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APPLICATION NUMBER:

208470Orig1s000

SUMMARY REVIEW

Deputy Division Director Summary Review

Date	November 16, 2016
From	Audrey Gassman, MD
NDA #	208470
Applicant name	Endoceutics, Inc.
Application Type	505(b)(2)
Date of receipt of original submission	October 16, 2016
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Proprietary name/established name	INTRAROSA/prasterone
Dosage Form/strength	Vaginal insert/6.5 mg
Proposed Indications	Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
Action	*Approval*

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CDTL=Cross-Discipline Team Leader
OND=Office of New Drugs
OPQ = Office of Product Quality
DMEPA=Division of Medication Error Prevention and Risk Management
OSI=Office of Scientific Investigations
DMEPA=Division of Medication Error Prevention and Analysis
DMPP= Division of Medical Policy Programs
CDRH=Center for Devices and Radiological Health

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1. Introduction

The Applicant (Endoceutics Inc.) submitted NDA 208470 seeking the marketing approval of prasterone vaginal insert (proposed tradename Intrarosa) for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Vulvar and vaginal atrophy (VVA) is a condition associated with declining estrogen levels that occur during menopause and initially results in decreased vaginal lubrication, but over time can lead to clinical symptoms including vaginal dryness, burning/irritation/itching, and dyspareunia. Dyspareunia can lead to vulvovaginal pain and sexual dysfunction.

Prasterone, also known as dehydroepiandrosterone (DHEA), has been marketed in the US as a dietary supplement and as an unapproved drug product. Because of the there are no approved drug products in the US that contain prasterone, Intrarosa is considered a new chemical entity from a drug regulation perspective. The mechanism of action for prasterone is unknown although it has a steroid structure. Prasterone has androgenic or estrogenic metabolites that may have a therapeutic effect on vaginal epithelium and microbial content. The proposed dosing regimen is one 6.5 mg vaginal insert applied vaginally once daily at bedtime.

The vaginal insert product is inserted with an applicator. As applicators are considered devices under 21 CFR 3, the Center for Devices and Radiological Health (CDRH) was consulted to evaluate the applicator. The CDRH Office of Device Evaluation reviewed the functionality of the clinical trial and to-be-marketed applicators and the CDRH Office of Compliance evaluated the manufacturing site for the applicator.

The clinical development program of Intrarosa consisted of 6 clinical trials: a pharmacokinetic profile and dose-finding trials (ERC-213 and ERC-210), two pivotal 12-week phase 3 trials (ERC-231 and ERC-238), one additional phase 3 Trial (ERC-234) and one 52-week, open-label trial (ERC-230).

The review teams concluded there are no outstanding clinical pharmacology, nonclinical toxicology, chemistry, manufacturing and control (CMC) or issues related to the applicator from a device perspective. All disciplines along with the Cross Discipline Team Leader (CDTL, who also was the Clinical Team Leader) have recommended approval of this Application; I concur with their recommendation.

This memorandum provides the basis for the regulatory action for this application.

2. Background

As women enter menopause, levels of estrogen hormones decline. These declines in estrogen alter vaginal tissues and result in atrophy. In some women, this atrophy results in a symptomatic condition known as vulvar and vaginal atrophy (VVA). VVA can have different symptoms, the most common of which is pain during sexual intercourse (dyspareunia). The majority of the approved therapies in the United States for VVA symptoms contain estrogen. These products are used alone in women without a uterus and with a progestin in women with a uterus.

Most of the previously approved, older products in the US for VVA symptoms were not evaluated in clinical trials, but received the indication based on estrogen class labeling. More recently, Applicants who seek a claim based on symptomatic relief of VVA are required to perform clinical trials to obtain approval. The approval is primarily based on the reduction of a specific symptom of VVA that is most bothersome to the patient.

The Applicant opened IND 78,027 for prasterone on July 17, 2007. The IND was opened with the protocol for Trial ERC-210 entitled, "Topical DHEA Against Vaginal Atrophy". The primary objective was to determine the dose-response of vaginal mucosa parameters to the local action of prasterone in postmenopausal women suffering from vaginal atrophy. An advice letter was sent on March 18, 2008, with comments on the methodology to evaluate vaginal parameters and recommendations on the design of a phase 3 trial.

Between 2009 and 2011, the Applicant submitted several phase 3 protocols for review: ERC-231, ERC-234 and a revised ERC-230 (the long-term safety clinical trial). In 2013,

the Applicant submitted an additional phase 3 protocol for review (ERC-238). None of these protocols were submitted for a Special Protocol Agreement, but the Applicant received detailed guidance from all review teams during drug development.

A Pre-NDA meeting was held on April 27, 2015 to discuss the format and content of the NDA. At this meeting, CMC, nonclinical and clinical issues were discussed. These issues included the acceptability of qualification of a commercial manufacturing site, nonclinical labeling and the content of the datasets.

The NDA submission for the Intrarosa was received on October 16, 2015, and filed on December 28, 2015, under NDA 208470. The Applicant requested a Priority Review Designation. DBRUP, however, denied this request based on the following two reasons:

1. "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. "Treatment of a novel population, such as 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."

The original goal date for the NDA was August 16, 2016, based on a Standard review cycle. On March 29, 2016, the Division sent an advice letter informing the Applicant that an additional blinded review of the histology endometrial biopsy specimens obtained in the clinical trials (ERC-210, ERC-231 and ERC-234) and the long-term clinical safety trial (ERC-230) was necessary. The Applicant agreed to conduct the re-reads in accordance with the Agency's 2003 draft clinical Guidance for Industry and agreement on the protocol for the rereads was reached. On July 12, 2016, the Agency received a Clinical Study Report from study ERC-237 (Re-Readings of Endometrial Biopsies).This submission was determined to be a major amendment and the clock was extended to November 16, 2016.

3. Chemistry, Manufacturing and Controls

The drug substance, prasterone, is prepared from diosgenin (a steroidal saponin). Prasterone is a chiral molecule with a steroid core. The drug substance, prasterone is a white to yellow powder that is (b) (4) insoluble in water. DMF (b) (4) was reviewed for the description of the commercial source. The DMF was reviewed by OPQ and found to be adequate to support the NDA.

The drug product contains Witepsol (b) (4) (Hard Fat, NF). (b) (4) Each vaginal insert contains 6.5 mg of prasterone in a 1.3 mL vaginal insert.

(b) (4) packaged in a carton with four blister (b) (4) of seven inserts and 28 applicators.

Analytical procedures for drug substance and drug product identification and other quality control attributes were verified and found acceptable by the FDA laboratory in St Louis, MO (Refer to Methods Verification Report dated July 27, 2016). Stability testing was determined to be adequate up to 36 months of shelf life.

During this review cycle, a manufacturing inspection of one drug product site (b) (4) it was noted that samples manufactured were cracked or crumbling. However, samples at the second plant (b) (4) were intact. The issues at the (b) (4) site were attributed to different (b) (4) (b) (4) The Applicant instituted changes at (b) (4) to match the processes at the (b) (4) site. After successfully manufactured three new registration and validation batches, the revised manufacturing process was considered acceptable to the OPQ review team. An in vitro dissolution method was developed by the Applicant to ensure quality control and consistent bioavailability of the vaginal insert product. Agreement was reached between the Applicant and the Biopharmaceutics team on the proposed acceptance criteria of not less than (b) (4) % Q dissolved in 180 minutes.

