Official Title:	PROTOCOL: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Cream, USP, 0.01% (Prasco LLC) to Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott) in the Treatment of Vulvar and Vaginal Atrophy
NCT Number:	NCT03332303
IRB Approval Date:	August 1, 2017

1.0 TITLE PAGE

Drug Product	Estradiol Vaginal Cream USP, 0.01%
Population	Approximately 535 postmenopausal females, 30-75 years of age inclusive, with moderate to severe vulvar and vaginal atrophy
Study Design	A randomized, double-blind, placebo-controlled, multiple-site, parallel-design bioequivalence study with clinical endpoints
Sponsor	Prasco LLC
Protocol/Study Number	71759501
Protocol Date	07/25/2017

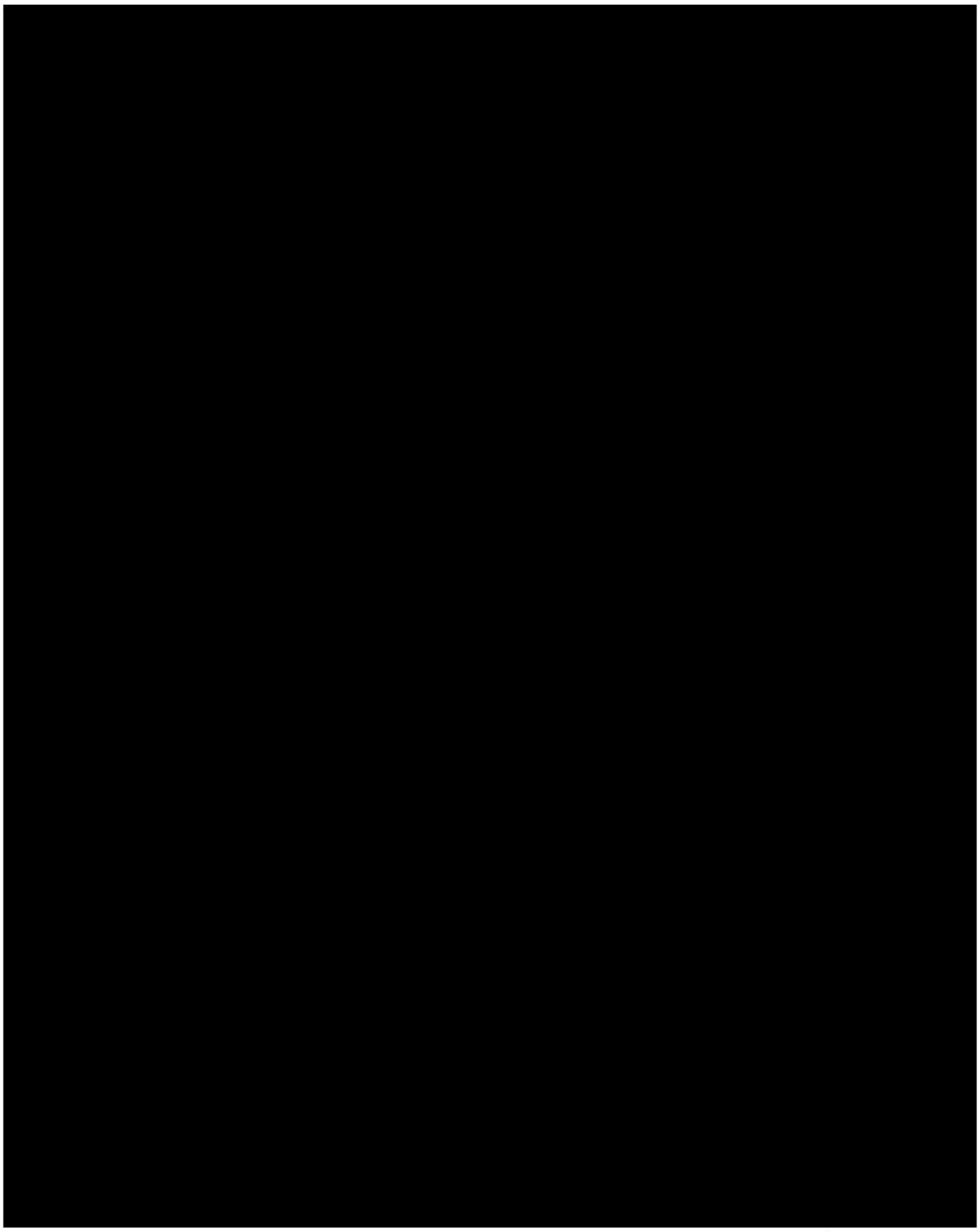
[redacted]

