in Trial ERC-238, should not be included in labeling.

The applicant confirms that serum estradiol and testosterone levels were not collected in these male partners in Trial ERC-238 because adult men have higher serum levels of estradiol and testosterone than postmenopausal women. Per the applicant, the normal serum estradiol level in an adult male is 5.2-fold higher than in a postmenopausal woman ( $21.5 \pm 0.3$  versus  $4.17 \pm 3.27$  pg/ml, respectively); the normal serum testosterone level in an adult male is 32.6-fold higher than in a postmenopausal woman ( $4.57 \pm 0.05$  versus  $0.14 \pm 0.7$  ng/mL, respectively). (See Labrie, Cusan et al. 2009 in the application.) Consequently, per the applicant, “the biologically non-significant changes observed in women could not even be detected in men where the baseline values are so much higher.”

**Clinical Reviewer’s Comments:**

This reviewer agrees that the collection of serum estradiol and testosterone concentrations in the male partners of study participants in Trial ERC-238 would not have provided useful information.

7.3.5.5 Transvaginal Ultrasound in 52-Week Trial ERC-230:

Transvaginal ultrasound (TVU) was used to evaluate endometrial thickness in 42 women at discontinuation or Week 52 in Trial ERC-230, particularly for those women who refused the end-of-trial endometrial biopsy or when an endometrial biopsy did not yield sufficient tissue for diagnosis. The endometrial double-wall thickness was < 4 mm in 37 women (88% 37 of 42 women; range 0.4 mm to 3.5 mm). Three (3) women (7%, 3 of 42 women) had a double-wall endometrial thickness evaluated at 5 mm (see Table 21 in this review). These women are discussed below:

- 1) Number 230-05-016: TVU performed two weeks after last dose of 0.50% DHEA vaginal insert on March 29, 2012 also showed an ultrasonographic anomaly near the uterine fundus. A dilatation and curettage was completed on May 11, 2012 that yielded fragments of atrophic endometrium.
- 2) Number 230-11-010: Discontinued Trial ERC-230 after 5.5 months of treatment with 0.50% DHEA vaginal insert. She had a TVU performed after 1 month of using of Estring®. Her radiologist considered the TVU findings of 5 mm as within normal limits.
- 3) Number 230-11-062: Refused her endometrial biopsy at Week 52 and had a TVU performed. Her radiologist considered the TVU finding of 5 mm as within normal limits

Two (2) women (5%, 2 of 42 women) had a double-wall endometrial thickness evaluated at 6 mm (see Table 21 in this review). These women are discussed below.

- 1) Number 230-11-035: Refused her endometrial biopsy at Week 52 and had a TVU performed 3 weeks after her last dose of 0.50% DHEA and 2 weeks after starting Vagifem®. The radiologist did not comment on the significance of an endometrial double-wall thickness of 6 mm.
- 2) Number 230-11-057: End-of-trial endometrial biopsy did not yield sufficient tissue for diagnosis. This woman had a hysterectomy performed at the time of her uterine prolapse and cystocele repair surgery approximately 12 weeks after completing Trial ERC-230. Histopathologic examination of the uterus showed an atrophic and inactive endometrium.

**Clinical Reviewer's Comments:**

These reported TVU findings do not raise safety concerns for the 0.50% DHEA vaginal insert. The average double-wall endometrial thickness reported in these 42 cases was  $2.2 \pm 1.4$  mm (means  $\pm$  standard deviation).

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Overall, in the DHEA development program, half of the women in the safety population experienced at least one TEAE of any nature with the following frequencies:

- Placebo = 47.7% (226 out of 474 women in placebo-treatment groups)
- DHEA 0.25% = 53.2% [150 out of 282 women in 0.25% DHEA treatment group(s)]
- DHEA 0.50% = 52.4% (627 out of 1196 women in 0.50% DHEA treatment group(s)]
- DHEA 1.0% = 64.1% [41 of 64 women in 1.0% DHEA treatment group(s)]
- Total DHEA = 53.0% [818 of 1542 women in 0.25%, 0.50%, and 1.0% DHEA treatment groups in Trials ERC-210, ERC-213, ERC-230 (up to Week 16), ERC-231, ERC-234, and ERC-238]

According to the investigators' assessments of severity, the majority of TEAEs were mild.

Per the applicant, "the only drug-related TEAEs were application site discharge and increased libido." "Application site discharge was due to melting of the vehicle Witepsol with the possible addition of increased vaginal secretions stimulated by DHEA." "It is the Sponsor's opinion that none of the remote (non-local) TEAEs can be attributed to

DHEA because there were no clinically meaningful changes in serum steroid levels in either the DHEA or placebo treatment groups, in agreement with the physiology of DHEA.”

**Clinical Reviewer’s Comments:**

See the Clinical Pharmacology Review for a full discussion of serum estradiol and testosterone concentrations in postmenopausal women following the use of the 0.50% DHEA vaginal insert.

Women with TEAEs by primary system organ class (SOC) and preferred terms are presented in Table 34. Table 34 includes TEAEs from the four 12-week, placebo-controlled Clinical Trials (ERC-210, ERC-231, ERC-234, and ERC-238), and TEAEs from the first 16-weeks of 52-week, open-label Trial ERC-230.

Table 34: Summary of Number (%) of Women with Treatment-Emergent Adverse Events in ≥ 1% by Preferred Term; Safety Population with an Incidence ≥ 1% in Any Treatment Group

Primary System Organ Class Preferred Term <sup>1</sup>	Placebo N = 474	0.25% DHEA N = 282	0.50% DHEA N = 1196	1.0% DHEA N = 64	Overall <sup>2</sup> N = 1542
<b>Number of women with at least one TEAE</b>	<b>226 (47.7%)</b>	<b>150 (53.2%)</b>	<b>627 (52.4%)</b>	<b>41 (64.1%)</b>	<b>818 (53.0%)</b>
<b>Gastrointestinal disorders</b>	<b>44 (9.3%)</b>	<b>30 (10.6%)</b>	<b>85 (7.1%)</b>	<b>11 (17.2%)</b>	<b>126 (8.2%)</b>
- Abdominal pain	14 (3.0%)	5 (1.8%)	21 (1.8%)	5 (7.8%)	31 (2.0%)
- Diarrhea	8 (1.7%)	6 (2.1%)	13 (1.1%)	1 (1.6%)	20 (1.3%)
- Nausea	14 (3.0%)	5 (1.8%)	19 (1.6%)	4 (6.3%)	28 (1.8%)
<b>General disorder and administrative site disorder</b>	<b>31 (6.5%)</b>	<b>17 (6.0%)</b>	<b>131 (11.0%)</b>	<b>10 (15.6%)</b>	<b>158 (10.2%)</b>
- Application site discharge	16 (3.4%)	11 (3.9%)	99 (8.3%)	0 (0.0%)	110 (7.1%)
- Fatigue	6 (1.3%)	3 (1.1%)	7 (0.6%)	6 (9.4%)	16 (1.0%)
<b>Infections and infestations</b>	<b>80 (16.9%)</b>	<b>56 (19.9%)</b>	<b>209 (17.5%)</b>	<b>20 (31.3%)</b>	<b>285 (18.5%)</b>
- Nasopharyngitis	22 (4.6%)	16 (5.7%)	40 (3.3%)	5 (7.8%)	61 (4.0%)
- Sinusitis	7 (1.5%)	4 (1.4%)	19 (1.6%)	2 (3.1%)	25 (1.6%)
- Urinary tract infection	21 (4.4%)	18 (6.4%)	57 (4.8%)	2 (3.1%)	77 (5.0%)
<b>Investigations</b>	<b>19 (4.0%)</b>	<b>10 (3.5%)</b>	<b>63 (5.3%)</b>	<b>0 (0.0%)</b>	<b>73 (4.7%)</b>
- Weight increased	6 (1.3%)	0 (0.0%)	21 (1.8%)	0 (0.0%)	21 (1.4%)
<b>Musculoskeletal and connective tissue disorders</b>	<b>37 (7.8%)</b>	<b>30 (10.6%)</b>	<b>69 (5.8%)</b>	<b>11 (17.2%)</b>	<b>110 (7.1%)</b>
- Arthralgia	7 (1.5%)	4 (1.5%)	15 (1.3%)	2 (3.1%)	21 (1.4%)
- Back pain	11 (2.3%)	8 (2.8%)	15 (1.3%)	5 (7.8%)	28 (1.8%)
- Pain in extremity	6 (1.3%)	11 (3.9%)	8 (0.7%)	3 (4.7%)	22 (1.4%)
<b>Nervous system disorder</b>	<b>18 (3.8%)</b>	<b>23 (8.2%)</b>	<b>58 (4.8%)</b>	<b>10 (15.6%)</b>	<b>91 (5.9%)</b>
- Headache	14 (3.0%)	12 (4.3%)	35 (2.9%)	6 (9.4%)	53 (3.4%)
<b>Reproductive system and breast disorders</b>	<b>59 (12.4%)</b>	<b>42 (14.9%)</b>	<b>155 (13.0%)</b>	<b>12 (18.8%)</b>	<b>209 (13.6%)</b>
- Cervical dysplasia	6 (1.3%)	8 (2.8%)	21 (1.8%)	0 (0.0%)	29 (1.9%)
- Hot flush	13 (2.7%)	7 (2.5%)	32 (2.7%)	5 (7.8%)	44 (2.9%)
- Vaginal discharge	6 (1.3%)	9 (3.2%)	19 (1.6%)	2 (3.1%)	30 (1.9%)
- Vaginal hemorrhage	6 (1.3%)	4 (1.4%)	14 (1.2%)	0 (0.0%)	18 (1.2%)
- Vulvovaginal burning	8 (1.7%)	1 (0.4%)	16 (1.3%)	4 (6.3%)	21 (1.4%)
- Vulvovaginal pruritus	8 (1.7%)	6 (2.1%)	17 (1.4%)	5 (7.8%)	28 (1.8%)