The drug substance, drug product and biopharmaceutics review teams recommended approval of the application. (See OPQ Technical Lead summary review dated October 20, 2016). The Applicant provided a claim for categorical exclusion from an environmental assessment and the OPQ review team concurred with the Applicant's claim.

Of note, during drug development, prasterone was considered a New Molecular Entity because there were no approved drug products or legally marketed drug products containing prasterone in the US. However, the Office of Compliance determined that prasterone had been unlawfully marketed as a drug product. Therefore, this application was determined to be a New Chemical Entity, but not a new molecular entity and not subject to the Program. Refer to the memo by Dr. Norman Schmuff dated December 21, 2015.

The Application Technical Lead evaluated the above review teams' assessments of the product quality. He stated that the DMF was reviewed and found to be adequate. In his first review dated October 20, 2016, he concluded that, "As of this review, this 505(b)(2) NDA is Not Ready for Approval in its present form per 21 CFR 314.125(b)(8)." This initial regulatory recommendation was solely based on receipt and review of revised product quality labeling as discussed above.

In an addendum to the October 2016 review, the Application Technical Lead for the Office of Product Quality (OPQ) concluded in his memo dated November 16, 2016 review, that, "On November 16, 2016 the NDA review team agreed to the labels and labeling as documented in Attachment 1 of this review. As revised, all information required under 21 CFR 201 is adequately presented. The storage statement has been revised throughout for completeness and consistency. The labels and labeling will include the statement: Manufactured for Endoceutics Inc., Quebec City, Canada, G1V 4M7, (b) (4) his NDA is now recommended for Approval from the OPQ perspective."

Comment: I concur with the OPQ review teams that there are no outstanding CMC issues related to this application. For additional discussion regarding the microbiological and CDRH reviews, refer to sections 6 and 11, respectively) of this summary review.

4. Nonclinical Pharmacology/Toxicology

Prasterone, also known as dehydroepiandrosterone or DHEA, is an endogenous circulating steroid hormone that circulates at high levels in premenopausal women. Prasterone is metabolized to testosterone and estradiol and decreases with age. The Applicant submitted 6 month and 12 month monkey toxicity studies with oral administration of prasterone. Safety margins to the expected human exposure were estimated in postmenopausal women using intravaginal prasterone $AUC_{0\text{-}24h}$ value of 56 ng.h/mL. The pharmacology/toxicology reviewer also noted that prasterone was negative in three genotoxicity studies: bacterial mutagenesis assay (Ames test), in vitro chromosomal aberrations assay with human peripheral blood lymphocytes, and in vivo mouse bone marrow micronucleus assay.

After review of the submitted in vitro and toxicology studies, the pharmacology/ toxicology reviewer concluded in his August 9, 2016, review that, "There is an absence of cause for concern based on the results of the one year toxicology study in monkeys and series of clinical studies performed with DHEA vaginal suppositories (submitted by the Applicant from the published literature)." He also stated that carcinogenicity studies were not required by the Agency because prasterone was an endogenous non-genotoxic steroid and systemic concentrations in the intended postmenopausal population were equal or less to those in younger women. Also, he noted that reproductive studies were not required by the Agency for this application because the product is intended only for use in postmenopausal women.

After review of the submission, the pharmacology/toxicology reviewer commented in his review dated August 9, 2016, that, "Intrarosa is approvable." No postmarketing commitments or requirements were recommended by the pharmacology/toxicology review team.

Comment: I concur with the approval recommendation of the pharmacology/toxicology review team. All labeling recommendations by the pharmacology/toxicology reviewer were incorporated into nonclinical labeling. No other outstanding pharmacology/ toxicology issues were identified by the nonclinical review team.

5. Clinical Pharmacology

The clinical pharmacology review team evaluated pharmacokinetic and pharmacodynamic data for the prasterone vaginal insert. The clinical pharmacologist focused their review on evaluation of the pharmacokinetic profile of prasterone and its metabolites. The pharmacokinetic profile was obtained in a phase 1 trial (ERC-213). Additional dose finding was evaluated in a phase 3 dose finding trial (ERC-210) in which three prasterone vaginal insert doses were evaluated (3.25 mg, 6.5 mg and 13 mg). Finally, additional trough concentrations of prasterone and pharmacodynamic endpoints were evaluated in the two phase 3 trials (ERC-231 and ERC-238) that supported approval as well as an addition phase 3 trial (ERC-234) and a long-term safety trial (ERC-230).

ERC-213: A randomized, double-blind, placebo controlled phase 1 study that was conducted in 40 postmenopausal women. The primary goal of this study was to evaluate the systemic bioavailability of prasterone vaginal insert and its metabolites. These women had pharmacokinetic and pharmacodynamic sampling during 7 days of treatment with the prasterone vaginal insert. Three doses of prasterone (6.5 mg, 13 mg and 23.4 mg) were evaluated along with a placebo vaginal insert. Pharmacokinetic profiles, vaginal maturation index and value and vaginal pH as well as safety and tolerability were evaluated on Days 1 and 7 of treatment. The primary goal of Trial ERC-213 was to evaluate the time-concentration profiles of the prasterone vaginal insert and its metabolites on Days 1 and 7. The trial was conducted in the intended population of postmenopausal women. This trial sampled serum prasterone and the following key metabolites: estradiol, estrone, testosterone, dihydrotestosterone as well as other known metabolites of prasterone.

The clinical pharmacology review evaluated the bioanalytic methodology used to obtain the systemic exposure data and concurred that the methods for measurement of prasterone and its metabolites was adequately validated. Pharmacokinetic parameters were calculated on Day 1 and Day 7, including $AUC_{0\text{-}24,}$ C_{trough}, and C_{max}, and summarized using means, median, minimum and maximum values, and other parameters including coefficients of variation. Confidence intervals (95% two-tailed) were calculated for $AUC_{0\text{-}24}$, basal and average serum steroid levels, vaginal maturation value and vaginal pH. Differences between Day 1 and Day 7 were summarized and Day 7 minus Day 1

differences was analyzed using paired t-tests within each treatment group without adjustment for multiple comparisons.

The results of Study ERC-213 showed serum concentrations of prasterone that appeared to be higher on Day 1 (after the first dose) than Day 7 following daily administration of 6.5mg prasterone vaginal insert. In contrast, the systemic exposure (based on AUC_{24}) of the metabolites including estradiol tended to be higher on Day 7 compared to Day 1. The clinical pharmacology reviewer stated in his October 2016 review that, "This result indicates a relatively higher absorption after the first dose than the following doses, which may be attributed to a higher vaginal permeability due to thinner mucosal epithelium before treatment in women with VVA. Otherwise, the systemic exposure (based on AUC_{24}) to the metabolites including E1 (estradiol), E2 (estrone) and testosterone tended to be higher on Day 7 compared to Day 1." From a pharmacodynamic standpoint, vaginal maturation value was significantly increased and vaginal pH was significantly decreased. No safety signal of excessive serum testosterone or estradiol levels was identified in this study.