[redacted]

2.0 KEY STUDY PERSONNEL AND FACILITIES

Sponsor:	Prasco LLC
CRO:	

	[redacted]
[redacted]	[redacted]



PRINCIPAL INVESTIGATOR'S SIGNATURE

I _____, agree to conduct protocol 71759501 Rev 0 in accordance with FDA regulations, ICH guidelines and GCPs. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Prasco LLC) or [redacted]he company managing the study.

_____ _____
Principal Investigator Date

4.0 TABLE OF CONTENTS

5.0 SYNOPSIS

Protocol Number	71759501
Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Cream USP, 0.01% (Prasco LLC) Compared to Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott) in the Treatment of Vulvar and Vaginal Atrophy.
Objectives	The objectives of this study are to: • Evaluate the therapeutic equivalence of a generic Estradiol Vaginal Cream USP, 0.01% (Prasco LLC) to the Reference product, Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott) in the treatment of vulvar and vaginal atrophy (VVA). • Demonstrate the superiority of the Test and Reference (active) treatments over Placebo (vehicle) treatment in patients with VVA. • Compare the safety of Test, Reference and Placebo treatments in patients with VVA.
Sponsor	Prasco LLC
Study Products	• **Test**: Estradiol Vaginal Cream, USP, 0.01% (Prasco LLC) • **Reference**: Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott) • **Placebo**: Placebo (Test vehicle cream) Vaginal Cream (Prasco LLC) Study products will be supplied in tubes, with a calibrated plastic applicator for dose (2 grams) administration.
Dosage Regimen	Patients will be instructed to apply 2 grams study product to the treatment area once daily for seven days. Each patient is expected to receive seven doses.
Route of Administration	Intravaginal
Treatment Randomization	2:2:1 (Test: Reference: Placebo)
Patient Population	Approximately [redacted] postmenopausal females, 30-75 years of age inclusive, with moderate to severe VVA.
Study Design	Randomized, double-blind, placebo-controlled, parallel-group, multiple-site bioequivalence study with clinical endpoints
Study Conduct	Eligible patients will be randomized in a 2:2:1 ratio to one of the three treatments (Test, Reference or Placebo). Following a 28-day screening

	period, at Visit 2 patients will be instructed to self-administer 2 grams of study product once daily at approximately the same time for seven consecutive days. During the study, patients will visit the clinical center for a total of three scheduled visits: • Visit 1/Screening (Day -28 to Day -1) • Visit 2/Randomization (Day 1) • Visit 3/End of Study (Day 8 or Day 9) Final assessments will be carried out on Day 8 or Day 9. Vaginal cytology and vaginal pH determination will be performed by the Investigator as a part of clinical evaluation at Visits 1 and 3.
Inclusion Criteria	1. Signed Institutional Review Boards (IRB)-approved informed consent form that meets all criteria of current FDA regulations. 2. Postmenopausal females aged 30-75 years inclusive. Postmenopausal is defined as follows: a. At least 6 months of spontaneous amenorrhea. b. At least 6 weeks post-surgical bilateral oophrectomy, with or without hysterectomy. c. Hysterectomy without oophrectomy if of age that the Investigator believes would have naturally reached 12 months of spontaneous amenorrhea if uterus had remained intact. 3. Patients with a serum Follicle Stimulating Hormone (FSH) level of ≥ 40 mIU/mL at Screening. 4. Have ≤ 5% superficial cells on vaginal smear cytology. 5. Have a vaginal pH > 5.0. 6. At least one of the following patient self-assessed moderate to severe symptoms of VVA from the following list that is identified by the patient as being most bothersome to her: • Vaginal Dryness • Vaginal and/or Vulvar Irritation/Itching • Dysuria • Vaginal Pain associated with sexual activity • Vaginal Bleeding associated with sexual activity (presence or absence) *Provided that patient is currently sexually active and plans to remain so throughout study. 7. Have "Normal" Screening mammogram completed within 9 months before Screening in all patients > 40 years old, with no findings that, in the opinion of the Investigator, would indicate any suspicion of breast

