CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208470Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	November 16, 2016
From	Shelley R. Slaughter, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	208470
Type of Submission	Original 505(b)(2)
Applicant	EndoCeutics
Date of Submission	August 16, 2015
PDUFA Goal Date	Original –August 16, 2016 Extended – November 16, 2016
Proprietary Name / Established (USAN) names	INTRAROSA/ prasterone
Dosage forms / Strength	6.5 mg vaginal insert
Proposed Indication(s)	Per Form 356h "Treatment of moderate to severe dyspareunia (or pain at sexual activity), a symptom of vulvovaginal atrophy due to menopause."
Recommendation:	Approval is recommended.

1. Introduction and Executive Summary

With this 505(b)(2) original NDA submission, the applicant is seeking approval for INTRAROSA for the indication of treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The drug substance, prasterone [dehydroepiandrosterone (DHEA)] is a new chemical entity. The terms DHEA and prasterone are used interchangeably throughout this review.

To support the NDA, the applicant conducted one double-blind, and placebo-controlled phase 2 dose pharmacokinetic (PK) trial, four double-blind, and placebo-controlled 12-Week phase 3 trials (ERC-210, ERC-231, ERC-238 and ERC-234), and 52 week open-label safety Trial ERC-230 (also allowed additional treatment of non-hysterectomized women only who actually received treatment with 0.25% and 0.5% DHEA during the 12-week double-blind treatment period of Trial ERC-231). Each of these trials was conducted with the to-be-marketed formulation. If it were to be approved, INTRAROSA would be the first non-estrogen steroid product to be approved for the treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy. The application for INTRAROSA is a 505(b)(2) application and the drug substance, prasterone, is a new chemical entity (NCE).

Key focus items for the application review were:

1. Efficacy
   INTRAROSA [(Prasterone [dehydroepiandrosterone (DHEA))] is a new chemical entity and as such at least two confirmatory randomized placebo-controlled phase 3 clinical trials were recommended to support efficacy in the U.S. 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.

   Primary efficacy data from Trials ERC-231 and ERC-238 demonstrate that 0.50% prasterone (DHEA) vaginal insert treatment group compared to placebo, demonstrates an improvement (i.e., increase) in the percentage of superficial vaginal cells **and** improvement (i.e., decrease) in the percentage of vaginal parabasal cells **and** improvement (i.e., decrease) in vaginal pH **and** improvement (i.e., decrease) in the mean change in severity from baseline. Therefore the clinical trial data support the effectiveness of INTRAROSA (6.5 mg prasterone) vaginal inserts in the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. See Section 7 of this review.

2. Safety
   Safety of the reproductive organs, specifically endometrium and breast, were the main focus of the safety evaluation of this product. While DHEA is a new chemical entity, the safety profile of its metabolite estradiol is well known. Unopposed exogenous estrogen use can result in endometrial hyperplasia and endometrial carcinoma. Estrogen is a known promotor of breast cancer, especially in women with estrogen receptor positive cancers. Exogenous estrogen use is contraindicated in

women with abnormal genital bleeding and women with a history of or active endometrial cancer and breast cancer.

The endometrial safety profile following use of INTRAROSA was evaluated in five phase 3 clinical trials including, one 52-week trial (for women who participated in Trial ERC-231, the first 12 weeks had a blinded and placebo-controlled design, while the remaining 40 weeks were open-label and uncontrolled).

Serious adverse events were also collected in all phase 3 clinical trials. One (1) cases of breast cancer was seen in the 52-week trial of INTRAROSA.

The maximum duration of use in this clinical development program, i.e. 52-weeks is insufficient to evaluate the risk for breast cancer. Review of the most frequently reported treatment emergent events noted vaginal discharge reported in greater than 2% of prasterone-treated participants (and greater than that reported in placebo participants) in the phase 3, 12-week trials and abnormal pap smears reported in greater than 2% of participants in the 52 week open-label trial. The applicant will be asked for additional quarterly reports based on postmarketing report of adverse events related abnormal Pap smear findings with use of INTRAROSA.

No concerning endometrial or general safety findings were observed in the trials conducted in the INTRAROSA clinical development program. See section 8 of this review.

3. Usability of the vaginal insert applicator
No formal use study was conducted with the vaginal insert applicators used in either the clinical trials or the to-be-marketed device. In the clinical trials the applicant administered a usability 7-response questionnaire to elicit user opinion on the device Section. The Clinical Review Team finds this questionnaire to be insufficient in the evaluation of consumer use of the combination drug/device product. Additionally, the Clinical Review Team has concerns from a Clinical standpoint regarding the flimsiness of the applicator device upon touch and tactile pressure. Because of this, we will ask that the applicant provide additional quarterly reports based on postmarketing report of adverse events related to use of the vaginal insert applicator.

2. **Background and Regulatory History**

- **July 17, 2007** – EndoCeutics submits IND 78,027 with 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.
- **September 4, 2007** and **March 18, 2008** – Agency provides Advice Letter to EndoCeutics advising the sponsor that they should follow the Agency's Draft 2003 Clinical Trial Guidance for the three co-primary endpoint to evaluate a symptomatic treatment claim for vulvar and vaginal atrophy. "We wish to clarify again that for an

indication for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, a subject participant for study inclusion should (1) self-identify the moderate to severe vulvar and vaginal atrophy symptom that is most bothersome to her, (2) have a vaginal pH > 5.0, and (3) have no greater than 5 percent superficial cells on a vaginal smear. The primary efficacy analyses (baseline to Week 12) should show a statistically significant (1) improvement in the moderate to severe symptom identified by the subject as most bothersome to her, (2) lowering of vaginal pH, and (3) decrease in parabasal cells and an increase in superficial cells."