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 8, Page 30 of 662.

<sup>1</sup>Women are counted only once within each preferred term.

<sup>2</sup>Includes data for 0.25%, 0.50%, and 1.0% DHEA doses from Trials ERC-210, ERC-213, ERC-230 (up to Week 16), ERC-231, ERC-234, and ERC-238. Data from 10 women treated for 1 week with 1.8% DHEA in ERC-213 are not included.

**Clinical Reviewer’s Comments:**

As shown in Table 34, the most commonly reported TEAE was application site discharge (7.1% for all DHEA doses studied compared to 3.4% in the placebo treatment groups). Per the applicant, application site discharge is likely “due to melting of the vehicle Witepsol with the possible addition of increased vaginal secretions stimulated by DHEA.” This reviewer concurs that the melting of the Witepsol vehicle, and the effect of DHEA on increased vaginal secretion, both contribute to the occurrence of application site discharge. The relationship between the occurrence of application site discharge between the 0.25% DHEA dose (3.9%, 11 of 282 women treated at this dose) and the 0.50% DHEA dose (8.3%, 99 of 1196 women treated at this dose) is less clear, however. This difference may have been influenced by the reduced dosing regimen utilized in Trial ERC-234 (daily for 2 weeks, then twice weekly for 10 weeks).

Urinary tract infection occurred similarly in all DHEA treatment groups (5.0%, 77 of 1542 DHEA women) and in the placebo treatment group (4.4%, 21 of 474 placebo-treated women) in Table 34.

The occurrences of headaches, fatigue, hot flashes, vulvovaginal pruritus, abdominal and back pain are clearly elevated at the 1.0% DHEA (23.4 mg) dose. The applicant is not requesting approval of 1.0% DHEA.

On April 21, 2016, DBRUP requested that EndoCeutics provide the pooled analysis of safety data obtained from the four 12-week, placebo-controlled clinical Trials ERC-210, ERC-231, ERC-234, and ERC-238 to examine the incidence of TEAEs in these placebo-controlled trials. EndoCeutics responded on April 28, 2016. Table 35 shows the number (%) of women with TEAEs with an incidence  $\geq$  1% in any treatment group.

Table 35: Number of Women with Treatment-Emergent Adverse Events in Placebo-controlled Clinical Trials with an Incidence  $\geq$  1% in Any Treatment Group

Primary System Organ Class Preferred Term	Placebo N = 464	0.25% DHEA N = 282	0.50% DHEA N = 665	1.0% DHEA N = 54	Overall <sup>1</sup> N = 1001
<b>Number of women with at least one TEAE</b>	<b>220 (47.4%)</b>	<b>150 (53.2%)</b>	<b>346 (52.0%)</b>	<b>35 (64.8%)</b>	<b>531 (53.0%)</b>
<b>Cardiac Disorders</b>					
- Palpitations	2 (0.4%)	1 (0.4%)	0 (0.0%)	1 (1.9%)	2 (0.2%)
<b>Ear and Labyrinth Disorders</b>					
- Ear pain	0 (0.0%)	3 (1.1%)	1 (0.2%)	0 (0.0%)	4 (0.4%)
<b>Eye Disorders</b>					
- Eye pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.7%)	2 (0.2%)
<b>Gastrointestinal Disorders</b>					
- Abdominal discomfort	0 (0.0%)	3 (1.1%)	2 (0.3%)	0 (0.0%)	5 (0.5%)

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- Abdominal distension	6 (1.3%)	1 (0.4%)	2 (0.3%)	1 (1.0%)	4 (0.4%)
- Abdominal pain	14 (3.0%)	5 (1.8%)	12 (1.8%)	5 (9.3%)	22 (2.2%)
- Abdominal pain upper	1 (0.2%)	1 (0.4%)	3 (0.5%)	1 (1.9%)	5 (0.5%)
- Constipation	3 (0.6%)	0 (0.0%)	3 (0.5%)	1 (1.9%)	4 (0.4%)
- Diarrhea	8 (1.7%)	6 (2.1%)	11 (1.7%)	1 (1.9%)	18 (1.8%)
- Gastrointestinal reflux Disease	0 (0.0%)	3 (1.1%)	2 (0.3%)	2 (3.7%)	7 (0.7%)
- Hemorrhoids	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (1.9%)	2 (0.2%)
- Nausea	14 (3.0%)	5 (1.8%)	12 (1.8%)	3 (5.6%)	20 (2.0%)
- Toothache	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (1.9%)	2 (0.2%)
- Vomiting	4 (0.9%)	0 (0.0%)	3 (0.5%)	1 (1.9%)	4 (0.4%)
<b>General Disorder and Administration Site</b>					
- Application site discharge	16 (3.4%)	11 (3.9%)	31 (4.7%)	0 (0.0%)	42 (4.2%)
- Facial pain	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (1.9%)	2 (0.2%)
- Fatigue	5 (1.1%)	3 (1.1%)	5 (0.8%)	5 (9.3%)	13 (1.3%)
- Pyrexia	2 (0.4%)	1 (0.4%)	3 (0.5%)	1 (1.9%)	5 (0.5%)
- Puncture site hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
<b>Infections and Infestations</b>					
- Candida infection	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
- Diverticulitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
- Infected cyst	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.7%)	2 (0.2%)
- Influenza	3 (0.6%)	3 (1.1%)	4 (0.6%)	2 (3.7%)	9 (0.9%)
- Laryngitis	2 (0.4%)	1 (0.4%)	1 (0.2%)	1 (1.9%)	3 (0.2%)
- Nasopharyngitis	21 (4.5%)	16 (5.7%)	22 (3.3%)	4 (7.4%)	42 (4.2%)
- Oral Herpes	0 (0.0%)	2 (0.7%)	0 (0.0%)	1 (1.9%)	3 (0.3%)
- Pneumonia	1 (0.2%)	3 (1.1%)	2 (0.3%)	0 (0.0%)	5 (0.5%)
- Sinusitis	7 (1.5%)	4 (1.4%)	7 (1.1%)	2 (3.7%)	13 (1.3%)
- Tooth abscess	1 (0.2%)	0 (0.0%)	1 (0.2%)	1 (1.9%)	2 (0.2%)
- Upper respiratory tract Infection	3 (0.6%)	3 (1.1%)	10 (1.5%)	0 (0.0%)	13 (1.3%)
- Urinary tract infection	21 (4.5%)	18 (6.4%)	38 (5.7%)	2 (3.7%)	58 (5.8%)
- Vaginal infection	2 (0.4%)	0 (0.0%)	3 (0.5%)	3 (5.6%)	6 (0.6%)
- Vaginitis bacterial	5 (1.1%)	1 (0.4%)	6 (0.9%)	1 (1.9%)	8 (0.8%)
- Viral infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
- Vulvitis	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (1.9%)	2 (0.2%)
- Vulvovaginal candidiasis	1 (0.2%)	2 (0.7%)	9 (1.4%)	0 (0.0%)	11 (1.1%)
- Vulvovaginal mycotic infection	3 (0.6%)	2 (0.7%)	7 (1.1%)	0 (0.0%)	9 (0.9%)
<b>Injury, Poisoning and Procedural Complications</b>					
- Contusion	1 (0.2%)	3 (1.1%)	0 (0.0%)	1 (1.9%)	4 (0.4%)
- Ligament sprain	2 (0.4%)	2 (0.7%)	2 (0.3%)	1 (1.9%)	5 (0.5%)
<b>Investigations</b>					
- Weight decreased	6 (1.3%)	1 (0.4%)	11 (1.7%)	0 (0.0%)	12 (1.2%)
- Weight increased	6 (1.3%)	0 (0.0%)	19 (2.9%)	0 (0.0%)	19 (1.9%)
<b>Musculoskeletal and Connective Tissue Disorders</b>					
- Arthralgia	7 (1.5%)	4 (1.4%)	6 (0.9%)	1 (1.9%)	11 (1.1%)
- Back pain	10 (2.2%)	8 (2.8%)	8 (1.2%)	5 (9.3%)	21 (2.1%)
- Bone pain	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (1.9%)	2 (0.2%)
- Bursitis	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (1.9%)	2 (0.2%)
- Musculoskeletal chest pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
- Musculoskeletal pain	2 (0.4%)	1 (0.4%)	5 (0.8%)	2 (3.7%)	8 (0.8%)
- Myalgia	5 (1.1%)	3 (1.1%)	3 (0.5%)	2 (3.7%)	8 (0.8%)
- Neck pain	2 (0.4%)	1 (0.4%)	1 (0.2%)	1 (1.9%)	3 (0.3%)
- Pain in extremity	6 (1.3%)	11 (3.9%)	4 (0.6%)	3 (5.6%)	18 (1.8%)
<b>Nervous System Disorders</b>					
- Dizziness	1 (0.2%)	4 (1.4%)	2 (0.2%)	2 (3.7%)	8 (0.8%)