	malignancy. 8. Normal clinical breast examination at Screening. 9. Patients with an intact uterus (including patients who underwent a partial hysterectomy) must have a documented papanicolaou (PAP) smear conducted within the previous 12 months with no findings that the Investigator believes would contraindicate the use of topical vaginal estradiol. 10. Patients with an intact uterus should have vaginal ultrasonography results within 3 months before Screening to confirm an inactive endometrial lining, defined as endometrial thickness < 4 mm.
Exclusion Criteria	1. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that in the Investigator's opinion would place the study patient at undue risk by participation or could jeopardize the integrity of the study evaluations. 2. Any clinically significant laboratory finding that, in the Investigator's opinion would contraindicate the use of estradiol or compromise patient safety. 3. Patients with known concurrent vaginal infections including but not limited to: Candida albicans, Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhea or Gardnerella vaginalis. 4. Patients with active vaginal herpes simplex infection or have had an outbreak within 30 days before the Screening. 5. Patients with known, suspected or current history of carcinoma of the breast. 6. Patients with baseline systolic blood pressure of > 150 mmHg and/or diastolic pressure > 90 mmHg. 7. Any patient with past or current undiagnosed vaginal bleeding or significant risk factors for endometrial cancer. 8. Any history of estrogen-dependent neoplasia (e.g., endometrial cancer). 9. Patients with known, suspected or current history of hormone dependent tumor. 10. History of acute thrombophlebitis or thromboembolic disorder. 11. Any prescription treatment for vaginal dryness/irritation within 14 days before Screening or any over-the-counter or natural remedies within 7 days before Screening. 12. Any prescription treatment for bacterial or yeast infections within 30 days before Screening. 13. Fasting triglyceride levels > 350 mg/dL. 14. History of radiation therapy or recent (within previous 6 weeks) surgical

	therapy to the vaginal or cervical areas. 15. Any known or suspected allergies that, in the Investigator's opinion, would compromise the safety of the patient. 16. Patients who have used vaginal hormonal products (rings, creams, gels) within the 7 days before Screening. 17. Patients who have used transdermal estrogen and/or progestin therapy within the 28 days before Screening. 18. Patients who have used oral estrogen and/ or progestin therapy or intrauterine progestin therapy within the 56 days before Screening. 19. Patients who have used progestin implants or estrogen alone injectable drug therapy within the 3 months before Screening. 20. Patients who have used estrogen pellet therapy or progestin injectable drug therapy within 6 months before Screening. 21. History of significant alcohol abuse within 1 year prior to Screening or regular use of alcohol within 6 months before Screening (more than 14 units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]). 22. History of significant drug abuse within 1 year prior to Screening, use of soft drugs (such as marijuana) within 3 months before Screening, or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 1 year before screening. 23. Use within 30 days of Screening with known strong CYP3A4 inducers or inhibitors that, in the opinion if the Investigator, may affect estrogen metabolism. Examples of strong CYP3A4 inhibitors are macrolide antibiotics such as clarithromycin and telithromycin; azole antifungals such as itraconazole and ketoconazole; antidepressants such as nefazodone; and foods such as grapefruit or grapefruit juice. Examples of strong CYP3A4 inducers are anticonvulsants such carbamazepine and phenytoin; bactericidals such as rifampin and rifabutin; and natural health products such as St John's wort. 24. Inability to understand the requirements of the study and the relative information or are unable or not willing to comply with the study protocol. 25. Receipt of any drug as part of a research study within 30 days before Screening. 26. Employees of the Investigator or research center or their immediate family members. 27. Patients who have participated in this study previously.

Efficacy Endpoints	**Primary Efficacy Endpoint** The primary efficacy endpoint is the proportion of patients in each treatment group that are identified as Responders at the end of the treatment period evaluated on Day 8 or Day 9. A Responder is defined as a patient with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5. **Secondary Efficacy Endpoint** The secondary efficacy endpoint is the proportion of patients in each treatment group that are considered a Treatment Success at the end of the treatment period evaluated on Day 8 or Day 9. A "Treatment Success" is defined as a score of 0 or 1 on Day 8 or Day 9 for the symptom identified at baseline as the most bothersome. This evaluation will be based on (one) patient self-assessed symptom of VVA (vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, or vaginal pain associated with sexual activity) on a scale of 0 to 3 where 0 = none and 3 = severe. Evaluation of vaginal bleeding during sexual activity will be based on a score of 1 (presence) if it is identified by the patient as the most bothersome symptom at baseline and a score of 0 (absent) on Day 8 or Day 9.
Evaluation of Therapeutic Equivalence and Superiority	**Primary Endpoint Analysis** Therapeutic Equivalence: Therapeutic equivalence will be evaluated for both primary and secondary endpoints in the per-protocol (PP) population. If the 90% confidence interval (calculated using Yates' continuity correction) on the absolute difference between the proportion of patients identified as Responders in the Test and Reference groups (p_T - p_R) is contained within the range [-20%, +20%] then therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated. The same statistical approach will be conducted for analysis of the secondary endpoint in the PP population. To declare therapeutic equivalence of the Test product to the Reference product, equivalence must be demonstrated for only the primary endpoints in the PP population. Superiority to Placebo Superiority of the Test and Reference products against the Placebo product for the primary endpoint will be evaluated in the modified Intent-to-Treat (mITT) population using last observation carried forward (LOCF). If the