(b) (4)

- **March 31, 2009** - A Type C Guidance Meeting was held with EndoCeutics. Issues discussed were:
    - 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.
    - The data submitted in NDA (b) (4) for Trial ERC-210 does not comply with the recommendations provided in the Agency's advice/information letters dated September 4, 2007 and December 11, 2007. Specifically, the data analyses submitted did not adhere to the following:
        - For a woman to be included in the efficacy analyses for a vulvar and vaginal atrophy symptom indication, she should have identified a moderate to severe symptom of vulvar and vaginal atrophy that is most bothersome and have a baseline percentage of superficial cells that does not exceed 5% and have a vaginal pH greater than 5.
        - For the most bothersome symptom endpoint, statistical significance must be demonstrated in the improvement of at least one specific symptom. If you chose not to pre-specify the symptom and choose to pick one or two statistically significant symptoms post hoc, an adjustment for multiplicity will need to be made, taking into account the correlation between the symptoms."
    - DHEA is considered to be a new molecular entity (NME). The Agency subsequently changed the designation of DHEA from an NME to a new

chemical entity following identification of an unapproved, but marketed product with this drug substance (See Section 11 of this review).
    - Two confirmatory trials in support of safety and efficacy are recommended for a vulvar and vaginal atrophy symptom indication.
    - The analysis from ERC-210 did not adhere to our previous recommendations.
  - The DBRUP 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.

- **July 12, 2013** - Written Responses Only (WRO) for Type C Meeting request was provided to EndoCeutics. Clinically relevant issues included:
  - DBRUP accepts 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%).
  - DBRUP agrees that an additional 322 subjects, with exposure at 0.50% or greater, would meet the ICH guidelines recommendation for overall exposure of 1500 subjects.
  - DBRUP finds acceptable subjects with "short-term exposures" including 1 week of daily administration and subject who discontinued after one dose of study medication.
  - DBRUP does 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 MBS-dyspareunia data) was not based on an adequate sample size and is not acceptable.
  - DBRUP 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.

- **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 sponsor questions and DBRUP responses are presented below:
    - Nonclinical Question: "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?
        - 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: "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.
        - DBRUP response: 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.
        - DBRUP response: 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).

- DBRUP response: 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).

- Clinical Question: "Does the Agency agree that data obtained for moderate to severe (MS) vaginal dryness 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 of treatment of moderate to severe vaginal dryness due to menopause. 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.
  - DBRUP Comment: No secondary efficacy endpoints, including vaginal dryness, (b) (4). 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 and vaginal dryness was self-selected as the most bothersome symptom, did not demonstrate improvement in vaginal dryness.
  - DBRUP Comment: 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.

- October 16, 2016 – NDA 208470 submitted by EndoCeutics

3. CMC/Biopharmaceutics/Device

The Chemistry and Biopharmaceutics data for this NDA were reviewed by the Office of Product Quality (OPQ) Review Team as listed in Table 1.

Table 1: Office of Product Quality (OPQ) Review Team

DISCIPLINE	REVIEWER	DIVISION / BRANCH
Drug Substance	Erika Englund	ONDP / New Drug API /Br. II
Drug Product	Caroline Strasinger	ONDP / DNDP II /Br. V
Process	Jingbo Xiao	OPF/DPAII/PABV
Microbiology	Jingbo Xiao	OPF/DPAII/PABV
Facility	Sherry Shen	OPF / DIA /Br. III
Biopharmaceutics	Kalpana Paudel	ONDP / DB / Br. II

The following is from the Executive Summary of the OPQ Review.

Drug Substance:
Prasterone is (b) (4) a white (b) (4) powder with a melting range of 146 to 151°C. It is practically insoluble in water, (b) (4) The solubility of

prasterone in Witepsol (b) (4) (Hard Fat, NF), the only excipient present in the drug product, at (b) (4) respectively. Prasterone has no functional groups that can be protonated; aqueous solubility is independent of pH across the range 2 – 12. The solid state form of prasterone is not relevant. (b) (4)

Prasterone (3β-hydroxy-5-androsten-17-one) (b) (4) The manufacture is documented in (b) (4) Type II Drug Master File (b) (4). This DMF was reviewed by Erika Englund, Ph.D., and was found adequate to support this NDA.

The drug substance specification includes tests, and suitable acceptance criteria, to ensure the identity, quality, purity and potency of prasterone API.

A retest period of (b) (4) has been established for drug substance stored at (b) (4).

Drug Product:
INTRAROSA (prasterone) vaginal inserts contain 6.5 mg prasterone in (b) (4) Hard Fat, NF (Witepsol (b) (4)). (b) (4)

(b) (4)

Each carton of drug product consists of four blister (b) (4) of seven inserts (in a small box) and 28 applicators. (b) (4)

(b) (4)

(b) (4)

The drug product specification includes tests, and suitable acceptance criteria, to ensure the identity, quality, purity, potency and bioavailability of prasterone. A shelf-life of 36 months has been established for drug product stored at 25°C.

Product Quality Microbiology

Because the route of administration is intravaginal the product is not required to be sterile. The manufacturing process is not an aseptic process. Nevertheless, the product is tested per USP Microbial Limit Tests <61> and <62> at release and on stability to ensure adequate control of TAMC (Total Aerobic Microbial Count), and Yeasts and Molds, and to ensure the absence of specified organisms (Pseudomonas aeruginosa, Staphylococcus aureus, and Candida albicans).

Biopharmaceutics

Release of the active ingredient from the product requires melting of the hard fat matrix and dissolution of prasterone. An in vitro dissolution method was developed by the applicant to assure quality control and consistent bioavailability of the drug product. The method employs USP Apparatus II (paddle) operated at 75 rpm. The dissolution medium consists of 1000 mL of 1% aqueous sodium lauryl sulfate (SLS) at 37.3°C. Additional data supporting the test conditions were submitted as requested. Because of the simple nature of the drug product (API dissolved in hard fat), generation of data to demonstrate that the method is discriminatory was problematic.

While at release, the available dissolution data support an acceptance criterion of Q = (b) (4)% at (b) (4) minutes, (b) (4) Dr. Theresa H. van der Vlugt, Medical Officer, has confirmed that the Trial ERC-238 was adequate as one of the two confirmatory efficacy trials to support the efficacy of the DHEA insert for the proposed indication.

Agreement was eventually reached on the proposed acceptance criterion of Not Less Than (NLT) (b) (4)% (Q) dissolved in 180 minutes. This will ensure that a mean of at least (b) (4)% of the active ingredient will be dissolved in 180 minutes. A tighter acceptance criterion can be used by the applicant for batch release.

Comparative dissolution profiles of (b) (4) product (used in Phase 3 studies and stability studies) and (b) (4) product demonstrated adequate similarity ($f2 > 50$).

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Manufacturing Facilities

The identification of the manufacturing facilities and their roles and responsibilities as well as final recommendations are presented in Table 2.