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- Dysgeusia	0 (0.0%)	2 (0.7%)	0 (0.0%)	1 (1.9%)	3 (0.3%)
- Headache	10 (2.2%)	12 (4.3%)	21 (3.2%)	4 (7.4%)	37 (3.7%)
- Presyncope	0 (0.0%)	2 (0.7%)	0 (0.0%)	1 (1.9%)	3 (0.3%)
<b>Psychiatric Disorders</b>					
- Abnormal dreams	3 (0.6%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
- Anxiety	5 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
- Insomnia	4 (0.9%)	1 (0.4%)	5 (0.8%)	1 (1.9%)	7 (0.7%)
- Mood altered	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
<b>Renal and Urinary Disorders</b>					
- Dysuria	3 (0.6%)	1 (0.4%)	4 (0.6%)	1 (1.9%)	6 (0.6%)
- Urine odor abnormal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
<b>Reproductive System and Breast Disorders</b>					
- Breast discharge	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
- Breast pain	1 (0.6%)	0 (0.0%)	1 (0.2%)	1 (1.9%)	2 (0.2%)
- Cervical dysplasia	1 (1.3%)	8 (2.8%)	20 (3.0%)	0 (0.0%)	28 (2.8%)
- Hot flush	13 (2.8%)	7 (2.5%)	13 (2.0%)	4 (7.4%)	24 (2.4%)
- Pelvic pain	5 (1.1%)	4 (1.4%)	3 (0.5%)	0 (0.0%)	7 (0.7%)
- Vaginal discharge	6 (1.3%)	9 (3.2%)	17 (2.6%)	2 (3.7%)	28 (2.8%)
- Vaginal hemorrhage	6 (1.3%)	4 (1.4%)	6 (0.9%)	0 (0.0%)	10 (1.0%)
- Vulvovaginal burning	8 (1.7%)	1 (0.4%)	10 (1.5%)	4 (7.4%)	15 (1.5%)
- Vulvovaginal pruritus	8 (1.7%)	6 (2.1%)	14 (2.1%)	5 (9.3%)	25 (2.5%)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>					
- Cough	2 (0.4%)	3 (1.1%)	10 (1.5%)	1 (1.9%)	14 (1.4%)
- Nasal congestion	1 (0.2%)	0 (0.0%)	4 (0.6%)	5 (9.3%)	9 (0.9%)
- Oropharyngeal pain	2 (0.4%)	3 (1.1%)	4 (0.6%)	3 (5.6%)	10 (1.0%)
<b>Skin and Subcutaneous Tissue Disorders</b>					
- Dermatitis contact	1 (0.2%)	2 (0.7%)	1 (0.2%)	1 (1.9%)	4 (0.4%)
- Ecchymosis	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (1.9%)	2 (0.2%)
- Erythema	0 (0.0%)	2 (0.7%)	2 (0.3%)	1 (1.9%)	5 (0.5%)
- Hypertrichosis	2 (0.4%)	1 (0.4%)	2 (0.3%)	1 (1.9%)	4 (0.4%)
- Seborrhea	2 (0.4%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
- Skin burning sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
<b>Surgical and Medical Procedures</b>					
- Cyst drainage	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (3.7%)	2 (0.2%)
- Eye laser surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)
- Skin cyst excision	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	1 (0.1%)

Source: NDA 208470, Clinical Information Amendment received April 28, 2016.

<sup>1</sup>Includes data for 0.25% DHEA, 0.50 % DHEA, and 1.0% DHEA doses from Trials ERC-210, ERC-231, ERC-234, and ERC-238.

**Clinical Reviewer's Comments:**

Of the TEAEs listed in Table 35, only application site discharge (commonly referred to as vaginal discharge) occurred at an incidence  $\geq 2$  percent over placebo in the 0.50% DHEA treatment group versus the placebo treatment group in the four placebo-controlled clinical trials in the DHEA development program, and was reported as drug-related by trial investigators.

This reviewer combined investigators' assessed cases of drug-related and possible-related vaginal discharge for inclusion in labeling. Vaginal discharge

should be reported in labeling as an adverse reaction for the 0.50% DHEA treatment group as follows:

“Thirty-eight (38) cases in 665 participating postmenopausal women (5.71 percent) in the Intrarosa treatment group compared to 17 cases in 464 participating postmenopausal women (3.66 percent) in the placebo treatment group.”

#### 7.4.2 Laboratory Findings

For the evaluation of the clinical laboratory parameters (hematology, chemistry and urinalysis), the 12-week safety data from 5 out of the 6 completed trials were pooled. Phase 1 Trial ERC-213 was not included due to the very short duration (7 days) of this PK trial.

The following studies were pooled for the ISS analysis of the clinical laboratory parameters:

- Placebo: ERC-210, ERC-231, ERC-234 and ERC-238
- 0.25% DHEA: ERC-210, ERC-231 and ERC-234
- 0.50% DHEA: ERC-210, ERC-230 (Week 12 data), ERC-231, ERC-234 and ERC-238
- 1.0% DHEA: ERC-210
- Overall: Combined data from 0.25%, 0.50% and 1.0% DHEA doses

Clinical laboratory data obtained at Week 12 was pooled with post-baseline data of shorter duration available from women who discontinued before Week 12.

The change from baseline to available post-baseline data (final assessment up to 12 weeks) was the focused presentation. Laboratory tests obtained at unscheduled visits were not included in the ISS clinical laboratory data. Clinical laboratory values are expressed using the International System of Units (SI). All clinical laboratory data, including abnormal clinical laboratory values (value outside normal ranges) for which the normal ranges are indicated, are available in appendices of each clinical trial report included in the ISS analysis. In the ISS, any significant change to clinical laboratory parameters was documented as a TEAE following the administration of the first dose of medication.

Hematology parameters included: white blood cell count (leukocytes), differential white blood cell counts, erythrocytes, platelet count, hemoglobin and hematocrit. In general, hematology parameters showed no statistically significant changes from baseline to the available post-baseline data (final assessment up to 12 weeks). Overall, hematology

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parameters were within the average normal ranges of adult women. The following three parameters had statistically significant mean changes from baseline without related TEAEs reported in the 0.50% DHEA treatment group:

- Hematocrit: Placebo (n=464) mean change (SD) from baseline = -0.00 (0.04)  
0.50% DHEA (n=1165) mean change (SD) from baseline = 0.01 (0.04); p-value <0.0001
- Platelets: Placebo (n=456) mean change (SD) from baseline = -1.82 (31.40)  
0.50% DHEA (n=1163) mean change (SD) from baseline = -4.70 (32.69); p-value <0.0001
- Leukocytes: Placebo (n=457) mean change (SD) from baseline = 0.04 (1.11)  
0.50% DHEA (n=1165) mean change (SD) from baseline = -0.08 (1.16); p-value = 0.0260

The serum chemistry included: glucose, serum electrolytes (sodium, potassium, and chloride), blood urea nitrogen, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, total serum protein, albumin, calcium, inorganic phosphorus, urate and lactate dehydrogenase (LDH). The urinalysis included: specific gravity and pH. For Trial ERC-210, glucose parameters were not included in the serum chemistry ISS analysis since blood glucose samples were not collected under fasting conditions.