	proportion of Responders in the Test and the Reference product groups is numerically and statistically superior to that of the Placebo ($p < 0.05$; using a two-sided Cochran-Mantel-Haenszel [CMH] test, stratified by clinical site) then superiority of the Test and Reference products over Placebo will be concluded. The same statistical approach will be conducted for analysis of the secondary endpoint in the mITT population. To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population. <u>Treatment-by-Site Interaction and Pooling of Clinical Sites</u> As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population for equivalence testing. The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$, 2-sided). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the stratification of the sites in the CMH test and in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population at the site with the highest enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant ($p < 0.05$) for the primary endpoint, then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of Responder rates at each site where sample sizes per treatment may be influential in the assessment of the interaction.
Safety Analysis	Adverse events (AEs) will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology Version 20.0 or higher and summarized by treatment group. Summary tables comparing the type, incidence, date of onset, date of resolution, severity, action taken, outcome and Investigator's opinion of relationship to the study product will be prepared by treatment group. If sufficient data exist, AE frequencies will be compared between treatments using Fisher's exact test or a similar test. Signs and symptoms of VVA will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their condition. Concomitant medication use during the study will be tabulated by patient.
Sample Size	For the primary endpoint analysis (proportion of patients in the PP population

Determination	that are identified as Responders at the end of the treatment period evaluated on Day 8 + 1), sample size is estimated for therapeutic equivalence of the Test to the Reference product and superiority of each of the active treatments groups over Placebo. [redacted]

6.0 STUDY SCHEMATIC

	Visit 1 (Day -28 to Day -1) Screening	**Visit 2** (Day 1) Randomization	**Visit 3** (Day 8 or Day 9) End of Study or Early Termination
Informed Consent	X		
Medical History and Demographics	X		
Review and Assessment of Concomitant Medications	X	X	X
Review and Assessment of Adverse Events	X	X	X
Vital Signs	X	X	X
Signs and Symptoms of VVA	X	X	X
Physical Exam	X		X
Vaginal Cytology and pH	X		X
PAP*Smear	X		
Serum FSH and Fasting Triglycerides	X		
Mammogram†	X		
Vaginal Ultrasound‡	X		
Inclusion/Exclusion Criteria Review	X	X	
Collect and Review Patient Diary		X	X
Provide Patient Diary	X	X	
Dispense Study Product		X	
Collect Study Product			X

*Patients with an intact uterus who do not have documentation of a PAP smear completed within the last [redacted].

†Patients over the age of 40 who do not have documentation of a mammogram completed within the [redacted] before Screening will have a mammogram as part of the Screening evaluations.

‡Patients with an intact uterus will have a vaginal ultrasound as part of the Screening evaluations which will be reviewed before randomization.

7.0 LIST OF ABBREVIATIONS AND TERMS

ADaM	Analysis Dataset Model
ADR	Adverse Drug Reaction
AE	Adverse Event
ANOVA	Analysis of variance
C	Celsius
CDISC	Clinical Data Interchange Consortium
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
CRO	Contract Research Organization
eCTD	Electronic Common Technical Document
F	Fahrenheit
FDA	Food & Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
NCR	No Carbon Required
NDA	New Drug Application
OHRP	Office of Human Rights Protection
OTC	Over-the-Counter
PAP	Papanicolaou
PP	Per-Protocol
p_R	Proportion of Subjects considered a Treatment Success in the Reference Treatment
p_T	Proportion of Subjects considered a Treatment Success in the Test Treatment
RS	Reference Standard
RSI	Reference Safety Information
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SUSAR	Suspected Unexpected Serious Adverse Reaction
USA	United States of America
VVA	Vulvar and Vaginal Atrophy

8.0 INTRODUCTION

8.1 Disease Being Treated

Female menopause is generally characterized by various signs and symptoms associated with the age-related decline in reproductive hormone levels.