Table 2: **Manufacturers for NDA 208470**

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		Manufacturing and packaging of the Drug Product. (SUP, DKA)	High	(b) (4) VAI	Approve based on PAI/GMP inspection and DO file review
		Manufacturing and packaging of the Drug Product. (SUP, DKA).	High	(b) (4) VAI	Approve based on PAI inspection
		Manufacturing and primary packaging of the applicator. ((b) (4))	High	(b) (4) VAI	Approve based on PAI inspection
EndoCeutics Inc.	3008716468	Quality Control and stability testing. (CTL)	High	only do paper reviews	No further evaluation

OPQ's Office of Process and Facilities, Division of Inspectional Assessment, determined that, there appears to be no significant risks to the drug product manufacturing based on the individual and composite evaluation of the listed facility's latest inspection results, inspectional history, and relevant experiences. All facilities are determined acceptable to support approval of NDA208470.

Device Evaluation

The vaginal insert is administered using a disposable white (b) (4) applicator. The applicators consist of an applicator body and a plunger. Four (b) (4) packages of seven applicators are supplied in a box with the 28 prasterone vaginal inserts. The applicators are manufactured by (b) (4) Three variations of applicator are described in the NDA: applicator used in the clinical studies, the proposed commercial applicator, and the final to-be- marketed version.

The applicators were evaluated by Sharon Andrews, CDRH-ODE, who, based on the straight forward nature of the design and her review of samples of the newest version of the applicator, concluded that there were no safety or effectiveness concerns. She determined that, "the samples provided indicate that the applicator is sufficiently robust for its intended use and comparable to other marketed vaginal applicators." A specific shelf-life for the applicator has not been established, nor is one required.

While all three applicators have similar dimensions and function the same, concerns about "flimsiness" of the proposed and final commercial versions, and the potential to cause injury to the patient, have been raised by the clinical review team. In light of the Clinical Review Team's concerns regarding the to-be-marketed product, the applicant will be asked for additional quarterly reports based on postmarketing report of adverse events related to use of the vaginal insert applicator.

Katelyn Bittleman, CDRH Office of Compliance concluded 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.

As a drug-device combination product, the device component (inserter) was reviewed by both CDRH-ODE and CDRH-OC. This NDA, as amended, is recommended for approval by both CDRH-ODE and CDRH-OC.

Environmental Assessment

The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The required statement of no extraordinary circumstances was included. FDA requested additional information due to the hormonal activity of the API, per recent FDA guidance. The claim and supporting information were reviewed and the claim found to be acceptable.

The reader is referred to OPQ NDA Review 1 and NDA Review 2 signed by Mark Seggel, Application Technical Lead and dated October 24, 2016 and November16, 2016, respectively for additional details regarding the chemistry, manufacturing and controls for INTRAROSA (prasterone) vaginal insert.

The Office of Pharmacology Quality concludes that sufficient information and supporting data have been provided in accordance with21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status.

When manufactured as described in the amended NDA, prasterone vaginal inserts present minimal risks associated with product quality to consumers, who may benefit from this product.

4. Nonclinical Pharmacology/Toxicology

The non-clinical pharmacology and toxicology information presented in the application was reviewed by Alexander Jordan, Ph.D., Office of New Drugs (OND), Office of Drug Evaluations 3 (ODE 3), DBRUP. The following is from the Executive Summary of Dr. Jordan's Nonclinical Pharmacology and Toxicology Review.

Prasterone is a steroid synthesized in the adrenals which acts primarily as a precursor to androgens and estrogens. It is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause.

All pivotal nonclinical studies were conducted using oral administration of the drug which differs from the clinical (intravaginal) exposure route, and in accordance with US FDA GLP (21CFR58), as stated by the sponsor. Safety margins to the expected human exposure were estimated in postmenopausal women using intravaginal DHEA $AUC_{0\text{-}24h}$ value of 56 ng.h/ml.

Prasterone [dehydroepiandrosterone (DHEA)] and its sulfated metabolite (DHEA-S) are the most abundant steroids in the body. DHEA is produced in the adrenals and is the biosynthetic precursor to the sex hormones testosterone and estradiol.

Vaginal and percutaneous administration of DHEA prevents the decreased weight and histological signs of vaginal atrophy induced by ovariectomy in rats.

In 6 month rat and 12 month monkey toxicology studies with oral administration, DHEA was essentially non-toxic and produced no adverse effects in monkeys at doses up to 10 mg/kg (7-12 times human exposure based on AUC). In rats there were some estrogen/androgen related effects including minimal to slight squamous metaplasia of the glandular epithelium of the uterus at doses of 10 and 100 mg/kg (0.2-16 times human exposure).

DHEA 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.

No reproductive studies were performed with DHEA since it is indicated solely for postmenopausal women.

No carcinogenicity studies were performed with prasterone. This is an endogenous non-genotoxic steroid and the systemic concentrations achieved in post-menopausal women taking the drug are equal or less than the endogenous concentrations seen in younger women. Vaginal concentrations of DHEA will be increased but the concentration of the active hormone, estrogen, will be no higher than the estrogen concentration achieved in women taking approved vaginal estrogens. According to the International Agency for Research on Cancer (IARC, member of the World Health Organization), “post-menopausal 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 reader is referred to Dr. Jordan’s review archived august 9, 2016 for a detailed discussion of the Preclinical Pharmacology/Toxicology development of INTRAROSA

From Preclinical Pharmacology/Toxicology standpoint, Dr. Jordan concludes that INTRAROSA is approvable.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review was performed by Jihong Shon, Ph.D., Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology (DCP) 3.

Study ERC-213 was conducted to evaluate the systemic bioavailability) of DHEA and its metabolites and the pharmacokinetics (PK) of vaginal inserts at three different DHEA concentrations versus a placebo. The trial was a randomized, placebo-controlled, double-blind phase 1 trial with four (4) treatment arms: 0.5%, 1.0%, and 1.8% prasterone and placebo. Ten naturally or surgically postmenopausal women per treatment arm participated in the trial. The women received for 1 week, daily administration of one vaginal insert in the evening between 10:00 PM and 11:00 PM. Blood collections were at 0 and 0.5, 1, 2, 4, 6, 8, 12, 18 and 24 hours after dosing on Days 1 and 7. Analytes were serum DHEA and related steroids (DHEA-S, 5-diol, DHT, testosterone, 4-dione, estrone (E_1), estradiol (E_2), estrone sulfate, ADT-G, 3α-diol-3G and 3α-diol-17G) utilizing validated LC-MS/MS for conjugated steroids and GC-MS/MS for unconjugated steroids. Major PK parameters evaluated were AUC_{24}, C_{max} and C_{ave} (the average 24h serum concentration = AUC24/24 hours).