ERC-210: A randomized, double-blind, placebo-controlled dose-finding trial in postmenopausal women. The primary goal of this trial was to determine the dose response of pharmacodynamic (vaginal) symptoms and physiologic parameters in women with VVA to prasterone vaginal insert. Safety and tolerability was also assessed. Women were enrolled and randomized to one of three doses of prasterone (3.25 mg, 6.5 mg or 13 mg) or a placebo insert containing only the Witepsol excipient. The efficacy parameters assessed in this trial included: vaginal cell maturation index, most bothersome symptom, vaginal dryness, vaginal and/or vulvar itching and irritation as well as vaginal pain with sexual activity. Other evaluations of vaginal epithelium, pharmacokinetics and safety assessments were performed over this twelve week trial.

The results of Trial ERC-210 demonstrated:

- All prasterone treatment groups showed significant changes in vaginal cell maturation indices, vaginal pH and bothersome symptom in a dose dependent manner. The placebo group showed less changes in the vaginal pH and bothersome symptom after 12 weeks, but less change than any of the studied prasterone doses with no accompanying change in vaginal maturation indices
- The trough serum concentrations of DHEA and its metabolites in the active treatment groups were increased at 2-week and then remain constant without any significant change.
- Treatment with 6.5 mg and 13 mg prasterone reach steady state for changes in the vaginal cells maturation and vaginal pH prior to the end of the 12 week treatment period. There was no significant difference between 6.5mg and 13mg prasterone treatment groups in the efficacy parameters.

Daily administration with the lowest dose, 3.25 mg prasterone, also showed significant changes in vaginal cell maturation and pH in the patient population (Trial ERC-231). However, this dose regimen failed to show statistically significant difference in the pain at sexual activity as a primary parameter compared to the placebo group. Additional

pharmacodynamic data from a clinical trial of twice weekly regimen with 6.5 mg prasterone following daily treatment for 2 weeks demonstrated that the effect on the parabasal and superficial cells and vaginal pH appeared to be diminished after reaching the maximum at 2 weeks (Trial ERC-234). Therefore, these two dosing regimens were not further evaluated by the Applicant.

The following pharmacology issues of interest were also discussed by the clinical pharmacology reviewer in his October 24, 2016, review:

- Renal impairment: The Applicant did not conduct a dedicated trial in postmenopausal women with renal impairment. Although women with renal impairment were not restricted from participating in the phase 3 trials (ERC-231 and ERC-238), only two women had serum creatinine greater than 1.5 of the upper limit of normal (ULN) in these trials. The clinical pharmacology reviewer noted in his October 2016 review that products containing a steroid hormone estrogen do not have any restrictions on women with renal impairment and also stated, "….when considering the limited contribution of kidney to metabolism and excretion of sex hormones and the local route of administration of this vaginal insert, it is not anticipated that there would be clinically significant changes in systemic exposure to DHEA and its metabolites in patients with renal impairment." The reviewer did not recommend additional data or restrictions for women with renal impairment who use prasterone vaginal inserts.
- Hepatic impairment: The Applicant did not conduct a dedicated trial in postmenopausal women with hepatic impairment. Although women with hepatic impairment were not restricted from participating in the phase 3 trials (ERC-231 and ERC-238), only 1.2% of the population had serum ALT levels greater than 2 fold higher than the ULN and no patients met the Hy's Law criteria at baseline. After review of the limited data from women with elevated liver enzymes, the clinical pharmacology reviewer concluded in his October 2016 review that there was insufficient safety information in women with hepatic disease. After further consideration by the clinical pharmacology review team, the review team recommended that labeling should state that prasterone (b) (4) had not been studied (b) (4).
- Relevant drug-drug interactions: The clinical pharmacologist concluded that a clinically significant pharmacokinetic interaction of prasterone vaginal insert with concomitant drug use was "unlikely to happen".

The clinical pharmacologist concluded that the pharmacokinetic and pharmacodynamic data supported 6.5 mg once daily as the lowest effective dose and dose regimen for the intended population of postmenopausal women who have moderate to severe dyspareunia as a symptom of VVA. The clinical pharmacology reviewer concluded that, "The Office of Clinical Pharmacology, Division of Clinical Pharmacology 3 has reviewed the clinical pharmacology information submitted for NDA 208470 of 6.5 mg prasterone vaginal insert. We find the application to be acceptable from a Clinical Pharmacology perspective, provided that an agreement on the language in the package insert is reached between the Applicant and the Division."

Comment: The clinical pharmacology review team has agreed to the text in the relevant clinical pharmacology sections in the final PI label for prasterone. The clinical pharmacology reviewer did not recommend any specific postmarketing commitments or postmarketing requirements. He did note in his supportive evidence of safety section that, "It may warrant that a long-term safety monitoring in a larger population be evaluated, particularly for patients with the risk factor of hormone dependent diseases." No specific study or data collection was recommended, however, and no other outstanding pharmacology issues were mentioned in the final October 2016 Clinical Pharmacology review.

Given this concern, the clinical review team evaluated the safety database for hormone dependent diseases (such as breast cancer and cardiovascular events) and did not detect any concerning safety signal or trend of an increased risk of hormone dependent disease. Therefore, I agree with the clinical review team that no postmarketing evaluation for these hormone dependent diseases is necessary for this application at this time.

6. Clinical Microbiology

The vaginal insert is not required to be a sterile product or manufactured under aseptic conditions. However, microbial limit testing was proposed to be conducted on each commercial batch at release and during stability testing. The Microbiological reviewer evaluated the microbial burden and limit testing. He stated that, "Information provided for the control of microbiology for the drug product is found adequate per microbiology review #1.Therefore, NDA 208470 is recommended for approval from the microbiology perspective." (Refer to the Application Technical Lead review dated for additional information related to Product Quality Microbiology.)

Comment: I concur with the recommendations of the Product Quality Microbiology review team that there are no outstanding issues. No postmarketing commitments or requirements were recommended by the Product Quality Microbiology review team.

7. Efficacy/Statistics

The two phase 3 trials (ERC- 231 and ERC- 238) were the primary support for the efficacy of prasterone for the treatment of moderate to severe dyspareunia in women with VVA due to menopause. In ERC-231, women were randomized to 3.25 mg of prasterone vaginal insert, 6.5 mg of prasterone vaginal insert or a placebo vaginal insert administered once daily at bedtime. In Trial ERC-238, only the 6.5 mg dose of prasterone and a placebo vaginal insert were studied. The Applicant requested consideration of the 6.5 mg dose only in this application; therefore, the focus of the clinical efficacy review was on the findings of the 6.5 mg prasterone vaginal insert dose.

Trials ERC-231 and ERC-238 were similar in design and conduct. Both trials were randomized double-blind, placebo-controlled and conducted entirely in the United States and Canada. The treatment period for both trials was 12 weeks. Subjects were to use the

assigned vaginal insert on a daily basis before bedtime. The primary objective of these phase 3 trials was to assess the efficacy, safety, and tolerability of prasterone versus placebo in the treatment of VVA in postmenopausal women.