Low dose, topical estrogen therapy is considered most appropriate and convenient for the treatment of vaginal symptoms associated with menopause, particularly when other symptoms including bone loss or vasomotor dysfunction do not need to be targeted.[8,9]

8.3 Scientific and Statistical Considerations

8.4 Justification for use of Placebo

A placebo group is included to confirm the sensitivity of the study and minimize the possibility of a false positive result of bioequivalence. Therefore, in addition to demonstrating bioequivalence between Test and Reference products, both active products should show statistical superiority to the Placebo.[14-16]

8.5 Risks and Benefits

The risks and benefits to patients enrolled in clinical research studies that include a placebo treatment group must be carefully considered based on three main criteria, namely: the disease being treated, the availability, efficacy and safety of already approved therapies, and the scientific and statistical requirements of the desired outcome of the research study. The Office of Human Rights Protection (OHRP), a Division of the USA Federal Government's Department of Health and Human Services,

has issued a detailed guidebook to Institutional Review Boards (IRBs) that includes discussion on the use of placebos in clinical studies.[17]

Qualified patients have a 20% chance they may be randomized to Placebo. Randomized patients will be enrolled in the study for 8 or 9 days. Although the potential for any drug-related side effects of significance occurring during the study are low, the risk is higher in the two active treatment groups than in the Placebo group.

All patients enrolled in this study will receive the benefit of free specialized medical care beyond standard medical treatment that would be expected through most health insurance plans. In addition, the patient will receive a stipend for participation to cover costs and expenses associated with trips to the medical facility.

9.0 STUDY OBJECTIVES

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of a generic Estradiol Vaginal Cream USP, 0.01% (Prasco LLC) to the Reference product, Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott) in the treatment of VVA.
2. Demonstrate the superiority of the Test and Reference (active) treatments over Placebo (vehicle) treatment in patients with VVA.
3. Compare the safety of Test, Reference and Placebo treatments in patients with VVA.

10.0 INVESTIGATIONAL PLAN

10.1 Study Design and Plan Description

This randomized, double-blind, placebo-controlled, parallel-design, multiple-site study is designed to evaluate the clinical (therapeutic) effect of a generic Estradiol Vaginal Cream USP, 0.01% (Prasco LLC) compared to the FDA Reference Standard (RS), Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01% (Warner Chilcott) in patients with VVA. Additionally, both the Test and Reference products will be tested for superiority against a Placebo.

Before any study-specific procedures are performed, all patients will read and sign the IRB-approved informed consent form (ICF).

Approximately [redacted] eligible postmenopausal female patients, with a confirmed diagnosis of VVA will be randomized in a 2:2:1 ratio (Test: Reference: Placebo) to one of the three study products as follows:

- **Test**: Estradiol Vaginal Cream, USP, 0.01% (Prasco LLC)
- **Reference**: Estrace® Cream (Estradiol Vaginal Cream, USP, 0.01%) (Warner Chilcott)
- **Placebo**: Placebo (Test vehicle cream) Vaginal Cream (Prasco LLC)

Following a 28-day screening period, at Visit 2 patients will be instructed to self-administer 2 grams of study product once daily at approximately the same time for seven consecutive days.

During the study, patients will visit the clinical center for a total of three scheduled visits:

- Visit 1/Screening (Day -28 to Day -1)
- Visit 2/Randomization (Day 1)
- Visit 3/End of Study (Day 8 or Day 9)

Final assessments will be carried out on Day 8 or Day 9

Vaginal cytology and vaginal pH determination will be performed by the Investigator as a part of clinical evaluation at Visits 1 and 3. The primary statistical analysis of interest is the proportion of patients in the PP population that are identified as Responders at the end of the treatment period evaluated on Day 8 or Day 9. A Responder is defined as a patient with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5.