Table 3 presents C_{max} and AUC_{24}, for DHEA, testosterone, estrone and estradiol.

Table 3: C_{max} and AUC_{24}, of DHEA, Testosterone, Estrone and Estradiol on Day 1 and 7 Following Daily Administration of Placebo or 6.5 mg Prasterone vaginal inserts (mean ± standard deviation).

		Placebo (N=9)		6.5 mg prasterone (N=10)	
		Day 1	Day 7	Day 1	Day 7
DHEA	**C_{max} (ng/mL)**	1.52 (±0.93)	1.60 (±0.95)	5.97 (±1.40)	4.42 (±1.49)
	AUC_{24} (ng·h/mL)	24.47 (±14.40)	24.82 (±14.31)	65.49 (±24.67)	56.17 (±28.27)
Testosterone	**C_{max} (ng/mL)**	0.17 (±0.15)	0.17 (±0.15)	0.15 (±0.05)	0.15 (±0.05)
	AUC_{24} (ng·h/mL)	2.71 (±1.02)	2.58 (±0.99)	2.79 (±0.92)	2.79 (±0.95)
E1	**C_{max} (pg/mL)**	15.19 (±5.00)	15.88 (±6.05)	17.10 (±6.36)	19.45 (±9.51)
	AUC_{24} (pg·h/mL)	305.58 (±103.68)	301.92 (±101.31)	336.52 (±120.04)	369.69 (±154.51)
E2	**C_{max} (pg/mL)**	3.59 (±1.46)	3.33 (±1.31)	4.62 (±2.28)	5.04 (±2.68)
	AUC_{24} (pg·h/mL)	69.51 (±22.89)	66.49 (±20.70)	87.79 (±35.86)	96.93 (±51.67)

Based on PK data from the two primary efficacy trials the OCP determined that there was an increase in systemic steroid concentrations following, daily administration of INTRAROSA vaginal insert for 12 weeks. Trials ERC-231 and ERC-238 demonstrated an increased mean serum C_{trough} of prasterone and its metabolites testosterone and estradiol by 47%, 21% and 19% from baseline, respectively. This comparison based on C_{trough} may underestimate the magnitude of increase in prasterone and metabolites' exposure because it does not take into account the overall concentration-time profile following administration of INTRAROSA.

The OCP reviewer concludes:

- The systemic exposure to DHEA and its metabolites showed dose-dependent increase pattern. The serum concentrations of DHEA appeared to be higher on Day 1 than Day 7. A relatively higher absorption after the first dose than the following doses may be attributed to a higher vaginal permeability of prasterone due to thinning mucosal epithelium in women with VVA before treatment. Otherwise, the systemic exposure (based on AUC_{24}) to the metabolites including E1, E2 and testosterone tended to be higher on Day 7 compared to Day 1.
- The systemic exposure to E1, E2 and testosterone in all active treatment groups appeared to be higher than that in the placebo group. It indicates that administration of DHEA vaginal inserts in the patients with VVA leads to additional systemic exposure to estrogens and androgens above endogenous hormone levels.
- The treatments of all three concentrations of DHEA vaginal inserts for 7 days led to significant changes of vaginal maturation and pH compared to baseline.

The Office of Clinical Pharmacology has determined that the application is acceptable from a Clinical Pharmacology perspective.

6. Clinical Microbiology

Because the route of administration is intravaginal the product is not required to be sterile. See Section 3 of this review.

From a clinical microbiology perspective, NDA208470 is recommended for approval.

7. Clinical/Statistical - Efficacy

The primary review of the efficacy information in NDA 2008470 was performed by Theresa van der Vlugt, M.D., Office of New Drugs (OND)/Office of Drug Evaluations (ODE) 3/DBRUP and Statistical Reviewer, Kate Dwyer, Ph.D., Office of Translational Science/Division of Biometrics III.

Prasterone is considered a new chemical entity (NCE) and as such DBRUP indicated that at least two confirmatory clinical trials should be conducted to support the efficacy. DBRUP recommended that trials conducted to support the treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause, evaluate the co-primary endpoints of superficial and parabasal cells from a smear of the middle or second third of the side wall of the vagina, vaginal pH, and change in the moderate-to-severe most bothersome symptom of dyspareunia, assessed at baseline. At baseline, enrollees should have 5% or fewer superficial cells, pH greater than 5 and identify dyspareunia as their most bothersome moderate-to-severe symptom of vulvar and vaginal atrophy. To be successful in support of the indication, results should demonstrate for INTRAROSA compared to placebo, an improvement (i.e., increase) in the percentage of superficial vaginal cells **and** improvement (i.e., decrease) in the percentage of vaginal parabasal cells **and** improvement (i.e., decrease) in vaginal pH **and** improvement (i.e., decrease) in the mean change in severity from baseline.

The applicant submitted four randomized and placebo controlled phase 3 trials, ERC-210, ERC-231, ERC-238 and ERC-234. Trials ERC-210 and ERC-234, did not meet the enrollment criteria necessary for a phase 3 trial to support the indication. Trial ERC-234 was

a **failed** trial conducted to support and indication for treatment of moderate-to-severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause. Trial ERC-231 assessed a composite endpoint and no information was collected at baseline on the individual most bothersome moderate-to-severe symptom of vulvar and vaginal atrophy. Therefore, support of efficacy was based on two of the four clinical trials, ERC 231 and ERC -238. Both trials were based on a randomized, double-blind and placebo-controlled design.