During drug development, the Division recommended that the Applicant follow the 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation", which outlines the following primary efficacy endpoints for two phase 3 trials seeking an indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy including:

1. Mean change from baseline to week 12 in the moderate to severe symptom that has been identified by the patient as most bothersome to her.
2. Mean change from baseline to week 12 in vaginal pH.
3. Mean change from baseline to week 12 in vaginal maturation index (parabasal and superficial cells).

In the Applicant's phase 3 trials, these co-primary efficacy endpoints were obtained using the following methodologies:

- Most bothersome symptom to the patient (MBS): To obtain the most bothersome symptom, a 4-point scale (none [0], mild [1], moderate [2], or severe [3]) was used where each subject self-identified one of two moderate to severe symptoms as was most bothersome to her. All subjects were required to have a moderate to severe (Grade 2 or 3) of a dyspareunia symptom at baseline visit.
- Vaginal pH: The vaginal pH measurement was obtained by pressing a pH indicator strip on an Ayre spatula (or equivalent) applied directly to the opposite lateral wall of the vagina. The subjects entering the trial were required to have a vaginal pH value greater than 5.0 at baseline visit. The subjects were advised not to have sexual intercourse and to refrain from using vaginal lubricant within 24 hours prior to the measurement.
- Vaginal Cell Maturation Index: To obtain the Maturation Index, vaginal smear samples were obtained by gently scraping the middle or second third of the side wall of the vaginal using a wooden or plastic spatula. The sample was applied to a glass slide and fixed. The vaginal smear samples were evaluated at the central pathology laboratory. This laboratory performed the cell count for superficial and parabasal cells for each slide sample. Subjects entering the trial were required to have less than 5% superficial cells on a lateral wall vaginal smear at baseline visit.

The Applicant used the following scale to determine whether the patient was sexually active and had identified dyspareunia as a moderate to severe "most bothersome symptom":

- Vaginal pain associated with sexual activity: Pain at penetration during intercourse or after sexual activity.
    - Not sexually active.
    - None (Grade 0): Comfortable sexual activity, no pain during sexual activity.

- Mild (Grade 1): Episodically occurs, not all the time, occasionally causes stop of sexual activity.
- Moderate (Grade 2): Most of the time, minimal satisfaction from sexual activity, often must stop sexual activity.
- Severe (Grade 3): Occurs all the time, cannot enjoy sexual activity, often must stop sexual activity. May be abstinent because of pain.

Only women who rated their dyspareunia as the most bothersome symptoms and reported their symptoms as Grade 2 or Grade 3 were enrolled in the phase 3 trials.

The Applicant evaluated multiple secondary efficacy endpoints in the two phase 3 trials including assessment of changes in vaginal dryness, vulvovaginal irritation/itching and other symptoms. The clinical team assessed these secondary endpoints and concluded that none of them had sufficient support (b) (4)

Key entry criteria common to trials ERC-231 and ERC-238:

- Women age between 40 to 75 years at the time of randomization (up to 80 in Trial ERC-238)
- Postmenopausal defined as:
  - at least 12 months since the last spontaneous menstrual bleeding (if uncertain, confirmed with FSH level > 40 IU/L)
  - had a hysterectomy with ovaries intact and a FSH level of > 40 IU/L
  - at least 6 weeks since bilateral oophorectomy with or without hysterectomy
  - Had the following criteria for vulvar and vaginal atrophy (VVA): 5% or fewer superficial cells confirmed by maturation index in the vaginal smear, vaginal pH greater than 5.0, and moderate to severe vaginal dryness or dyspareunia as the self-reported most bothersome symptom (MBS).

Subjects with or without an intact uterus were eligible for enrollment in both phase 3 trials.

<u>Demographics and patient characteristics in trials ERC-231 and ERC-238:</u>

All clinical trial sites in these two phase 3 trials were in the US or Canada. A brief overview of some key demographics from the ITT populations in Trials ERC-231 and ERC-238 are summarized in Tables 1 and 2 below:

Table 1: Key Subject Demographics/Characteristics – Trial ERC-231*

Demographic Parameters	Placebo insert N=77 n(%)	Prasterone insert (3.25 mg) N=79 n(%)	Prasterone insert (6.5 mg) N=81 n(%)
Age (years)			
Mean years (SD)	59.1(5.8)	59.7 (6.1)	57.7 (5.5)
Median	59	60	57
Range (min-max)	45-73	40-75	41-69
Race			
White	67(87)	75(95)	79(98)
Black or African American	8(10)	3(4)	1(1.2)
Asian	1(1.3)	0	1(1.2)
Other	1(0.6)	1(1.3)	0(0)
Body Mass Index (kg/m^2)	25.7	26.2	25.9
Cause of last menses			
Natural (%)	36(47)	39(49)	39(48)
Surgical (%)	41(53)	40(51)	42(52)

*Obtained from Tables 4 and 5 of the Statistical Review dated July 1, 2016.

Table 2: Key Subject Demographics/Characteristics – Trial ERC-238*

Demographic Parameters	Placebo insert N=157 n(%)	Prasterone insert (6.5 mg) N=325 n(%)
Age		
Mean years (SD)	59.6 (5.6)	59.6 (6.7)
Median years	59	59
Range (min – max)	47-75	40-80
Race		
White	144 (92)	296(91)
Black or African American	10(6)	21(6)
Asian	2(1.3)	4(1.2)
Other	1(0.6)	4(1.2)
Body Mass Index (kg/m^2)	25.6	26.3
Cause of last menses		
Natural (%)	105 (67)	208(64)
Surgical (%)	52(33)	117(36)

*Obtained from Table 6 and 7 of the Statistical Review dated July 1, 2016.

The demographics and treatment characteristics were similar between the treatment groups in the two phase 3 trials and between the two trials. In both trials, the mean age was approximately 59 years of age and the mean Body Mass Index was 26 kg/m^2. The Medical Officer concluded in her November 16, 2016, review that, "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."

Comment: I concur with the conclusions of the Medical Officer regarding the demographic and baseline characteristics of these phase 3 trials.

Trial Design and Conduct:

Trial ERC-231 was entitled: "DHEA (Prasterone) 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). In this trial, 255 postmenopausal women were randomized 1:1:1 ratio to receive vaginal insert containing prasterone 3.25 mg (N=87), prasterone 6.5 mg (N=87), or placebo (N=81).

Trial ERC-238 was 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). In this trial, 558 postmenopausal women were randomized in a 2:1 ratio to receive a vaginal insert containing prasterone 6.25 mg (N=356) or placebo (N=182).

The two phase 3 clinical trials were similar in that there was a screening period followed by a treatment period of 12 weeks. All trial participants were instructed to use the insert daily at bedtime during the 12 week treatment period.

Subject Disposition:

A brief summary of the disposition of subjects in these two trials are summarized in Tables 3 and 4 below:

Table 3: Disposition of Women in Trial ERC-231*

Category	Placebo insert	Prasterone insert 3.25 mg	Prasterone insert 6.5 mg
Randomized	81	87	87
Safety population	80	86	87
ITT population	77 (100%)	79(100%)	81(100%)
Completed trial	72(93.5%)	73(92.4%)	76 (93.8%)
Discontinued	5(6.5%)	6(7.6%)	5(6.2%)
Discontinued for:			
Adverse event	1(1.3%)	4(5.1%)	2(2.5%)
Non-compliance	1(1.3%)	0	0
Withdrew consent	4(5.2%)	0	2(2.5%)
Investigator's decision	0	1(1.3%)	0
Lack of efficacy	0	1(1.3%)	1(1.2%)

*Obtained from Table 2 in the Statistical Review dated July 1, 2016.