10.2 Selection of Study Design

This study has been designed based on the draft FDA Guidance for Industry; Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and VVA (January 2003) and the Draft FDA Guidance on Estradiol Vaginal Cream (revised September 2014).[12,13] Statistical analyses of the clinical data will be based on recommendations in the FDA Guidances.[12-16,18]

10.3 Selection of Study Population

10.3.1 Inclusion Criteria

1. Signed IRB-approved ICF that meets all criteria of current FDA regulations.
2. Postmenopausal females aged 30-75 years inclusive. Postmenopausal is defined as follows:
    a. At least 6 months of spontaneous amenorrhea.
    b. At least 6 weeks post-surgical bilateral oophrectomy, with or without hysterectomy.
    c. Hysterectomy without oophrectomy if of age that the Investigator believes would have naturally reached 12 months of spontaneous amenorrhea if uterus had remained intact.
3. Patients with a serum Follicle Stimulating Hormone (FSH) level of ≥ 40 mIU/mL at Screening.
4. Have ≤ 5% superficial cells on vaginal smear cytology.
5. Have a vaginal pH > 5.0.
6. At least one of the following patient self-assessed moderate to severe symptoms of VVA from the following list that is identified by the patient as being most bothersome to her:

- Vaginal Dryness
- Vaginal and/or Vulvar Irritation/Itching
- Dysuria
- Vaginal Pain associated with sexual activity
- Vaginal Bleeding associated with sexual activity (presence or absence)

*Provided that patient is currently sexually active and plans to remain so throughout study.

7. Have "Normal" Screening mammogram completed within 9 months before Screening in all patients > 40 years old, with no findings that, in the opinion of the Investigator, would indicate any suspicion of breast malignancy.
8. Normal clinical breast examination at Screening.
9. Patients with an intact uterus (including patients who underwent a partial hysterectomy) must have a documented papanicolaou (PAP) smear conducted within the previous 12 months with no findings that the Investigator believes would contraindicate the use of topical vaginal estradiol.
10. Patients with an intact uterus should have vaginal ultrasonography results within 3 months before Screening to confirm an inactive endometrial lining, defined as endometrial thickness < 4 mm.

10.3.2 Exclusion Criteria

1. Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that in the Investigator's opinion would place the study patient at undue risk by participation or could jeopardize the integrity of the study evaluations.
2. Any clinically significant laboratory finding that, in the Investigator's opinion, would contraindicate the use of estradiol or compromise patient safety.
3. Patients with known concurrent vaginal infections including but not limited to: Candida albicans, Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhea or Gardnerella vaginalis.
4. Patients with active vaginal herpes simplex infection or have had an outbreak within 30 days before the Screening.
5. Patients with known, suspected or current history of carcinoma of the breast.
6. Patients with baseline systolic blood pressure of > 150 mmHg and/or diastolic pressure > 90 mmHg.

7. Any patient with past or current undiagnosed vaginal bleeding or significant risk factors for endometrial cancer.
8. Any history of estrogen-dependent neoplasia (e.g., endometrial cancer).
9. Patients with known, suspected or current history of hormone dependent tumor.
10. History of acute thrombophlebitis or thromboembolic disorder.
11. Any prescription treatment for vaginal dryness/irritation within 14 days before Screening or any OTC or natural remedies within 7 days before Screening.
12. Any prescription treatment for bacterial or yeast infections within 30 days before Screening.
13. Fasting triglyceride levels > 350 mg/dL.
14. History of radiation therapy or recent (within previous 6 weeks) surgical therapy to the vaginal or cervical areas.
15. Any known or suspected allergies that, in the Investigator's opinion, would compromise the safety of the patient.
16. Patients who have used vaginal hormonal products (rings, creams, gels) within the 7 days before Screening.
17. Patients who have used transdermal estrogen and/or progestin therapy within the 28 days before Screening.
18. Patients who have used oral estrogen and/ or progestin therapy or intrauterine progestin therapy within the 56 days before Screening.
19. Patients who have used progestin implants or estrogen alone injectable drug therapy within the 3 months before Screening.
20. Patients who have used estrogen pellet therapy or progestin injectable drug therapy within 6 months before Screening.
21. History of significant alcohol abuse within 1 year prior to Screening or regular use of alcohol within 6 months before Screening (more than 14 units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).
22. History of significant drug abuse within 1 year prior to Screening, use of soft drugs (such as marijuana) within 3 months before Screening, or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 1 year before screening.
23. Use within 30 days of Screening with known strong CYP3A4 inducers or inhibitors that, in the opinion if the Investigator, may affect estrogen metabolism. Examples of strong CYP3A4 inhibitors are macrolide antibiotics such as clarithromycin and telithromycin; azole antifungals such as itraconazole and ketoconazole; antidepressants such as

nefazodone; and foods such as grapefruit or grapefruit juice. Examples of strong CYP3A4 inducers are anticonvulsants such carbamazepine and phenytoin; bactericidals such as rifampin and rifabutin; and natural health products such as St John's wort.