Trial ERC-231

In Trial ERC 231, healthy (no active or ongoing chronic conditions/disease) postmenopausal women (meeting criteria of 1 year of no menses, greater than 6 months but less than one year of no menses or hysterectomized with FSH greater than 40 IU per mL) who were to be between 40 and 75 years of age [mean age 58.84 ± 0.38 years (mean ± standard error of the mean)], with normal mammogram within 9 months of trial start, normal breast exam, normal Pap smear within the last 12 months and normal hematology, clinical chemistry, and urinalysis. Only women who met the criteria of having 5% or fewer superficial cells, pH greater than 5 and identified dyspareunia as their most bothersome moderate-to-severe symptom of vulvar and vaginal atrophy were included in the efficacy analyses. The trial was conducted between November 30, 2010 and July 29, 2011. 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)
- Placebo vaginal insert (82 women)

For additional details of the design and conduct of Trial ERC-231, including evaluated primary and secondary endpoints and their analyses, the reader is referred to Drs. van der Vlugt and Dr. Dwyer's reviews.

Demographic parameters of age, race and ethnicity for Trial ERC-231 are shown in Table 4.

Table 4: Baseline Demographics of Postmenopausal Women in Trial ERC-231, Intent-To-Treat Population

Demographic Parameters	**0.25% DHEA** **N = 79** n (%)	**0.50% DHEA** **N = 81** n (%)	**Placebo** **N = 77** n (%)
Age			
Mean years (SD)	59.7 (6.1)	57.7 (5.5)	59.1 (5.8)
Range (min-max)	40 - 75	41 - 69	45 -73
Race			
Caucasian/White	75 (95)	79 (98)	67 (87)
Black/ African America	3 (4)	1 (1.2)	8 (10)
Asian	0 (0)	1 (1.2)	1 (1.3)
Other	1 (1.3)	0 (0)	1 (1.6)
Ethnicity			
Hispanic or Latino	5 6)	8 (10)	1 (1)
Not Hispanic or Latino	74 (94)	73 (90)	76 (99)

Source: Adapted from Statistical Review Table 4, page 10 and Medical Officer Review Table 5.

As with other phase 3 clinical trials conducted with other products to support a symptomatic vulvar and vaginal atrophy indication, racial and ethnic diversity of Trial ERC-231 was lacking.

The overall disposition of postmenopausal women participating in Trial ERC-231 is summarized in Table 5.

Table 5: Disposition of Postmenopausal Women in Trial ERC-231

Disposition	**DHEA 0.25%**	**DHEA 0.50%**	**Placebo**
Number Randomized	87 (100%)	87 (100%)	81 (100%)
Safety Population	86 (98.9%)	87 (100%)	80 (99%)
Intent-to-Treat (ITT)	79 (91%)	81 (93%)	77 (95%)
Number Completed Trial	74 (85.0%)	76 (87.3%)	72 (88.8%)
Total Discontinued	13 (14.9%)	11 (12.6%)	9 (11.1%)
Reason Discontinued			
- Adverse Event	4 (4.5%)	2 (2.2%)	1 (1.2%)
- Non-Compliance	0 (0.0%)	0 (0.0%)	1 (1.2%)
- Withdrew Consent	0 (0.0%)	2 (2.2%)	4 (4.9%)
- Investigator's Decision	1 (1.1%)	0 (0.0%)	0 (0.0%)
- Other	8 (9.1%)	7 (8.0%)	3 (3.7%)

Source: Adapted from Statistical Review Table 2, page 9, Medical Officer Review Table 6, page 54, and NDA 208470, Trial ERC-231 Clinical Trial Report, Figure 8-1, page 66 of 591.

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).

The primary efficacy analyses were performed on the Intent-to-Treat (ITT) population. The primary efficacy analysis was performed using analysis of covariance (ANCOVA), with the treatment group as the main factor and the baseline value as the covariate. Efficacy results from Trial ERC-231 are provided in Table 6

Table 6: Efficacy Summary of Trial ERC-231, Intent-to-Treat Population, Last Observation Carried Forward

Co-Primary Endpoint	0.025% DHEA N = 79	0.50% DHEA N = 81	Placebo N = 77
%Superficial Cells			
- Baseline Mean	0.68	0.70	0.73
- Week 12 Mean	5.43	6.30	1.64
- Mean Change from Baseline (SD)	4.75 (5.15)	5.62 (5.49)	0.91 (2.69)
-Difference vs. placebo*	3.84	4.71	--
- P-value**	<0.0001	<0.0001	--
% Parabasal Cells			
- Baseline Mean	65.72	65.05	68.48
- Week 12 Mean	28.43	17.65	66.86
- Mean Change from Baseline (SD)	-37.29 (37.00)	-47.40 (42.50)	-1.62 (28.22)
-Difference vs. placebo*	-35.67	-45.8	--
- P-value**	<0.0001	<0.0001	--
Vaginal pH			
- Baseline Mean	6.48	6.47	6.51
- Week 12 Mean	5.70	5.43	6.31
- Mean Change from Baseline (SD)	-0.77 (0.90)	01.04 (1.00)	-0.21 (0.69)
-Difference vs. placebo*	-0.57	-0.83	--
- P-value**	<0.0001	<0.0001	--
Dyspareunia			
- Baseline Mean	2.56	2.63	2.58
- Week 12 Mean	1.54	1.36	1.71
- Mean Change from Baseline (SD)	-1.01 (1.02)	-1.27 (0.99)	-0.87 (0.95)
-Difference vs. placebo*	-0.14	-0.40	--
- P-value**	0.3423	0.0132	--

*Difference vs. placebo is the (Week 12 mean for DHEA minus baseline mean for DHEA) minus (Week 12 mean for placebo minus baseline mean for placebo).

** ANCOVA: treatment as the main factor and baseline value as the covariate.

Source: Adapted from Statistical Review Tables 8, 11 and 13, pages 12, 14 and 15, respectively; Medical Officer Review Table 7, page 56; and 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.

Only the 0.50% DHEA vaginal insert treatment group compared to placebo, demonstrates an improvement (i.e., increase) in the percentage of superficial vaginal cells **and** improvement (i.e., decrease) in the percentage of vaginal parabasal cells **and** improvement (i.e., decrease) in vaginal pH **and** improvement (i.e., decrease) in the mean change in severity from baseline.

For additional information on per protocol, modified ITT sensitivity and secondary analyses, the reader is referred to Drs. van der Vlugt and Dr. Dwyer's reviews.