In general, serum chemistry parameters had no statistically significant changes from baseline to the available post-baseline data (final assessment up to 12 weeks). Overall, serum chemistry parameters were within the average normal ranges of adult women. The following three parameters had statistically significant mean changes from baseline without related TEAEs reported in the 0.50% DHEA treatment group:

- AST: Placebo (n=457) mean change (SD) from baseline = -0.43 (6.46)  
0.50% DHEA (n=1161) mean change (SD) from baseline = 0.57 (7.79); p-value = 0.0122
- Phosphorus: Placebo (n=455) mean change (SD) from baseline = -0.00 (0.00)  
0.50% DHEA (n=1161) mean change (SD) from baseline = -0.01 (0.14); p-value = 0.0072
- Protein: Placebo (n=457) mean change (SD) from baseline = -0.36 (3.39)  
0.50%DHEA (n=1162) mean change (SD) from baseline = -0.39 (3.28); p-value <0.0001

Urinalysis parameters (specific gravity and pH) were performed during the Screening period in all women as a safety assessment to exclude women with possible pathologies. Specific gravity and urine pH showed no significant changes from baseline to the available post-baseline data (final assessment up to 12 weeks). Urinalysis parameters were within the average normal ranges of adult women.

In 52-week Trial ERC-230, four (4) women had seven (7) changes in laboratory parameters at Week 52 estimated as drug-related or possibly drug-related by investigators. These women are identified as follows:

1. Number 230-31-011 - increased apolipoprotein B: mild in severity, no action taken, outcome reported as ongoing; blood cholesterol increased: mild in severity, no action taken, outcome reported as ongoing; LDL increased: mild in severity, no action taken, outcome reported as ongoing
2. Number 230-38-004 - increased apolipoprotein B: mild in severity, no action taken, outcome reported as ongoing; blood cholesterol increased: mild in severity, no action taken, outcome reported as ongoing.
3. Number 230-03-001 – blood creatinine increased: mild in severity, no action taken, outcome reported as ongoing.
4. Number 230-31-007 – blood triglycerides increased: mild in severity, no action taken, outcome reported as ongoing.

**Clinical Reviewer’s Comments:**

No safety concerns arise from the reported changes in clinical laboratory parameters in the DHEA development program.

For the evaluation of serum DHEA and related metabolites, the ISS analysis also pooled the 12-week safety data from 5 of the 6 clinical trials as listed above. The mean change from baseline for DHEA and related steroids in the pooled analysis for the Safety-S population (those women having steroid measurements performed at baseline and up to 12-weeks post-baseline) are shown on page 38 of this review.

The mean change from baseline for DHEA and related steroids in the combined analysis for the Safety-S population (those women having steroid measurements performed at baseline and up to 12-weeks post-baseline) are shown on Table 36.

Table 36: Mean Change from Baseline for DHEA and Related Steroids: Safety-S Population in 52-Week Clinical Trial ERC-230

Dehydroepiandrosterone (DHEA) and related steroids parameters and units of measure	0.50% DHEA							
	All Women with Baseline and Week 26 Data				All Women with Baseline and Week 52 Data			
	N <sup>1</sup>	BL <sup>2</sup>	PB <sup>3</sup>	Change from BL <sup>4</sup>	N <sup>1</sup>	BL <sup>2</sup>	PB <sup>3</sup>	Change from BL <sup>4</sup>
DHEA (pg/mL)	446	2087.68	2820.11	732.33	426	2071.61	2997.25	925.65
5-diol (pg/mL)	452	300.56	463.24	162.68	429	300.92	472.72	171.80
4-dione (pg/mL)	446	409.80	459.46	49.66	426	409.08	4780.5	68.97
Testosterone (pg/mL)	452	163.63	185.13	21.50	429	161.28	189.44	28.17
Dihydrotestosterone (pg/mL)	449	48.73	65.89	17.17	426	48.85	66.89	18.04
Estrone (pg/mL)	449	16.92	18.27	1.35	425	17.07	18.10	1.03

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Estradiol (pg/mL)	452	5.93	4.32	-1.61	429	6.05	4.46	-1.59
Dehydroepiandrosterone sulfate (ng/mL)	453	692.59	755.39	62.80	426	694.49	761.39	66.90
Estrone sulfate (pg/mL)	453	232.67	245.98	13.31	428	238.11	249.27	11.16
ADT-G (ng/mL)	453	15.38	18.85	3.47	428	15.34	19.33	3.99
Androstane-3 $\alpha$ , 17 $\beta$ -diol 17-glucuronide (pg/mL)	450	617.67	793.04	175.37	424	623.96	842.48	218.52

Source: Adapted from NDA 208470, Integrated Summary of Safety, Section 10.6 Serum steroid levels, Table 10-53, Table 10-55, Table 10-57, Table 10-61, Table 10-63, Table 10-65, Table 10-67, Table 10-69, Table 10-71, and Table 10-73.

<sup>1</sup> N= the number of women who had the serum parameter of interest measured at baseline and up to 26 and 52 weeks.

<sup>2</sup> BL= baseline mean

<sup>3</sup> PB= post-baseline mean (up to 26 and 52 weeks).

<sup>4</sup> Change from BL= the mean change from baseline.

### **Clinical Reviewer's Comments:**

Table 36 demonstrates a mean increase in serum DHEA and testosterone levels, over baseline, at Weeks 26 and 52, for those women with data for these two time points. Likewise, a mean increase, over baseline, is observed for serum estrone and estrone-sulfate levels at Weeks 26 and 52, for those women with data for these two time points. These findings in 52-week Trial ERC-230 are consistent with the steroid findings in the combined 12-week ERC-231 and ERC-238 trials (see Subsection 4.4.3 Pharmacokinetics in this review) for DHEA, testosterone, estrone and estrone-sulfate levels.

However, in 12-week Trials ERC-231 and ERC-238, the mean estradiol level increased 19% from 2.76 pg/mL to 3.28 pg/mL at Week 12. In 52-week Trial ERC-230, the mean estradiol levels decreased at both time points for those women with data for these two time points. This decrease in estradiol in Trial ERC-230 is not readily explained in light of the demonstrated increase in the levels of estrone-sulfate, a well-recognized parameter of total estrogen.

In Trial ERC-230, the concentrations of DHEA, testosterone, estrone, estrone-sulfate, and estradiol at Weeks 26 and 52 appear to be within the normal ranges reported for postmenopausal women. Nonetheless, these results demonstrate a systemic change, albeit minimal, in serum DHEA, estrogens and/or testosterone levels following the daily intravaginal administration of 6.5 mg prasterone vaginal insert.

### 7.4.3 Vital Signs

Per the statistical analysis plan for DHEA, any significant change to the vital signs and/or physical exam parameters were documented as a TEAE following administration

of the first dose of trial medication and were reflected in the ISS analysis of TEAEs. Therefore, no additional ISS analysis was performed for vital signs and physical exam.

In 52-week Trial ERC-230, a total of 13 women developed intermittent hypertension during the clinical trial (blood pressure obtained at Screening, Day 1, Weeks 12, 26, 39, and 52) which returned to normal at Week 52. Two (2) women developed hypertension and remained hypertensive at Week 52 (Trial participant Numbers 230-05-007 and 230-35-011). Both of these women received drug therapy for their hypertension.

**Clinical Reviewer's Comments:**

These two cases of hypertension do not raise safety concerns for the 0.50% DHEA vaginal insert.

#### 7.4.4 Electrocardiograms (ECGs)

Per the statistical analysis plan for DHEA, any significant change to the vital signs and/or physical exam parameters were documented as a TEAE following administration of the first dose of trial medication and were reflected in the ISS analysis of TEAEs. Therefore, no additional ISS analysis was performed for vital signs and physical exam.

No abnormal ECG findings were reported as TEAEs in the 6 trials conducted under the DHEA development program.

#### 7.4.5 Special Safety Studies/Clinical Trials

Refer to Subsection 7.3.5.1 for a discussion of safety of the endometrium with the use of DHEA.

Refer to Subsection 7.3.5.2 for a discussion of the questionnaire included in Trial ERC- to assess usability of the combination drug-device insert.

#### 7.4.6 Immunogenicity

No human immunogenicity studies were submitted in the NDA application.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

No adverse effects related to a dose-response was observed across the 0.25%, 0.50%, and 1.0% DHEA doses studied in the DHEA development program. The integrated analysis of TEAEs, SAEs, and laboratory parameters presented in Section 5 and Section 6, respectively, of this review provide information on the absence of effect of dose-response.