Table 4: Disposition of Women in Trial ERC-238*

Category	Placebo Insert	Prasterone insert 6.5 mg
Randomized	182	376
Safety population	130	374
ITT population	157(100%)	325(100%)
Completed trial	152(96.8%)	311(95.7%)
Discontinued	5(3.2%)	14(4.3%)
Discontinued for:		
Adverse event	3(1.9%)	5(1.5%)
Lost to follow-up	0	2(0.6%)
Withdrew consent	2(1.3%)	7(2.2%)
Others	0	0

*Obtained from Table 3 in the Statistical Review dated July 1, 2016.

For both trials, the most common reasons for discontinuation were adverse events and patient withdrawal of consent. The Medical Officer and Statistical reviewer did not identify important imbalances in subject disposition between treatment groups, within or between trials.

Statistical Methodology:

The primary efficacy analyses for the two phase 3 trials were based on the Intent to Treat (ITT population) consisting of all women who received at least one dose of trial drug with a baseline (Day 1) evaluation meeting the entry criteria. For the ITT primary

efficacy analysis, if there were missing time points due to subject discontinuation, the Last Observation Carried Forward (LOCF) method was used to impute the missing data.

Analysis methods included analysis of covariance (ANCOVA) with the treatment group as the main factor and the baseline value as the covariate to compare the changes from baseline to week 12 (end-of-study) for vaginal pH, and vaginal maturation (parabasal, intermediate and superficial cells) between prasterone dose groups and placebo. As all 4 co-primary endpoints needed to demonstrate statistically significant effect relative to placebo at Week 12, no statistical adjustment was required for multiple endpoints. The primary time point for analysis and data presentation was the 12-week assessment.

The p-value for the baseline adjusted least square mean (LSM) difference between treatment groups were presented (specifically, p-values for the placebo versus prasterone). Additionally, change from baseline for each treatment group were presented and assessed via a 1-sample t-test.

All statistical analyses were performed at the two-sided significance (alpha) level of 0.025.

Results of the primary efficacy analyses for Trials ERC-231 and ERC-238:

Key results of the primary efficacy analyses for Trials ERC-231 and ERC-238 are summarized in Tables 5 and 6 below:

Table 5: Applicant Reported Efficacy Summary Results from Trial ERC-231*

	Placebo N = 77	Prasterone 3.25 mg N = 79	Prasterone 6.5 mg N = 81
%Superficial Cells			
- 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**	-	<0.0001	<0.0001
% Parabasal Cells			
- 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**	-	<0.0001	<0.0001
Vaginal pH			
- 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**	-	<0.0001	<0.0001
Dyspareunia			
- 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**	-	0.3423	0.0132

*Obtained from Table 7 in the Medical Officer's review dated November 16, 2016.
** ANCOVA test with treatment group as the main factor and baseline value as the covariate (p-value versus placebo).

Table 6: Applicant Reported Efficacy Summary Results from Trial ERC-238

	Placebo N = 157	0.50% DHEA N = 325
%Superficial Cells		
- 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**	-	<0.0001
% Parabasal Cells		
- 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**	-	<0.0001
Vaginal pH		
- 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**	-	<0.0001
Dyspareunia		
- 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**	-	0.0002

*Obtained from Table 11 from the Medical Officer's review dated November 16, 2016.
**ANCOVA test with treatment group as the main factor and baseline value as the co-variate (p value versus placebo)

Using the pre-specified approach, the statistical reviewer confirmed that the 6.5 mg prasterone vaginal insert statistically improved vaginal pH, superficial and parabasal cell counts and relieved moderate to severe dyspareunia over placebo for each of the two phase 3 trials. The statistical reviewer, however, commented that the study was insufficiently powered to have valid conclusions based on subgroup analyses, such as efficacy in women age 65 and older.

Comment: The Applicant was advised during drug development that based on the design of the phase 3 trials, no secondary efficacy endpoints related to the effectiveness of prasterone vaginal inserts would appear in product labeling.

Statistical conclusions of the primary efficacy results for trials ERC-231 and ERC-238:

The efficacy of prasterone vaginal insert 6.5 mg were based on the findings of trials ERC-231 and ERC-238. The statistical reviewer stated that there were no statistical issues with these phase 3 trials. In a review dated July 1, 2016, the statistical reviewer stated that, "From a statistical perspective, data from the two submitted studies provided statistical evidence in support of Prasterone Vaginal Insert, administered intravaginally at the 6.5 mg dose once daily, in the treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause." Both the Medical Officer and CDTL concurred with the statistical reviewer's conclusion regarding efficacy (Refer to Medical Officer's review dated November 16, 2016, and the CDTL review dated November 16, 2016).

Comment: I concur with the statistical and clinical review teams that trials ERC-231 and ERC-238 demonstrated substantial evidence of efficacy for the 6.5 mg prasterone vaginal insert for the proposed indication.

Efficacy summary:

The main objective of the Applicant's NDA submission was to demonstrate that INTRAROSA (prasterone) was effective in the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The statistical reviewer concluded in her July 1, 2016 review that "From a statistical perspective, data from the two submitted studies provided statistical evidence in support of Prasterone Vaginal Insert, administered intravaginally at the 6.5 mg dose once daily, in the treatment of treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause." The Medical Officer concurred with the statistical reviewer and summarized her findings of the efficacy outcomes in her November 16, 2016, review as follows, "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)." The CDTL concurred with the Medical Officer's conclusion (See CDTL review dated November 16, 2016).

I agree with the statistical reviewer, Medical Officer and Cross-Discipline Team Leader (CDTL) that substantial evidence of effectiveness of prasterone has been demonstrated for treatment of moderate to severe dyspareunia, due to menopause. Therefore, I concur with the conclusions of the statistical review team, Medical Officer, and CDTL that there are no outstanding efficacy concerns for this new steroid vaginal insert product.

8. Safety

The data supporting the safety of the 6.5 mg prasterone vaginal insert for the treatment of moderate to severe dyspareunia symptoms from vulvar and vaginal atrophy due to menopause come from 6 clinical trials contained in this NDA submission. The Applicant provided several safety cohorts for evaluation and an integrated safety summary (ISS) containing all safety data obtained from all doses of prasterone, ranging from 3.25 to 13 mg, evaluated during the clinical development program.

The primary safety database consisted of a total of 1542 postmenopausal women were exposed to at least one dose of study medication (prasterone vaginal insert or placebo) in six double-blind, placebo-controlled phase 2 and 3 trials (referred to as the double blind phase 2/3 population). The mean total exposure to proposed prasterone vaginal insert dose of 6.5 mg was 73.22 days and the mean duration of treatment was 80.53 days. In subjects treated with the 6.5 mg prasterone vaginal insert dose:

- A total of 1196 postmenopausal women received the proposed 6.5 mg prasterone vaginal insert dose
- A total of 521 postmenopausal women received treated up to 52 weeks with the proposed 6.5 mg prasterone vaginal insert dose

Comment: The clinical review team concluded that the safety database was adequate to characterize the risk of prasterone (6.5 mg) vaginal insert.