Trial ERC-238

In Trial ERC 238, healthy (no active or ongoing chronic conditions/disease) postmenopausal women (meeting criteria of 1 year of no menses, greater than 6 months but less than one year of no menses or hysterectomized with FSH greater than 40 IU per mL or six months or greater following bilateral oophorectomy with or without hysterectomy) who were to be between 40 and 80 years of age (mean age 59.6), with normal mammogram within 9 months of trial start, normal breast exam, normal Pap smear within the last 12 months and normal hematology, clinical chemistry, and urinalysis. Women self-identified at screening and baseline (Day 1), pain at sexual activity as moderate to severe and as the most bothersome vulvar and vaginal atrophy symptom and had 5% or less superficial cells on vaginal smear at screening and baseline (Day 1) and vaginal pH greater than 5 at screening and baseline (Day 1).

The trial was conducted between February 11, 2014 and January 6, 2015. Five hundred and fifty-eight (558) postmenopausal women were randomized in a 21 ratio to receive:

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

For additional details of the design and conduct of ERC-238, including evaluated primary and secondary endpoints and their analyses, the reader is referred to Drs. van der Vlugt and Dr. Dwyer's reviews.

Demographic parameters of age, race and ethnicity for Trial ERC-238 are shown in Table 7.

Table 7: Baseline Demographics of Postmenopausal Women in Trial ERC-238, Intent-to-Treat Population

Demographic Parameters	**0.50% DHEA** **N = 325** n (%)	**Placebo** **N = 157** n (%)
Age		
Mean years (SD)	59.6 (6.7)	59.6 (5.6)
Range (min-max)	40 - 80	47 -75
Race		
Caucasian/White	296 (91)	144 (92)
Black/ African America	21 (6)	10 (6)
Asian	4 (1.2)	2 (1.3)
Other	4 (1.2)	1 (0.6)
Ethnicity		
Hispanic or Latino	38 (12)	11 (7)
Not Hispanic or Latino	287 (88)	146 (93)

Source: Adapted from Statistical Review Table 6, page 11, Medical Officer Review Table 9, page 65 and NDA 208470, Trial ERC-238 Clinical Trial Report, Table 8-3, page 87 of 601.

As stated for Trial ERC-231, racial and ethnic diversity in Trial ERC-238 was lacking.

Overall disposition of postmenopausal women participating in Trial ERC-238 is summarized in Table 8.

Table 8: Disposition of Postmenopausal Women in Trial ERC-238

Disposition	**DHEA 0.50%**	**Placebo**
Number Randomized	376 (100%)	182 (100%)
Safety Population	374 (98.4 %)	180 (99%)
Intent-to-Treat (ITT)	325 (86.4 %)	157 (86.3%)
Number Completed Trial	311 (95.6%)	152 (96.8.8%)
Total Discontinued	14 (4.3%)	5 (3.1%)
Reason Discontinued - Adverse Event - Lost to Follow-up - Withdrew Consent - Other	 5 (1.5%) 2 (0.1%) 7 (2.1%) 0 (8.0%)	 3 (1.9%) 0 (0.0%) 2 (1.2%) 0 (0.0%)

Source: Adapted from Statistical Review Table 3, pages 9 -10, Medical Officer Review Table 10, page 66, and NDA 208470, Trial ERC-238 Clinical Trial Report, Figure 8-1, page 81of 601.

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.

Efficacy results from Trial ERC-238 are provided in Table 9.

Table 9: Efficacy Summary of Trial ERC-238, Intent-to-Treat Population, Last Observation Carried Forward

Co-Primary Endpoint	0.50% DHEA N = 325	Placebo N = 157
%Superficial Cells		
- Baseline Mean	1.02	1.04
- Week 12 Mean	11.22	2.78
- Mean Change from Baseline (SD)	10.20 (10.35)	1.75 (3.33
-Difference vs. placebo	8.46	--
- P-value*	<0.0001	--
% Parabasal Cells		
- Baseline Mean	54.25	51.66
- Week 12 Mean	12.74	39.68
- Mean Change from Baseline (SD)	-41.51 (36.26	-11.98 (29.58
-Difference vs. placebo	-29.53	--
- P-value*	<0.0001	--
Vaginal pH		
- Baseline Mean	6.34	6.32
- Week 12 Mean	5.39	6.05
- Mean Change from Baseline (SD)	-0.94 (0.94)	-0.27 (0.74)
-Difference vs. placebo	-0.67	--
- P-value*	<0.0001	--
Dyspareunia		
- Baseline Mean	2.54	2.56
- Week 12 Mean	1.13	1.50
- Mean Change from Baseline (SD)	-1.42 (1.00)	-1.06 (1.02)
-Difference vs. placebo	-0.35	--
- P-value*	0.0002	--

Source: Adapted from Statistical Review Tables 9, 12and 14, pages 13, 15 and 17, respectively; Medical Officer Review Table 11, page 67, and NDA 208470, Trial ERC-238 Clinical Trial Report, Table 9-3on page 95 of 601, Table 9-5 on page 98 of 60`, Table 9-8 on page 88 of 591, and Table 9-7on page 102 of 601.

The 0.50% DHEA vaginal insert treatment group compared to placebo, demonstrates an improvement (i.e., increase) in the percentage of superficial vaginal cells **and** improvement (i.e., decrease) in the percentage of vaginal parabasal cells **and** improvement (i.e., decrease) in vaginal pH **and** improvement (i.e., decrease) in the mean change in severity from baseline.

Based on Trial ERC-238 inclusion criterion that participating women would have sexual activity at least once during the 12-week treatment and evaluation period, it was expected that women would have one experience of sexual intercourse 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 intercourse at least once before Weeks 6 and 12 (or discontinuation). The mITT analysis

demonstrated difference from placebo in the severity score for dyspareunia at Week 12 of (-) 0.34 with a statistical significance (p-value) of 0.0003. This finding is similar to that of the ITT population [(-) 0.35 and p =0.0002].

For additional information on per protocol, modified ITT sensitivity and secondary analyses, the reader is referred to Drs. van der Vlugt and Dr. Dwyer's reviews

Primary efficacy data from Trials ERC-231 and ERC-238 support the effectiveness of 0.50% DHEA (6.5 mg prasterone) vaginal inserts in the treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause

8. Safety

The primary review of the safety information in NDA (b) (4) was performed by Theresa van der Vlugt.