**Clinical Reviewer's Comments:**

Seven (7) women experienced severe TEAEs at the 1.0% DHEA dosage strength in Trial ERC-210 including back pain, urinary tract infection, generalized abdominal pain, diarrhea, nausea, dizziness, and vaginal burning and itching. One case of dizziness and hypotension was reported in 7-day Trial ERC-213 at the 1.8% DHEA dosage strength. However, these reported severe TEAEs do not clearly establish dose dependency for TEAEs in the DHEA development program.

#### 7.5.2 Time Dependency for Adverse Events

The pivotal long-term safety trial in the application is 52-weeks phase 3, open-label Trial ERC-230. The main objective of this trial was the examination of long-term safety of daily intravaginal administration of 0.50% (6.5mg) DHEA vaginal inserts in postmenopausal women having self-identified at least one mild to severe vaginal atrophy symptom. The safety population consisted of 521 postmenopausal women. Four hundred thirty-five (435) women (83%) completed this 52-week trial.

The safety population in Trial ERC-230 consisted mainly of White Caucasian non-Hispanic women (92%, 478 of 521 women). Black or African American women were the second most represented race with 6% of the women (31 of 521 women). The average age of the women was 57.9 years (range 43 to 75 years). All trial participants had a natural menopause without hysterectomy. Twenty-eight (28) of trial participants had one or both ovaries removed (5%, 28 of 521 women). Two hundred sixty-eight (268) of trial participants had previously used hormone therapy (51%, 268 of 521 women).

In order to see a potential change in incidence of TEAEs over time or delayed adverse events, the applicant divided TEAEs in Trial ERC-230 into periods of 16 weeks (4 months). Safety data from the first 4 months of treatment is presented elsewhere in this review. (See Subheading 7.3.2 Nonfatal Serious Adverse events, and Subheading 7.4.1 Common Adverse Events.) TEAEs in Trial ERC-230 with an onset date after 16 weeks of the first dose are analyzed for the following time intervals:

- TEAEs having an onset date from Day 1 (after the first dose) up to 16 weeks (data used in the ISS analysis)
- TEAEs having an onset date starting after 16 weeks up to 32 weeks

- TEAEs having an onset date starting after 32 weeks up to 44 weeks
- TEAEs having an onset date starting after 44 weeks up to 56 weeks (including the 30-day follow-up period)

Long-term TEAEs by time intervals over 52-week trial ERC-230 are presented in Table 37.

Table 37: Number (%) of Women with Treatment-Emergent Adverse Events by Preferred Term (MedDRA Version 16.1) for 52-Week Trial ERC-230 (Safety Population) by Time Intervals (Incidence ≥ 1%)

MedDRA/Preferred Term Number (%) of Women	Day 1 up to 16 W N = 521	After 16 W up to 32 W N = 498	After 32 W up to 44 W N = 456	After 44 W up to 56 W N = 448	Overall (Day 1 up to 52 W) N = 521
Abdominal pain	9 (1.7%)	2 (0.4%)	2 (0.4%)	4 (0.9%)	16 (3.1%)
Abdominal pain lower	4 (0.8%)	1 (0.2%)	3 (0.7%)	1 (0.2%)	9 (1.7%)
Acne	9 (1.7%)	3 (0.6%)	1 (0.2%)	1 (0.2%)	12 (2.3%)
Application site discharge	68 (13.1)	5 (1.0%)	0 (0.0%)	0 (0.0%)	73 (14.0%)
Arthralgia	9 (1.7%)	3 (0.6%)	1 (0.2%)	1 (0.2%)	14 (2.7%)
Back pain	7 (1.3%)	8 (1.6%)	5 (1.1%)	3 (0.7%)	22 (4.2%)
Cholesterol increased	1 (0.2%)	2 (0.4%)	0 (0.0%)	3 (0.7%)	6 (1.2%)
Bronchitis	2 (0.4%)	4 (0.8%)	5 (1.1%)	3 (0.7%)	13 (2.5%)
Cervical dysplasia	1 (0.2%)	4 (0.8%)	0 (0.0%)	15 (3.3%)	20 (3.8%)
Contusion	4 (0.4%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	7 (1.3%)
Cough	3 (0.6%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	7 (1.3%)
Depression	2 (0.4%)	1 (0.2%)	3 (0.7%)	0 (0.0%)	6 (1.2%)
Dizziness	3 (0.6%)	2 (0.4%)	0 (0.0%)	2 (0.4%)	6 (1.2%)
Dyspepsia	1 (0.2%)	4 (0.8%)	2 (0.4%)	1 (0.2%)	7 (1.3%)
Erythema	4 (0.8%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	6 (1.2%)
Gastroenteritis	4 (0.8%)	3 (0.6%)	1 (0.2%)	3 (0.7%)	11 (2.1%)
Headache	9 (1.7%)	6 (1.2%)	3 (0.7%)	4 (0.9%)	19 (3.6%)
Hot flush	19 (3.6%)	1 (0.2%)	1 (0.2%)	3 (0.7%)	23 (4.4%)
Hypertension	4 (0.8%)	4 (0.8%)	5 (1.1%)	2 (0.4%)	15 (2.9%)
Influenza	1 (0.2%)	5 (1.0%)	7 (1.5%)	3 (0.7%)	16 (3.1%)
Insomnia	7 (1.3%)	1 (0.2%)	1 (0.2%)	2 (0.4%)	11 (2.1%)
Musculoskeletal pain	0 (0.0%)	1 (0.2%)	4 (0.9%)	2 (0.4%)	7 (1.3%)
Nasopharyngitis	18 (3.5%)	10 (2.0%)	21 (4.6%)	10 (2.2%)	51 (9.8%)
Nausea	7 (1.3%)	6 (1.2%)	1 (0.2%)	2 (0.4%)	16 (3.1%)
Oropharyngeal pain	5 (1.0%)	2 (0.4%)	1 (0.2%)	1 (0.2%)	8 (1.5%)
Osteoarthritis	3 (0.6%)	0 (0.0%)	3 (0.7%)	2 (0.4%)	7 (1.3%)
Pain in extremity	4 (0.8%)	2 (0.4%)	1 (0.2%)	2 (0.4%)	8 (1.5%)
Pelvic pain	3 (0.6%)	0 (0.0%)	1 (0.2%)	2 (0.4%)	6 (1.2%)
Post-procedural hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (1.8%)	8 (1.5%)
Procedural pain	3 (0.6%)	5 (1.0%)	1 (0.2%)	6 (1.3%)	14 (2.7%)
Sinus tis	12 (2.3%)	3 (0.6%)	4 (0.9%)	4 (0.9%)	20 (3.8%)
Upper respiratory tract infection	2 (0.4%)	4 (0.8%)	5 (1.1%)	3 (0.7%)	14 (2.7%)
Urinary tract infection	19 (3.6%)	18 (3.6%)	12 (2.6%)	18 (4.0%)	53 (10.2%)
Vaginal discharge	2 (0.4%)	4 (0.8%)	0 (0.0%)	5 (1.1%)	10 (1.9%)
Vaginal hemorrhage	8 (1.5%)	2 (0.4%)	1 (0.2%)	3 (0.7%)	13 (2.5%)
Vaginal infection	7 (1.3%)	3 (0.6%)	1 (0.2%)	1 (0.2%)	11 (2.1%)
Vaginitis bacterial	1 (0.2%)	3 (0.6%)	1 (0.2%)	4 (0.9%)	9 (1.7%)
Vomiting	1 (0.2%)	4 (0.8%)	0 (0.0%)	2 (0.4%)	7 (1.3%)
Vulvo aginal burning	6 (1.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	6 (1.2%)

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Vulvo aginal candidiasis	2 (0.4%)	3 (0.6%)	0 (0.0%)	2 (0.4%)	7 (1.3%)
Vulvo aginal myocotic infection	5 (1.0%)	0 (0.0%)	2 (0.4%)	1 (0.2%)	8 (1.5%)
Weight decreased	2 (0.4%)	10 (2.0%)	1 (0.2%)	7 (1.6%)	20 (3.8%)
Weight increased	2 (0.4%)	6 (1.2%)	0 (0.0%)	5 (1.1%)	11 (2.1%)

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 39, page 131 of 662.

Abbreviation: W = Weeks

Note: Percentages are based on number of women on trial during the corresponding time interval.

**Clinical Reviewer’s Comments:**

Urinary tract infection and nasopharyngitis were consistently reported at an incidence  $\geq 2$  throughout the designated reporting periods in 52-week Trial ERC-230. The incidence of application site discharge decreased across the 4 reporting periods. The CRFs for these TEAEs were not reviewed by this reviewer.