Deaths:

Deaths: No deaths occurred during the prasterone clinical development program during the six clinical trials.

Non-fatal Serious Adverse Events (SAE):

In the prasterone clinical development program, a total of 26 of 1196 women [2.2%] experienced serious adverse events (SAEs) in the 6.5 mg prasterone treatment group compared to 5 of 474 women [1%] treated with placebo. Of these serious adverse events, only two were related to reproductive organs:

- One SAE (invasive ductal breast carcinoma) in the 6.5 mg prasterone vaginal insert treatment group was considered possibly drug-related to prasterone by the investigator.
- One SAE (uterine prolapse) in the 6.5 mg prasterone vaginal insert treatment group was reported, although not considered drug related. This patient had mild,

preexisting prolapse which worsened. This event was not considered related to prasterone use by the investigator or the clinical review team.

- One report of a pulmonary embolism in the 3.25 mg prasterone vaginal insert treatment group. This was not considered related to prasterone use by the investigator or the clinical review team as the patient appeared to have preexisting respiratory symptoms.

Comment: After review of the narratives of the serious adverse events reported in the safety database, no safety signals or trends were identified by the Medical Officer. Given the prevalence of breast cancer in the postmenopausal population, this occurrence does not raise a safety concern.

Discontinuations for adverse events:

Fifty two of 177 women who discontinued from double blind phase 2/3 trials with prasterone did so as a result of an adverse event. There was no dose-related increase in adverse events that led to discontinuation; the incidences were 34%, 28% and 33% for the prasterone vaginal insert 3.25 mg, 6.5 mg, and 13 mg groups, respectively. The incidence of discontinuation for adverse events was slightly lower for placebo treated women (23%). The most common adverse events leading to discontinuation in the prasterone groups were application site (vaginal) discharge (0.5%) and human papilloma virus test positive (0.2%).

Comment: The Medical Officer also evaluated the discontinuations for adverse events for the three prasterone vaginal dose groups (3.25 mg, 6.5 mg and 13 mg) and placebo treatment. No relevant differences or trends in SAEs or AEs resulting in discontinuation were identified and the majority of these events were unrelated to prasterone treatment. In her November 16, 2016 review, she concluded that the discontinuations for adverse events did not raise new safety concerns or trends pertinent to chronic use of the proposed 6.5 mg prasterone vaginal insert dose.

Treatment-Emergent Adverse Events (TEAEs)

In the double-blind phase 2/3 population, approximately half of the postmenopausal women who were treated with prasterone had an adverse event (818 of 1542 [53%]) as compared to 47.7% of women treated with a placebo insert (226 of 474). See Table 7 for adverse events reported in > 1% of subjects in the double-blind phase 2/3 trials in the prasterone and placebo treated groups:

Table 7: Summary of Number (%) of Women with TEAEs in ≥1% in the Double-Blind Phase 2/3 Population*

Primary System Organ Class Preferred Term[1]	Placebo N = 474	Prasterone 3.25 mg N = 282	Prasterone 6.5 mg N = 1196	Prasterone 13 mg N = 64	Total N = 1542
Number of Women with at least one TEAE	**226 (47.7%)**	**150 (53.2%)**	**627 (52.4%)**	**41 (64.1%)**	**818 (53.0%)**
Gastrointestinal disorders	**44 (9.3%)**	**30 (10.6%)**	**85 (7.1%)**	**11 (17.2%)**	**126 (8.2%)**
- 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%)
General disorder and administrative site disorder	**31 (6.5%)**	**17 (6.0%)**	**131 (11.0%)**	**10 (15.6%)**	**158 (10.2%)**
- 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%)
Infections and infestations	**80 (16.9%)**	**56 (19.9%)**	**209 (17.5%)**	**20 (31.3%)**	**285 (18.5%)**
- 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%)
Investigations	**19 (4.0%)**	**10 (3.5%)**	**63 (5.3%)**	**0 (0.0%)**	**73 (4.7%)**
- Weight increased	6 (1.3%)	0 (0.0%)	21 (1.8%)	0 (0.0%)	21 (1.4%)
Musculoskeletal and connective tissue disorders	**37 (7.8%)**	**30 (10.6%)**	**69 (5.8%)**	**11 (17.2%)**	**110 (7.1%)**
- Arthralgia	7 (1.5%)	4 (1.5%)	15 (1.3%)	2 (3.1%)	21 (1.4%)
- Back pain	11 (2.3%)	8 (2.8%0	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%)
Nervous system disorder	**18 (3.8%)**	**23 (8.2%)**	**58 (4.8%)**	**10 (15.6%)**	**91 (5.9%)**
- Headache	14 (3.0%)	12 (4.3%)	35 (2.9%)	6 (9.4%)	53 (3.4%)
Reproductive system and breast disorders	**59 (12.4%)**	**42 (14.9%)**	**155 (13.0%)**	**12 (18.8%)**	**209 (13.6%)**
- 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%)

*Obtained from Table 34 of the Medical Officer's review dated November 16, 2016.

The most commonly reported adverse event was application site (vaginal) discharge which was reported in 2.7% of women in the 6.5 mg prasterone group compared to 1.3% in the placebo group. The Medical Officer concurred with the Applicant's conclusion that that this adverse event may be a result of melting of the excipient (Witepsol) in the insert and also a direct effect of prasterone on vaginal secretion.

Adverse events that could possibly be related to prasterone vaginal insert use, including urinary tract infections and vulvovaginal complaints were infrequent and had similar reporting across the treatment groups and placebo treatment. Other adverse events that have been related to estrogen use, such as headache and hot flashes were uncommon across all treatment groups.

Comment: After review of the adverse event data from double-blind, phase 2/3 population, the Medical Officer reported that, "In the above listing, only drug-related application site discharge occurred at an incidence ≥ 1 percent over placebo in the 0.50% DHEA treatment group (6.5 mg) versus the placebo treatment group in the 4 placebo-controlled clinical trials in the DHEA development program. Application site

discharge should be reported in labeling as an adverse reaction for the 0.50% DHEA (6.5 mg) treatment group." I agree with the Medical Officer's assessment that the majority of adverse events seen in the prasterone groups were unlikely to be drug-related; also there were no dose-related adverse events identified. The low rates of reproductive-related adverse events provided further support that the safety profile for prasterone is acceptable.

Vital Sign and Laboratory Findings

The Medical Officer performed a focused evaluation of laboratory parameters that were previously identified as potential safety signals based on data from other estrogen products indicated for symptoms of vulvar and vaginal atrophy. This safety evaluation included evaluation of mean changes in vital signs, lipid and liver function parameters. In her November 16, 2016, review, the Medical Officer stated that she did not identify any safety concerns related to either vital sign changes or clinical laboratory parameters.