A total six trials [five (5) phase 3 trials (ERC-210, ERC-230, ERC-231, ERC-234,and ERC-238) and one phase 1 trial, ERC-213 support the safety profile of the NDA. 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 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. Approval is sought for only the 0.50% (6.5) mg prasterone vaginal insert for the treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

The Agency recommended that the applicant follow ICH E-1 guidelines for premarket exposure (1500 subjects exposed overall, 500 exposure for at least 6 months and 100 exposed for at least one year) for this product intended for chronic use. In the prasterone (DHEA) development program, at 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.

Safety findings in the following trials were 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

No deaths occurred in any of the six clinical trials.

For the to-be-marketed dose, a total of 26 postmenopausal women experienced 33 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 (6.5 mg) compared with 5 postmenopausal women in the placebo treatment group (1%, 5 of 474 women treated with placebo).

The five cases of SAE in placebo included: one case of pancreatitis with right rotator cuff injury during hospitalization; one case of pulmonary embolism in the superior segment of the inferior lobe of the right lung; one case of partial small bowel obstruction; one case of hiatal hernia and small gastric erosion in the hernia; and one case of bizarre behavior and seizure-like activity that had evolved over a period of 2 months. All of these cases were determined to be unrelated to trial medication.

Twenty-five (25) of the 26 women with SAEs in the 0.50% prasterone (6.5 mg) treatment group were classified as having SAEs unrelated to drug, while only one was assessed as possibly-related.

SAEs in the 0.50% prasterone (6.5 mg) treatment group noted as unrelated to the trial medication include:

- Two cases of inflammation of the appendix (one appendicitis and one appendicular peritonitis)
- One case of ischemic colitis of the splenic flexure
- One case of Crohn's disease
- One case of ulcerative colitis flare with development of anemia requiring transfusions
- One case of bilateral small sub-segmental pulmonary emboli following a lumbar-sacral laminectomy
- Two cases knee replacement (one of right and one left +left total hip arthroplasty
- One case of elective total knee arthroplasty
- One case of fracture femur following an automobile accident,.one case of right posterior tibial tendon tear
- One case of life-threatening staphylococcal infection following a right total hip arthroplasty
- One case of Stage IIIC ovarian cancer
- One case of work-place injury resulting in thumb lacerations
- One case of drug allergy to a concomitant medication, Lisinopril
- Two case of hysterectomy (one secondary to uterine prolapse and one secondary to bladder prolapse, cyctocele and rectocele
- One case of pancreatitis
- One case of depression with suicidal ideation
- One case of left-side facial cellulitis/surgical incision of facial abscess
- One case of elective hiatal hernia repair
- One case of elective gastric bypass surgery/post-surgery gastric bypass complications
- One case of left humerus fracture.

Serious adverse effects of the reproductive track are of particular interest for any product intended to impact the reproductive track. Only one of the 26 SAEs was classified as possibly related to prasterone by the investigator. This was a case of invasive ductal breast

carcinoma in a woman 55 years of age with a history of a stereotactic biopsy of the right breast for microcalcifications (September 2005). The woman did not have a history of hormone therapy. She had a pre-trial mammogram considered normal based on the absence of changes compared to the previous exam (December 2010). She took her first dose of trial medication on (b) (6); her last dose on (b) (6). Her Week 52 breast examination was normal. Her post-trial mammogram on Day (b) (6) 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 (b) (6) she had a segmental mastectomy (b) (6) with a final histologic diagnosis of infiltrating carcinoma positive for estrogen and progesterone receptors. One case of breast cancer is not concerning in a 52 week trial of a population of women who by age criteria alone would be at increased risk for breast cancer. That said a 52-week trial is not of sufficient duration to assess the risk for breast cancer in association with steroid use. Breast cancer is generally slow growing. In this instance the woman may have had breast cancer *in situ* for which steroid became a promotor.

The endometrium is the other hormonally responsive reproductive organ for which the use of a steroid could be called into question. 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. The long-term endometrial safety of 0.50% prasterone (6.5 mg) vaginal insert was investigated in 52-week safety clinical trial (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.

The following Table 10 provides an overview of end-of trial endometrial biopsy data for Trials ERC-210, ERC-231, ERC-234

Table 10: 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**
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%)

[1] Woman identified by applicant as having an estrogen signature.

[2] 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.

Source: Medical Officer Review, Table 23, page 125 and 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.

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% prasterone (6.5 mg) vaginal insert administered daily over a 12 week duration. The findings of two (2) cases of weakly proliferative endometrium and one case of complex hyperplasia with atypia in the placebo vaginal insert treatment group do 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.

The following Table 11 provides an overview of end-of trial endometrial biopsy data for Trial ERC-230.

Table 11: 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 N = 435	**26 - < 52 Weeks N = 24**	**All[1] N = 521**
Total Number of Women in Treatment Interval (%)	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%)
Final Diagnosis Histologic Characteristics (N, % of women with biopsy)			
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%)[2]	0 (0.0%)	1 (0.2%)[2]
Other Findings			
Polyps			
- Atrophic	7 (2%)	0 (0.0%)	7 (2%)
- Functional	0 (0.0%)	1 (7%)[2]	1 (0%)

[1] Includes women who discontinued after 12 weeks but before 26 weeks.
[2] Woman identified by applicant as having an estrogen signature.

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.

The reported findings of the three independent, blinded pathologists support the absence of substantial endometrial effects for the 0.50% prasterone (6.5 mg) 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.

In the four (4) placebo-controlled, 12-week clinical trials (ERC-210, ERC-234, ERC -231, and ERC-238), vaginal discharge was the most frequently reported treatment-emergent adverse reaction in the 0.50% prasterone (6.5 mg) vaginal insert treatment group with an incidence of ≥ 2 percent and greater than reported in the placebo treatment group. There were 38 cases in 665 participating postmenopausal women (5.71 percent) in the 0.50% prasterone (6.5 mg) vaginal insert treatment group compared to 17 cases in 464 participating postmenopausal women (3.66 percent) in the placebo treatment group.