The incidence of cervical dysplasia is increased in the last reporting period (after 44 weeks up to 56 weeks). This finding, from Pap smears obtained at Week 52 in Trial ERC-230, is discussed in Subsection 7.3.5.2 Cervical Cytology Evaluation, in this review.

A summary of the TEAEs which were considered drug-related by the investigators in Trial ERC-230 is presented in Table 38.

Table 38: Incidence of Drug-Related Treatment-Emergent Adverse Events (TEAEs) by Primary System Organ Class and Preferred Term in 52-Week Trial ERC-230; Safety Population

MedDRA/Preferred Term Number of omen	Day 1 up to 16 W N = 521	After 16 W up to 32 W N = 498	After 32 W up to 44 W N = 456	After 44 W up to 56 W N = 448	Overall (Day 1 up to 52 W) N = 521
Number of women with at least 1 drug-related TEAE	<b>75 (1.4%)</b>	<b>5 (1.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>80 (15.4%)</b>
<b>General Disorder and Administration Site Conditions</b>	<b>69 (13.2%)</b>	<b>5 (1.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>74 (14.2%)</b>
- Application site discharge	68 (13.1%)	5 (1.0%)	0 (0.0%)	0 (0.0%)	73 (14.0%)
- Application site pain	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
<b>Reproductive System and Breast Disorders</b>	<b>7 (1.3%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>7 (1.3%)</b>
- Hot flush	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
- Vaginal hemorrhage	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
- Vaginal odor	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
- Vulvovaginal burning	3 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.6%)
- Vulvovaginal pruritus	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
<b>Skin and Subcutaneous Tissue Disorders</b>	<b>1 (0.2%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>0 (0.0%)</b>	<b>1 (0.2%)</b>
- Hypertrichosis	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Adapted from NDA 208470, Integrated Summary of Safety, Table 40, page 133 of 662.

Abbreviation: W = Weeks

Note: Percentages are based on number of women on trial during the corresponding time interval.

**Clinical Reviewer's Comments:**

This reviewer agrees that these reported TEAEs are drug related with the possible exception of hot flush. A women experiencing dyspareunia may also experience hot flushes that are unrelated to her dyspareunia.

As shown in Table 38, per the applicant, only drug-related application site discharge occurred at an incidence  $\geq 2$  percent in open-label, 52-week Trial ERC-230. Application site discharge, commonly referred to as vaginal discharge, should be reported in labeling as an adverse reaction for the 0.50% DHEA treatment group.

As previously stated, this reviewer recommends that abnormal Pap smears obtained at Week 52 in Trial ERC-230 be reported as an adverse reaction in labeling. Eleven cases of abnormal Pap smears were reported for an incidence of 2.1 percent. The following is recommended language for inclusion in labeling:

“There were 74 cases of vaginal discharge (14.2 percent) and 11 cases of abnormal Pap smear (2.1 percent) in 521 participating postmenopausal women. The eleven (11) cases of abnormal Pap smear at 52 weeks include one (1) case of low-grade squamous intraepithelial lesion (LSIL), and ten (10) cases of atypical cells of undetermined significance (ASCUS).”

### 7.5.3 Drug-Demographic Interactions

No analysis of drug-demographics is presented in the application. Per the applicant, the baseline characteristics of the postmenopausal women enrolled in the 6 clinical trials in the DHEA development program are very similar. Therefore, no analysis of drug-demographic was performed.

**Clinical Reviewer's Comments:**

The reviewer agrees with the applicant that the baseline characteristics of the postmenopausal women in the 6 clinical trials in the application are very similar.

Unfortunately, the majority of trial participants were Caucasians (92.2%) with an underrepresentation of other races in the application. Therefore, it was not possible to present any drug-demographics interactions.

### 7.5.4 Drug-Disease Interactions

Per the application, no drug-disease interactions were expected, nor have drug-disease interactions been observed, in the DHEA vaginal insert development program.

Per the applicant, “DHEA acts exclusively locally in the vagina with no biologically significant increase of DHEA and its metabolites [estrogens (estrone sulfate) and/or androgens (mainly ADT-G)] in the systemic circulation. Postmenopausal women are already exposed to high circulating levels of endogenous DHEA. Therefore, the intravaginal administration of 0.50% DHEA (the proposed dose for the relief of dyspareunia) was not expected to increase endogenous DHEA levels or to exert a significant influence on any disease, including hepatic and renal impairment.”

#### 7.5.5 Drug-Drug Interactions

Per the applicant, no drug-disease interactions have been observed in the DHEA vaginal insert development program.

The application discusses an *in vitro* experiment with human liver microsomes. Per the applicant, no interference (inhibition) was observed at concentrations of DHEA up to 10  $\mu$ M on the cytochrome P450 isoforms (CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) involved in the metabolism of drugs.

### 7.6 Additional Safety Evaluations

#### 7.6.1 Human Carcinogenicity

All preclinical studies were submitted in the NDA application. See the Pharmacology/Toxicology review of NDA 208470 for a full discussion of this information.

#### 7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported during the DHEA development program.

#### 7.6.3 Pediatrics and Assessment of Effects on Growth

The DHEA development program addressed indications which are applicable only to postmenopausal women.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose, drug abuse, withdrawal, or rebound potential was demonstrated in the application.

## 7.7 Additional Submissions / Safety Issues

See Subsections 7.3.5.1 and 7.3.5.2 for discussion of safety/effects on the endometrium and use/partner evaluation, respectively.

## 8 Postmarket Experience

There is no postmarketing data for NDA 208470. DHEA is not currently approved in the U.S. for any indication.

## 9 Appendices

### 9.1 Literature Review/References

For all summary documents (nonclinical and clinical), numerous literature references are included in the application. These literature references could be accessed through hyperlinks provided directly from the summary documents or from the list of references at the end of the summary documents.

In addition, the application presents literature references listed in the reference section at the end of each Clinical Study Trial Report (CSR), including references based on trial results which could also be accessed through hyperlinks from the list of references in CSR.

### 9.2 Labeling Recommendations

This reviewer recommends the approval of Intrarosa (prasterone) vaginal inserts for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause once the DBRUP final agreed upon labeling with the applicant has been approved.

### 9.3 Advisory Committee Meeting

No Advisory committee was conducted for NDA 208470.

#### 9.4 Table of Currently Available Treatments for a Non-Specific VVA Indication

##### Estrogen-Alone Products Approved for the Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

<b>Oral Estrogen-Alone Products</b>	<b>Available Dosage Strengths</b>
Cenestin® (synthetic conjugated estrogens, A)	0.3 mg once daily
Menest® (esterified estrogens)*	0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg once daily
Ogen (estropipate)	0.625 mg, 1.25 mg, or 2.5 mg once daily
Premarin® (conjugated estrogens) Tablets	0.3 mg, 0.45 mg, 0.625 mg, 0.9 m, or 1.25 mg once daily
Various Generics (estradiol) Tablets	0.5 mg, 1.0 mg, 2.0 mg
<b>Transdermal Products</b>	<b>Available Dosage Strengths</b>
Alora® (estradiol matrix patch)	0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Climara® (estradiol matrix patch)	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied once weekly
Estraderm® (estradiol reservoir patch)	0.05 mg or 0.1 mg; patch applied twice weekly
VivelleDot® (estradiol matrix patch)	0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Minivelle® (estradiol matric patch)	0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Various Generics (estradiol matrix patch)	0.05 mg or 0.1 mg; patch applied once or twice weekly
<b>Topical Products</b>	<b>Available Dosage Strengths</b>
EstroGel® 0.06% (estradiol gel)	1.25 grams containing 0.75 mg estradiol applied once daily
<b>Vaginal Cream</b>	<b>Available Dosage Strengths</b>
Estrace (estradiol) Vaginal Cream	2 to 4 grams (0.1 mg per gram) inserted intravaginal daily for 1 to 2 weeks, then 1 gram inserted intravaginal daily thereafter
Premarin® (conjugated estrogens) Vaginal Cream	0.5 to 2 grams (0.625 mg per gram) inserted intravaginal daily
<b>Vaginal Rings</b>	<b>Available Dosage Strengths</b>
Estring® (estradiol)	Release of 7.5 mcg estradiol; ring worn for 90 days
Femring® (estradiol acetate)	Release of 0.05 mg estradiol or 0.10 mg estradiol; ring worn for 90 days
<b>Vaginal Tablet</b>	<b>Available Dosage Strengths</b>
Vagifem® (estradiol hemihydrate)	10 mcg vaginal tablet inserted daily for 2 weeks, then inserted twice weekly