Other Significant Safety Issues:

The clinical review team identified specific safety issues during drug development and during the review of the submission. Their safety review included assessment of endometrial safety and data on breast adverse events including breast cancer. These issues were discussed with the Applicant and these were addressed through labeling and included:

1. Endometrial safety:

   As previously discussed, the clinical review team had concerns related to the endometrial safety of prasterone as these reproductive adverse events were reported with use of other estrogen products, and prasterone may have estrogenic-like effects on the endometrium. All subjects with an intact uterus received evaluation of their endometrial lining at baseline and end-of-study through an endometrial biopsy. Evaluation of endometrial biopsies was performed using standard criteria (Blaustein's) as outlined in the 2003 draft Guidance for Industry. Endometrial biopsies were performed as part of routine monitoring or "for cause" if vaginal bleeding and/or spotting occurred. To evaluate long-term endometrial safety, Trial ERC-230 was conducted to allow endometrial biopsy data to be collected through 52 weeks of prasterone insert treatment. In total, 1149 women exposed to prasterone had an endometrial biopsy at screening and 747 women had a post-baseline biopsy.

   During the review cycle, DBRUP requested the Applicant conduct re-readings of the endometrial biopsies for all 6 six clinical trials, because the Applicant had not done so according to the standards set in the Agency's 2003 draft guidance for Industry. The Applicant submitted Protocol ERC-237 that proposed second and third blind readings of the endometrial histology by qualified pathologists. The Applicant and the Division had further discussion regarding the sites for the blinded pathology readings. The Applicant agreed to the Division's recommendations and also to providing copies

of the actual endometrial readings in clinical trials ERC-210, ERC-230, ERC-231, ERC-234, and ERC-238.

Table 8 below outlines the Final Study Report results of Protocol ERC-237 for endometrial histology, as determined by three independent, blinded pathologists from the clinical amendment received on July 12, 2016:

Table 8: Endometrial Biopsy Histology from All Women Treated with Prasterone up to 52 Weeks in Trials ERC-210, ERC-231, ERC-234, ERC-238 and ERC-230*

Parameters	**Treatment Groups**				
	Placebo insert N=284	**Prasterone 3.25 mg N=283**	**Prasterone 6.5 mg N=291**	**Prasterone 13 mg N=54**	**Total N=912**
Total Number of Women At Week-12 (%)	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%)
Final Diagnosis Histologic Characteristics (N, % of women with biopsy)					
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%)[1]	1 (0.2%)
Complex hyperplasia with atypia[2]	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Other Findings					
Polyps - Atrophic	2 (1.5%)	3 (2.3%)	1 (0.7%)	1 (3.1%)	7 (1.6%)

*Obtained from Table 23 of the Medical Officer's review dated November 16, 2016.

The Medical Officer evaluated the endometrial histology data. After review, she concluded in her November 2016 review that, "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% (6.5 mg) DHEA vaginal insert administered intravaginally daily over a 12-week duration."

Comments:

- *From a clinical perspective, I believe that the Applicant's evaluation of endometrial safety for prasterone was acceptable for the purposes of review, as the reading of the histology slides was performed as outlined in the 2003 draft guidance.*
- *The safety data do not indicate that prasterone has a stimulatory effect on endometrial tissue. Therefore, no specific safety labeling (such as a WARNING) for a risk of abnormal endometrial pathology with use of prasterone vaginal inserts is necessary.*

2. Breast cancer

   Because of the potential negative hormone-mediated impact of prasterone on breast tissue, the Medical Officer evaluated all breast-related adverse events that were reported in the double-blind phase 2/3 population. Of the breast-related events of interest, one event of breast cancer (invasive ductal breast cancer) was identified in a subject receiving 6.5 mg of prasterone vaginal insert. In her Medical Officer review dated November 16, 2016, the Medical Officer concluded that, "One reported case of breast cancer does not raise safety concerns for the 6.5 mg prasterone vaginal insert."

   Comment: I concur that the single identified event of breast cancer in a prasterone treated subject, given the prevalence of breast cancer in the postmenopausal population, does not represent a new safety trend or signal. However, because there is no data to support safe use in women with breast cancer or a current history of breast cancer, the label will warn these patients not to use prasterone vaginal inserts.

3. Abnormal Papanicolaou smear:

   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 using the Bethesda system for reporting cervical and vaginal cytological diagnoses.

   Eleven (11) women in Trial ERC-230 had an abnormal PAP smear recorded at week 52 with an incidence of $\geq$ 2 percent (2.1 percent, 11 of 521 participating postmenopausal women). Ten (10) of these eleven women had atypical cells of undetermined significance (ASCUS) diagnosed on a PAP smear at week 52. One (1) of these 11 women had low grade squamous intraepithelial lesion (LSIL) diagnosed on a PAP smear at week 52. In her Medical Officer's review dated November 16, 2016, the Medical Officer states, "This reviewer notes an association with DHEA and treatment-emergent abnormal Pap smears consisting of ASCUS and LSIL. These abnormal Pap smear results should be included in labeling."

   Comment: I concur with the Medical Officer that these 11 cases of abnormal PAP smears reported at week 52 in Trial ERC-230 should be included in the ADVERSE REACTIONS section of labeling.

4. Postmarketing data summary:

> Although prasterone (also terms dehydroepiandrosterone [DHEA] is marketed worldwide as a dietary supplement, this prasterone vaginal insert has not been approved in any country and, therefore, postmarketing data related to use of this insert for VVA symptoms were not available for review.

In summary, the clinical review team did not identify major safety concerns or any outstanding safety issues in the application that required additional data or studies. Relevant safety issues for prasterone that were identified have been addressed in labeling, including the descriptions of the endometrial and other reproductive adverse events identified from the clinical trial database.

The co-packaged to be marketed applicator was evaluated and determined by the CDRH biomedical engineer to be sufficiently similar to the applicator used in the clinical trial. No human factors studies or other biocompatibility studies were recommended by the CDRH biomedical engineer or by the DMEPA review team (See section 11).

However, the clinical review team remained concerned with use of the to-be-marketed applicator because there were no clinical data with use of this new applicator and recommended enhanced pharmacovigilance. The Applicant will be informed that the Division requests reporting of any applicator-related adverse events in the quarterly adverse event reports for the first 3 years after launch. This will allow the Division to determine if there are any safety signals or issues with the applicator. I concur that enhanced pharmacovigilance is sufficient to detect any safety signal or trend with this applicator which has not been clinically evaluated.

In addition, the clinical review team remains concerned with the reports of women with an abnormal PAP smear with the 6.5 mg prasterone vaginal insert from the safety database. The Applicant will also be informed that the Division requests quarterly reporting of postmarketing adverse events of abnormal PAP smears with use of prasterone vaginal insert including: ASCUS, LSIL, high grade squamous intraepithelial lesion (HSIL), squamous cell carcinoma, atypical-glandular cells not otherwise specified (AGS-NOS), atypical glandular cells, suspicious for adenocarcinoma in situ or cancer (AGC-neoplastic), adenocarcinoma in situ and adenocarcinoma. I concur that this enhanced postmarketing pharmacovigilance reporting is sufficient to detect any safety signal or trend to determine if additional gynecologic safety data are necessary.

In summary, the Medical Officer concluded the following on the safety profile in her November 16, 2016, review as follows, “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.”

The Cross-Discipline Team Leader (CDTL) concurred with the primary Medical Officer’s assessment of the safety profile was acceptable in her CDTL review (dated November 16, 2016).

I concur with the recommendations of the primary Medical Officer and CDTL that there are no remaining safety concerns that preclude approval of this NDA.