24. Inability to understand the requirements of the study and the relative information or are unable or not willing to comply with the study protocol.
25. Receipt of any drug as part of a research study within 30 days before Screening.
26. Employees of the Investigator or research center or their immediate family members.
27. Patients who have participated in this study previously.

10.3.3 Restrictions During the Study

Patients will be instructed to refrain from the following throughout the study:

- Any kind of estrogen, progesterone or androgen hormone replacement.
- Any other treatments, prescription, OTC or natural products or natural methods, for the treatment of vaginal dryness/irritation including but not limited to vaginal lubricants, oils, creams, jellies, food products or saliva.
- Any vaginal drug products other than the study product (e.g., vaginal anti-fungals).
- Use within 30 days of Screening with known strong CYP3A4 inducers or inhibitors that, in the opinion if the Investigator, may affect estrogen metabolism. Examples of strong CYP3A4 inhibitors are macrolide antibiotics such as clarithromycin and telithromycin; azole antifungals such as itraconazole and ketoconazole; antidepressants such as nefazodone; and foods such as grapefruit or grapefruit juice. Examples of strong CYP3A4 inducers are anticonvulsants such carbamazepine and phenytoin; bactericidals such as rifampin and rifabutin; and natural health products such as St John's wort.

10.3.4 Removal of Patients from the Study

Patients will be advised that they are free to withdraw from the study at any time for any reason or, if necessary, the Investigator or Sponsor may withdraw a patient from the study to protect the health of that patient. A patient may also be withdrawn for not complying with study procedures. Patients who withdraw or are withdrawn from the study will not be replaced. The clinical report will include all reasons for early withdrawals.

Reasons for early termination may include, but are not limited to the following:

- Patient withdrew consent.
- Significant adverse event (AE) that led the Investigator/Sponsor or patient to withdraw for safety reasons.
- Non-compliance with protocol requirements (e.g., use of restricted medication, not following dosing procedures, failure to make scheduled study visits in a timely fashion).

- Pregnancy.
- Significant worsening of VVA such that the Investigator/Sponsor and/or patient believe it is in the best interest of the patient to withdraw from the study and be provided alternative treatment.
- Participant enrolls in another clinical trial, or is found to have previously enrolled in this clinical trial.

10.3.5 Early Terminations

If a patient terminates from the study early after being randomized, all efforts will be made to complete the patient's next visit study procedures. For early termination, Visit 3 (Day 8 or Day 9) End of Study or Early Termination (See Section 6.0) shall be completed and the Investigator shall fully document the reason for early termination.

10.4 Treatments

10.4.1 Treatment Administration

At Visit 2, following a 28-day screening period, eligible patients will be provided with 1 x 42.5 gram tube of study product along with verbal and written instructions on its administration. Patients will be required to self-administer 2 grams of study product once daily at approximately the same time of the day, for seven consecutive days. The last dose should be applied on the day before Visit 3. Patients should not dose on the day of Visit 3.

Patients will gently squeeze the cream out of the tube and into the applicator until the required amount (2 grams) is filled based on the calibrated markings on the applicator. The applicator is then to be unscrewed from the tube and cap replaced on the tube. To deliver study product, patients are to lie on back and insert the applicator into the vagina and deliver the dose by pressing down on the plunger. The applicator is to be cleaned with mild soap and warm water after each application.

Based on an approximate 2 grams application per day, 1 x 42.5 gram tube of cream should be sufficient to last for the full treatment period of the study (seven days). Patients will begin dosing on the day of Visit 2 (i.e., Day 1).

10.4.2 Identity of Investigational Product

The following products will be used in the study:

- **Test**: Estradiol Vaginal Cream USP, 0.01% (Prasco LLC)
- **Reference**: Estrace® Cream (Estradiol Vaginal Cream USP, 0.01%) (Warner Chilcott)
- **Placebo**: Placebo (Test vehicle cream) Vaginal Cream (Prasco LLC)

10.4.3 Study Product Shipment, Storage, and Retention

The study product will be shipped to each Investigator’s site from a central location. The Principal Investigator at each site is responsible for ensuring that all study products are stored in

locked, secure location, with access limited to the Investigator and his/her designee(s). An accurate inventory of the study product will be maintained in accordance with federal regulations.