##### Estrogen Plus Progestin Products Approved for the Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

<b>Oral Estrogen Plus Progestin Products</b>	<b>Available Dosage Strengths</b>
Angeliq® (drospirinone [DRSP] plus estradiol	0.25 mg DRSP plus 0.5 mcg E2 taken daily or 0.5

estradiol [E2])	mg DRSP plus 1 mg E2 taken daily
Prefest® (estradiol [E2] plus norgestimate)	1 mg E2 taken daily for 3 days, then 1 mg E2 plus 0.09 mg norgestimate taken daily for 3 days, repeated continuously
Premphase® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.625 mg CE taken daily for 14 days, then 0.625 mg CE plus 5.0 mg MPA taken daily on days 15-18
Prempro® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.3 mg or 0.45 mg CE plus 1.5 mg MPA taken daily or 0.625 mg CE plus 2.5 mg or 5.0 mg MPA taken daily
<b>Transdermal Estrogen Plus Progestin Products</b>	<b>Available Dosage Strengths</b>
CombiPatch® (estradiol [E2] plus norethindrone Acetate [NETA])	Release of 0.05 mg E2 plus 0.14 mg NETA; patch applied twice weekly or 0.05 mg E2 plus 0.25 mg NETA; patch applied twice weekly

## 9.5 Individual Studies Not Reviewed For Efficacy

### 9.5.1 Phase 3 Clinical Trial ERC-234:

Clinical Trial ERC-234 entitled, “DHEA Against Vaginal Dryness (Placebo-Controlled, Double-Blind and Randomized Phase III Study of 3-Month Intravaginal DHEA)” was a multicenter (10 trial sites in /Canada and 21 trial sites in the US), randomized, double-blind, placebo-controlled trial conducted between June 21, 2011 (first subject, first visit) and April 12, 2013 (last subject, last visit) conducted to (b) (4)

Four hundred and fifty (450) postmenopausal women were randomized to receive:

- 0.25% DHEA vaginal insert (3.25 mg DHEA; 148 women randomized; 128 completers)
- 0.50% DHEA vaginal insert (6.5 mg DHEA; 150 women randomized; 125 completers)
- Placebo vaginal insert (152 women randomized; 130 completers)

The primary objective of Trial ERC-234 was to:

- Confirm the efficacy of intravaginal DHEA on vaginal dryness, a symptom of vaginal atrophy, in postmenopausal women suffering from vaginal dryness.

Secondary objectives of Trial ERC-234 were to:

- Assess tolerance to local administration of DHEA vaginal insert

## Clinical Review

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

NDA 208470

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- Assess efficacy on arousal/lubrication, subjective arousal, desire, satisfaction, pain at sexual activity and orgasm evaluated by the female sexual function index (FSFI) questionnaire.
- Assess efficacy on the other symptoms of vaginal atrophy, namely pain at sexual activity and irritation/itching

The primary endpoints of Trial ERC-234 were:

- Evaluation of efficacy of DHEA compared to placebo from Day 1 to Week 12 for 0.25% and 0.50% DHEA
- Change in severity score of vaginal dryness as a co-primary objective as well as changes in % of parabasal cells, % of superficial cells, and vaginal pH.

Postmenopausal women were eligible for inclusion if they met the following inclusion criteria and none of the acceptable exclusion criteria:

1. Postmenopausal women (non hysterectomized or hysterectomized), 40 to 75 years of age, must satisfy either a or b or c:
  - a) No menses for at least one year for non hysterectomized women, or
  - b) Follicle stimulating hormone (FSH) levels >40 IU/L or > postmenopausal value of the laboratory where the FSH assay is performed (a subject with previously measured elevated serum FSH meets the inclusion criteria) in women with no menses >6 months but <12 months, or in hysterectomized women who were premenopausal at the time of hysterectomy, or
  - c) Six months (of screening visit) or more following bilateral oophorectomy with or without hysterectomy.
2. Women who have self-identified at screening and baseline (Day 1) vaginal dryness as moderate to severe and as the most bothersome vaginal atrophy symptom.
3. Women who have  $\leq 5\%$  of superficial cells on vaginal smear at baseline.
4. Women who have a vaginal pH above 5 at baseline
6. Have a normal mammogram within 9 months of trial start, normal breast examination, and Normal PAP smear within the last 12 months (of Day 1).
7. Willing to participate in the trial and sign an informed consent.
8. No former or present narcotic addiction or alcoholism.
9. For non-hysterectomized women, willing to have endometrial biopsy at baseline and end-of-trial.

### Dosage and Administration:

(b) (4)

Assessments of Safety:

Throughout the trial, vital signs, physical examination, gynecological examination and clinical laboratory tests were performed. For non-hysterectomized women, an endometrial biopsy was done at screening and at the end of the trial. Adverse events were recorded for safety evaluation and then coded into system organ class and preferred terms using the MedDRA version 14.1. The safety population in Trial ERC-234 consisted of a total of 441 postmenopausal women: 150 postmenopausal women in the placebo vaginal insert treatment group, 143 postmenopausal women in the 0.25% DHEA vaginal insert treatment group, and 134 postmenopausal women in the 0.50% DHEA vaginal insert treatment group.

Statistical Methodology:

Statistical analyses were performed at the two-sided significance level of 0.025 unless otherwise stated. The categories for summarization for the analysis of data from baseline through Week 12 consist of the placebo, the 0.25% DHEA and the 0.50% DHEA treatment groups. The co-primary objectives analyzed were the changes in

percentage of parabasal and superficial cells, vaginal pH and severity score of moderate to severe and most bothersome vaginal dryness. Efficacy analyses were performed primarily on the Intent-to-Treat (ITT) population [all women who received at least one dose of trial drug with a baseline (Day 1) evaluation meeting the entry criteria], with additional secondary analysis done on the Per-Protocol (PP) population. In particular, women must have met all of the following inclusion criteria at Screening and Day 1:

- $\leq 5\%$  of superficial cells on vaginal smear,
- a vaginal pH above 5, and
- who self-identified moderate to severe vaginal dryness as their most bothersome symptom.

The ITT population consisted of a total of 407 postmenopausal women: 139 women in the placebo vaginal insert treatment group, 134 postmenopausal women in the 0.25% DHEA treatment group, and 134 postmenopausal women in the 0.50% DHEA vaginal insert treatment group.

Safety analyses were performed on the safety population (all women who receive any amount of trial treatment and who have any safety information available).

**Clinical Reviewer's Comments:**

Clinical Trial ERC-234 was not considered in the efficacy evaluation of this NDA for the indication for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. (b) (4)

9.5.2 Phase 3 Clinical Trial ERC-210:

Clinical Trial ERC-210 entitled, "Topical DHEA Against vaginal atrophy (3-Months Placebo-Controlled Double-Blind Randomized Phase III Study)" was a randomized, double-blind, multicenter [2 centers in US (Jones Institute, Norfolk, VA and Women's Health Research Clinic, Cleveland, OH), 5 in Quebec, Canada, and 1 in Montreal, Canada], placebo-controlled dose-response trial conducted between June 28, 2007 (first subject enrolled) and May 23, 2008 (last subject completed trial). Two hundred eighteen (218) postmenopausal women were randomized to receive a daily dose of:

- 0.25% (3.25 mg of DHEA vaginal insert dissolved in Whitepsol H-15 base),
- 0.50% (6.5 mg of DHEA vaginal insert dissolved in Whitepsol H-15 base),
- 1.0% (13 mg of DHEA vaginal insert dissolved in Whitepsol H-15 base), or
- Placebo vaginal insert (0 mg of DHEA dissolved in Whitepsol H-15 base).

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The primary objective of Trial ERC-210 was to determine the dose-response (minimal concentration) of DHEA having a maximal effect on vaginal mucosa parameters. The local activity of DHEA was measured by changes in vaginal epithelial cell maturation (parabasal and superficial cells), and changes in vaginal pH. In addition, self-assessment was made of the three symptoms of vaginal atrophy (moderate to severe vaginal dryness, vaginal and/or vulvar irritation/itching, and vaginal pain associated with sexual activity). Initially, trial participants did not identify their individual most-bothersome moderate to severe symptom of vaginal atrophy. Subsequently (post-hoc), trial participants were asked to identify their most-bothersome symptom among those symptoms previously identified as moderate or severe.

Changes in sexual function and quality of life were evaluated as secondary objectives by utilizing the Menopause Specific Quality of Life (MENQOL), the Abbreviated Sexual Function (ASF), the Sexual Concern (SC) and the Psychological General Well-Being (PGWB) questionnaires (Screening, Day 1, Weeks 4, 8, and 12). In addition, visual evaluation of vaginal secretions, color, and epithelial integrity was performed. Tolerance to local DHEA application was also evaluated.