In 52-week Trial ERC-230 vaginal discharge and abnormal Pap smear at 52 weeks were the most frequently reported treatment-emergent adverse reaction in women receiving 0.50% prasterone (6.5 mg) vaginal insert with an incidence of ≥ 2 percent. 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). Because of some expression of concern on the part of the applicant over labeling these adverse reactions, DBRUP would like to follow the occurrence of these adverse events in the postmarketing period. The applicant will be asked for additional quarterly reports based on postmarketing report of adverse events related abnormal Pap smear findings with use of INTRAROSA. Specifically, we will ask for reports of findings of atypical squamous cell of undetermined significance (ASC-US), low grade squamous intraepithelial lesion (LGSIL), high grade squamous intraepithelial lesion (HGSIL), squamous cell carcinoma, atypical glandular cells not otherwise specified (AGC-NOS), atypical glandular cells, suspicious for adenocarcinoma *in situ* or cancer (AGC-neoplastic), adenocarcinoma *in situ* and adenocarcinoma. Additionally, we will ask for submission of reporting for a period of three years following launch of INTRAROSA in the US.

The reader is encourage to review the Medical Officer Review of Dr. Theresa van der Vlugt for a more detailed discussion of the safety data presented in the NDA.

Overall, the safety profile of 0.50% prasterone (6.5 mg) vaginal insert is well supported in the NDA and there are no findings that would preclude a recommendation to approve the product.

9. Advisory Committee Meeting

Because no major issues were anticipated at Filing, Advisory Committee input was not sought for the decision on this supplement.

10. Pediatrics

A full pediatric waiver for ages 0-18 was requested by EndoCeutics with the rationale that the condition (treatment of moderate-to-severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause) does not apply to children. DBRUP concurs with the Applicant's assessment. EndoCeutics' request for a full pediatric waiver for INTRAROSA was discussed at the July 6. 2016 Pediatric Research Committee (PeRC)/Pediatric Research Equity Act (PREA) Subcommittee meeting. The committee determined that INTRAROSA would be granted a full waiver based on a condition that qualifies for waiver because studies would be impossible or highly impractical.

11. Other Relevant Regulatory Issues

Priority Review Request/Decision

EndoCeutics request for Priority Review was included in the NDA. The applicant holds that they meet the criteria for priority review [redacted] (b) (4)

DBRUP did not grant 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. Should the NDA be approved, INTRAROSA (prasterone) vaginal 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.

User Fee

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).

New Chemical Entity

Although lawfully marketed as a dietary supplement, prasterone (DHEA) is not **approved** for any indication nationally or internationally.

(b) (4)

Throughout the course of INTRAROSA clinical development, the Agency referred to the drug substance as a new molecular entity (NME). The Office of Compliance records indicate that prasterone has been unlawfully marketed as a drug product, "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.[6]

Consequently, the prasterone active ingredient in the INTRAROSA (prasterone insert) NDA is not an NME." Therefore it was determined that prasterone could not be designated as an NME, but instead is properly designated as a new chemical entity (NCE).

Clearance by 505(b)(2) Committee

505(b)(2) designation for NDA 208470 for INTRAROSA based on reliance on the published literature to support the Pharmacology/ Toxicology labeling, was discussed by 505(b)(2) Committee on October 24, 2016. The Division presented to the committee, the following scientific bridge for the 505(b)(2) submission designation.

> The applicant is relying on published literature that describes the carcinogenic effects of estrogen and testosterone. There are no long-term studies in animals evaluating the carcinogenic potential of prasterone. Multiple studies show estradiol and testosterone are carcinogenic in animals; e.g. postmenopausal estrogen therapy is considered to be carcinogenic in humans (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 72: 399-503, 1999) and testosterone is considered an animal and presumptive human carcinogen (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans 21:519-547, 1979). The literature does not describe branded drugs. The carcinogenic risk from the literature is communicated in the prasterone label.
>
> The data described in the submitted literature is scientifically relevant to the proposed product because the studies evaluate the two predominant and active metabolites of the active pharmaceutical ingredient in the applicant's drug product, and the doses used in the reported animal studies are scientifically relevant to the proposed human dose.

The 505(b)(2) Committee confirmed 505(b)(2) application status for NDA 208470.

Inspections by the Office of Scientific Investigations (OSI)

After consultation with the Office of Scientific Investigations (OSI), five (5) centers were selected for inspection. These centers included:

- 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).
  - OSI/DGCPC inspected Site #15 (Dr. David Portman) from March 7-17, 2016.
  - 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." No FDA Form 483 was issued at the conclusion of the inspection. Site #15 received a NAI classification

- 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).
  - OSI/DGCPC inspected Site #21 (Dr. Douglas Young) from May 9-13, 2016.

- On July 13, 2016, OSI/DGCPC provided evaluations of clinical inspections Site #21. Dr. Young 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." No FDA Form 483 was issued at the conclusion of the inspection. Site #21 received a NAI classification.

- 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).
  - OSI/DGCPC inspected Site #02 (Dr. Celine Bouchard) from April 25-28, 2016
  - On July 13, 2016, OSI/DGCPC provided evaluations of clinical inspections for Site #02 and Site #21. Dr. Bouchard 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." No FDA Form 483 was issued at the conclusion of the inspections. Site #02 received a NAI classification.

- 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.
  - Sites #81 was not inspected by OSI/DGCPC.

- 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.
  - Sites #60 was not inspected by OSI/DGCPC

The Division concurs with OSI's recommendation.

The Office of Prescription Drug Promotion (OPDP)

OPDP's recommendations (Review dated November 8, 2016) for Highlights and Full Prescribing Information, Patient Information and Carton/Container labeling were taken into consideration for negotiations with the applicant to reach agreed-to labeling.

Office of Medical Policy/Division of Medical Policy Programs (DMPP)

DMPP's recommendations for the Patient Information were taken into consideration for negotiations with the applicant to reach agreed-to labeling. The majority of the recommendations were incorporated into the final Patient Information.

The recommendations from DMPP on the WARNINGS AND PRECAUTIONS in women with current and past history of breast cancer were not appropriately parallel to the

HIGHLIGHTS and FULL PRESCRIBING INFORMATION and were, therefore, modified to correct this.

Financial Disclosure

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.

Tradename Review

On December 30, 2015, the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the tradename "INTRAROSA" was acceptable.

12. Labeling

Agreed-to labeling (Highlights and Full Prescribing Information, Patient Information and Instructions for Use and Container and Carton labeling) are attached to this review.

13. Conclusions/Recommendations/Risk Benefit Assessment

I concur with the Primary Clinical, Clinical Pharmacology, Statistical, Preclinical and Chemistry Reviewers that NDA 208470 for INTRAROSA should receive an Approval action.

15 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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.

/s/

SHELLEY R SLAUGHTER
11/16/2016