9. Advisory Committee Meeting

The first topical hormonal product for treatment of symptoms of moderate to severe vulvar and vaginal atrophy was Premarin® (conjugated equine estrogens, USP). Premarin (NDA 05-900) was marketed in 1946 for vaginal use for the indications of atrophic vaginitis which is now described clinically as vulvar and vaginal atrophy with the specific symptom(s) studied identified in labeling. Since then, other topical and oral hormonal products (primarily estrogen products) have been approved for treatment of vulvar and vaginal atrophy and used in clinical practice in the US. Prasterone is not designated as a New Molecular Entity (NME) and no efficacy issues were identified in the phase 3 trials. The safety issues associated with hormone therapies, such as prasterone, are well known and can be adequately labeled. In addition, no other concerns were identified for prasterone. Therefore, an advisory committee was not convened to discuss the risk benefit of prasterone vaginal inserts.

10. Pediatrics

The Applicant requested a full waiver of pediatric studies in patients from birth to < 17 years as the condition only occurs in adults. The Division concurred with the Applicant's request, and the Pediatric Review Committee (PeRC) granted the full waiver.

11. Other Relevant Regulatory Issues

<u>Center for Devices and Radiologic Health – co-packaged applicator review:</u>

The applicator is considered a Class I device product that is 510(k) exempt. The Office of Device Evaluation biomedical engineer reviewer evaluated the co-packaged applicator from a device perspective. The reviewer evaluated that there had been several changes to the to-be-marketed applicator as compared to the one used in the clinical trials. However, these changes in (b) (4) were not considered relevant to support biocompatibility. She concurred with the Applicant's determination that the changes made to the applicator were minor and unlikely to result in vaginal morbidity. She also noted that the original and to be marketed applicator were sufficiently similar enough to meet the requirement of the practical use of the applicator. She also stated that she did not have any outstanding safety or efficacy concerns with the to-be-marketed applicator. The biomedical engineer concluded in her review of the applicator that, "I have no additional comments/concerns and recommend approval of the applicator." (Refer to the Biomedical Engineer's review dated September 23, 2016)

The CDRH Office of Compliance (OC) Division of Manufacturing and Quality reviewer concluded in her July 21, 2016 memo that, "The application for Prasterone – NDA 208470 is approvable from the perspective of the applicable Quality System Requirements. The documentation review of the application for compliance with the

Quality System Requirements showed no deficiencies. The recommended inspections were conducted and deemed acceptable."

Comment: Although from an engineering perspective the change in type of applicator was not sufficient to warrant biocompatibility testing, it is unclear whether this change could result in an increase in vaginal adverse events such as laceration. At this time, there is clinical data to determine whether there is a safety issue with the untested applicator. Therefore, to ensure that the new applicator does not cause an increase in clinical morbidity, the Applicant will be asked to provide additional adverse event data on any event related to the applicator in the quarterly safety updates.

Office of Scientific Investigations (OSI):

A total of three clinical sites (Portman, Young and Bouchard) that participated in contributing efficacy and safety data in the phase 3 trials ERC-234 and ERC-210 were selected for inspection. The final classification of these inspections was No Action Indicated (NAI). The OSI reviewer concluded in his clinical inspection summary that, "A Form 483 was not issued at the conclusion of the inspection. The studies appear to have been conducted adequately and the data generated by this site appear acceptable in support of the respective indication (See OSI review dated July 8, 2016).

Comment: I concur that there are no outstanding issues related to the clinical sites for this submission.

Division of Medication Error Prevention and Analysis (DMEPA):

DMEPA reviewers evaluated the proposed tradename "INTRAROSA" and conveyed to the Applicant that the Agency had found it acceptable on December 30, 2015.

The DMEPA review team also reviewed the blister pack, carton labeling and prescribing information for INTRAROSA (prasterone) on November 8, 2016 for vulnerability to medication errors. The DMEPA reviewers also evaluated the use related risk analysis for the applicator and concluded that no human factors validation study was necessary. Their recommendations on improving the drug identifying information and readability on container and carton labeling as well as use of dosage form "vaginal insert" were implemented in final labeling.

Financial Disclosures**:**

Financial disclosure certificates were reviewed by the Medical Officer. After review of the provided information in the application, the reviewer concluded that, "…the applicant has adequately disclosed financial agreements for participating investigators/sub-investigators in the clinical trials conducted to support this NDA application." (Refer to the Medical Officer's clinical review dated November 16, 2016).

Comment: Based on the conclusions of the Medical Officer, there are no outstanding issues related to financial disclosures for this application.

Labeling Development Team (LDT):

The Division's Associate Director for Labeling (ADL) worked with the LDT to ensure that the Applicant's label complied with current labeling regulations and guidances including the Pregnancy Labeling and Lactation Rule. Their recommendations were incorporated in the prescribing information (PI) that was sent to the Applicant.

Comment: There are no outstanding labeling issues related to the PI.

12. Labeling

Labeling discussions are complete. Labeling for INTRAROSA (prasterone) was acceptable to the review teams. Labeling was also evaluated by the following groups:

- Office of Medical Policy Programs (DMPP) reviewed the Patient Package Insert (PPI) and completed their review on November 8, 2016. Their recommendations were incorporated into the revised PPI during labeling negotiations with Applicant.
- Office of Prescription Drug Promotion (OPDP) reviewed the Prescribing Information (PI) and the Patient Package Insert (PPI) on November 8, 2016. Their recommendations were incorporated into the PI and PPI during labeling negotiations with the Applicant.

13. Decision/Action/Risk Benefit Assessment

Decision:

I agree with the Cross-Discipline Team Leader, Medical Officer and other review teams that the INTRAROSA (prasterone) application should receive an Approval action.

Risk Benefit Assessment:

Data from the two adequately controlled phase 3 trials (ERC-231 and ERC-238) using accepted endpoints have demonstrated that daily use of prasterone vaginal inserts were effective in the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The results from these two trials were consistently statistically significant and are clinically meaningful.

No significant safety concerns were identified in the safety database of prasterone that preclude approval. The size and scope of the safety database were sufficient to adequately characterize the safety profile of prasterone. Identified risks are addressed in labeling including use in women with or with a history of breast cancer, application (vaginal) discharge and the occurrence of abnormal PAP smears in the safety database were evaluated and are adequately addressed in labeling. None of the identified reproductive

adverse events in the safety database raised concerns for prasterone vaginal insert that would preclude approval.

As the Applicant's to-be-marketed applicator was not evaluated in the phase 3 trials, the Applicant will be asked to provide additional adverse event data on the applicator through quarterly safety reports over a 3 year period from launch. In addition, the Applicant will also be asked to provide additional adverse event data on reports of abnormal PAP adverse events in these safety reports. These additional pharmacovigilance data will allow the clinical review team to identify safety issues or trends that might require further clinical evaluation.

In my opinion, the risk/benefit assessment favors approval of INTRAROSA (prasterone) for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Post-Marketing Requirement/Commitments:

- The review teams have determined that no new postmarketing requirements or commitments are necessary for this product prior to approval.
- The review teams have also determined that no risk evaluation and mitigation strategies (REMS) are necessary for this product prior to approval.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AUDREY L GASSMAN
11/16/2016