Postmenopausal women were eligible for inclusion if they met the following inclusion criteria and none of the exclusion criteria:

1. Postmenopausal women (non hysterectomized or hysterectomized), 40 to 75 years of age, defined as:
  - No menses for at least one year, or
  - FSH levels > 40 mIU/mL (within 60 days prior to Day 1) in women with no menses > 6 months but < 12 months, or hysterectomized women who were premenopausal at the time of hysterectomy, or
  - Six weeks (of screening visit) or more following bilateral oophorectomy.
2. Self-identified at least one moderate to severe of the following symptoms:
  - Vaginal dryness (none, mild, moderate or severe),
  - Vaginal and/or vulvar irritation/itching (none, mild, moderate or severe),
  - Vaginal pain associated with sexual activity (none, mild, moderate or severe),
3. No greater than 5% of superficial cells on vaginal smear.
4. A vaginal pH above 5.
5. Normal mammogram within 9 months of the start of the trial (Day 1).

Trial ERC-210 was divided into two phases, a screening period of 4 to 6 weeks and a treatment period of 12 weeks.

All women were instructed to apply the trial medication in the evening before bedtime daily for 12 weeks. Before first application of the trial medication and following proper instructions on how to apply the vaginal suppository, the participant inserted intravaginally, a dummy insert.

**Clinical Reviewer's Comments:**

Trial ERC-210 was not assessed by the Agency for efficacy. That said, the Agency does not assess in its evaluation of efficacy, MV. Rather, the Agency assesses the percentage of superficial and parabasal cells.

**Safety Assessments:**

Throughout the trial, vital signs, physical examinations, hematology and coagulation, blood chemistry, urinalysis and gynecological examinations were performed. An endometrial biopsy was performed at the beginning and end-of-trial.

Adverse events were recorded for safety evaluation and then coded into system organ class and preferred terms using the Medical Dictionary for Regulatory Authorities (MedDRA version 14.1).

**Statistical Methodology:**

The primary time point for analysis was the 12-week assessment in the Intent-to-Treat (ITT) population, with additional assessments at 2, 4, and 8 weeks.

The significance of the change from baseline within each treatment group was also statistically assessed. Consistent with the design of this trial, for each co-primary

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endpoint, a preliminary dose-response analysis was used that included all treatment groups, to determine if there was a statistically significant change using a regression analysis of the efficacy parameter (y-value) as a function of increasing dose (x-value). This analysis confirmed the efficacy of DHEA. The independent dose factor had values of DHEA of 0%, 0.25%, 0.5% and 1.0%. Given the significance of this analysis, the difference between each DHEA dose and placebo then was tested. Following the significant dose response analysis, analysis of variance was used to test each DHEA treatment group against placebo. Similar analyses were conducted on the most bothersome symptom and the gynecological evaluations of vaginal health, namely secretions, color, epithelial integrity and epithelial surface thickness.

The secondary parameters of sexual dysfunction and quality of life were analyzed by first calculating the total score and then using a similar analysis model as used for the primary endpoints. The sexual concern questionnaire was analyzed using chi-square methods. Safety analyses were performed on the Safety population. All available safety data were used for analysis. For adverse events and laboratory data, standard methods of analysis were used.

(b) (4)

(b) (4)

**Clinical Reviewer's Comments:**

The reported efficacy results for clinical Trial ERC-210 are not considered in the determination of approval of 0.50% DHEA vaginal insert for the intended indication. (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

Trial ERC-210, submitted in this sNDA application, is considered supportive of safety of the 0.50% DHEA vaginal insert. Trial ERC-210 will not be considered in the determination of the effectiveness of 0.50% DHEA vaginal insert to relieve moderate to severe dyspareunia. The safety data in Trial ERC-210 is included in the Integrated Summary of Safety (ISS) in this application.

**Safety Results:**

Refer to Section 7.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THERESA H VAN DER VLUGT  
11/16/2016

SHELLEY R SLAUGHTER  
11/16/2016

I concur with the conclusions and recommendations of Dr. van der Vlugt.

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: 208470**

**Applicant: EndoCeutics**

**Stamp Date: October 16, 2015**

**Drug Name: Prasterone Vaginal (b) (4) NDA/BLA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			eCTD
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
<b>LABELING</b>					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see <a href="http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm">http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm</a> )	X			Overall conforms to PLR formatting.
<b>SUMMARIES</b>					
7.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			The application includes an ISS of the six completed clinical trials.
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		Prasterone is a new molecular entity. Consideration of the efficacy of the drug product will be based on the results of phase 3 clinical trials ERC-231 and ERC-238.
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(1)
<b>505(b)(2) Applications</b>					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
<b>DOSAGE</b>					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g.,	X			ERC-210, phase 3, 12-week clinical trial was

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:				conducted to determine dose-response (0.25%, 0.50%, and 1.0% DHEA versus placebo) of the vaginal mucosa parameters.
<b>EFFICACY</b>					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?  Pivotal Study #1: ERC-231 <p style="text-align: center;">Indication: Treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause.</p> Pivotal Study #2: ERC-238 <p style="text-align: center;">Indication: Treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause.</p>				#1, ERC-231, "Effects of Intravaginal 0.25% and 0.50% DHEA on MBS Dyspareunia and Other Symptoms and Signs of VVA" randomized 255 postmenopausal women in a 1:1:1 fashion (0.25% DHEA, 0.50% DHEA, versus placebo). #2, ERC-238, "Effects of Intravaginal 0.50% DHEA on MBS Dyspareunia and Other Symptoms and Signs of VVA" randomized 558 postmenopausal women in a 2:1 fashion (0.50% DHEA versus placebo).
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
<b>SAFETY</b>					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	Defer to the Office of Clinical Pharmacology (OCP). Per OCP, a formal QT/QTc trial may not be needed. OCP is requesting that the Applicant submit a

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	Content Parameter	Yes	No	NA	Comment
					justification for not conducting a thorough QT/QTc study.
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	Prasterone is not currently approved.
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dosage (or dosage range) believed to be efficacious?	X			The requirements of ICH E1 guidelines for a NME are met with 1552 postmenopausal women exposed including 435 women treated for 1 year. The safety population consist of 1,542 postmenopausal women exposed to 0.25%, 0.50% or 1.0% DHEA, and 474 women exposed to placebo in 6 clinical trials,
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
25.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			MedDRA version 16.1
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			No deaths occurred in the 6 completed clinical trials. Narratives are available for serious adverse events (SAEs) and discontinuations.
<b>OTHER STUDIES</b>					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
30.	Has the applicant submitted the pediatric assessment, or	X			

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
	provided documentation for a waiver and/or deferral?				
<b>PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE</b>					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see <a href="http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm">http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm</a> )?		X		Labeling does not conform to required PLLR format. Subsection 8.4 Pediatric Use is not present.
<b>ABUSE LIABILITY</b>					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
<b>FOREIGN STUDIES</b>					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	All phase 3 studies were conducted in the United States and Canada.
<b>DATASETS</b>					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?				
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
41.	Has the applicant submitted the required Financial Disclosure information?	X			The Applicant submitted a Form FDA 3454 certifying that no compensation that could be affected by study outcome was provided to any investigator.
<b>GOOD CLINICAL PRACTICE</b>					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ Yes \_\_\_**

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Labeling does not conform to required PLLR format for Section 8 Use in Specific Populations. Subsection 8.4 Pediatric Use is required. A labeling amendment should be submitted.

See Appendix A: Memorandum to the File regarding the Applicant's request for Priority Review Designation for NDA 208470.

Information Request for the Applicant:

For each evaluable subject in 12-week ERC-231 and 52-week ERC-230, provide a copy of both the baseline and the end-of-study (or early termination) endometrial biopsy reports. The end-of-study reports should be provided per each of the three independent, blinded pathologists participating in ERC-231 and ERC-238. If the actual endometrial biopsy reports have already been included in the NDA, advise the Agency as to their location.

Theresa H. van der Vlugt, MD, MPH

\_\_\_\_\_  
Reviewing Medical Officer

\_\_\_\_\_  
Date

Shelley R. Slaughter, MD, PhD

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Clinical Team Leader

\_\_\_\_\_  
Date

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

## APPENDIX A

### I. Priority Review Designation



n208470PriorityDesignationReview.pdf

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THERESA H VAN DER VLUGT  
12/15/2015

SHELLEY R SLAUGHTER  
12/15/2015

I concur with the recommendation made by Dr. van der Vlugt that NDA 208470 is fileable from a clinical standpoint.