Study product will be stored in a secure, locked location, at room temperature, protected from temperatures in excess of 40 ºC (104 ºF). Any excursions from the permitted temperature will require prompt notification to [redacted] and thereafter [redacted] will notify the Sponsor.

[redacted]

[redacted]

10.4.4 Method of Assigning Patients to Treatment Groups

All randomized study product will be blinded and packaged in sealed boxes by an independent packaging company. Randomization will be pre-planned according to a computer-generated randomization schedule. [redacted]

[redacted]

[redacted]

10.4.5 Study Blind

The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the patient assignment. Each study site will have at least one Independent Dispenser. The role of the Independent Dispenser is to dispense and collect study product to/from the patients, maintain dispensing records, and ensure the study product logs are complete and accurate. The patient will be requested not to discuss the appearance of the study product with the Investigator or study staff.

[redacted]

[redacted]

10.4.6 Compliance

Patients will be provided with a diary to record the time and date of dosing, other concomitant medications and AEs. Patients will be considered compliant if they take a total of at least six doses and no more than eight doses, and not more than two doses on any day. Patients taking fewer than 75% or more than 125% of the required doses will be considered non-compliant with dosing. Compliance with dosing will be verified by the use of the patient diaries. Compliance criteria are as outlined in the table below:

For patients who have completed the study:

Study Design			Compliance Criteria	
Visit 3	Treatment Duration	Required Doses	Not more than 125% (doses)	Not less than 75% (doses)
Days 8-9	7 days	7	8	6

For patients who are early terminated, compliance will be determined from their duration in the study, up to the time they are considered early terminated. For example, if a patient is dropped after six days of participation and starts application of study product on the day of Visit 2 (i.e., Day 1) and once daily for the four of the five remaining days, then percent compliance would be 83% (4 out of 5 doses).

10.5 Study Conduct

10.5.1 Visit 1 (Day -28 to Day -1): Screening

1. **Informed Consent**: Patients who are willing to comply with study procedures will read, understand and sign the ICF.
2. **Medical History and Demographics**: Review the patient's demographic and medical history.
3. **Concomitant Medications**: Review the patient's use of any medications in the last six months.
4. **Adverse Events**: Patients will be questioned about any AEs experienced during the visit.
5. **Vital Signs**: The patient's vital signs will be recorded (blood pressure, pulse, temperature and respiration rate).
6. **Signs and Symptoms**: Complete the Signs and Symptoms rating scales. See Appendix B.
7. **Physical Exam**: Perform a general physical exam including pelvic exam and breast exam.
8. **Vaginal Cytology and pH**: Obtain samples for vaginal cytology and pH.
9. **PAP Smear**: Obtain the results of a PAP smear conducted within the last 12 months or conduct a PAP smear during the pelvic exam for patients with an intact uterus (including patients who underwent partial hysterectomy).
10. **Serum FSH and Fasting Triglycerides**: Collect a fasted blood sample for FSH and Triglyceride testing (see Appendix A)
11. **Mammogram**: Obtain results from a mammogram performed within the last nine months or schedule a mammogram.
12. **Vaginal Ultrasound**: Perform or schedule a vaginal ultrasound for patients with an intact uterus which will be reviewed before randomization.
13. **Inclusion/Exclusion Criteria Review**: Review inclusion/exclusion criteria.

14. **Provide Patient Diary**: A diary will be provided to record AEs and concomitant medications and patients will receive training on completing the diary.
15. Schedule Visit 2.

10.5.2 Visit 2 (Day 1): Randomization

1. **Concomitant Medication**: Review the patient's use of any new or ongoing concomitant medications since the last visit.
2. **Adverse Events**: Patients will be questioned about any health status changes/AEs since last visit. All AEs will be recorded.
3. **Vital Signs**: The patient's vital signs will be recorded (blood pressure, pulse, temperature and respiration rate).
4. **Signs and Symptoms**: Complete the Signs and Symptoms ratings. See Appendix B.
5. **Inclusion/Exclusion Criteria Review**: Confirm that inclusion/exclusion criteria are met.
6. **Collect and Review Patient Diary**: Collect and review the previously dispensed diary.
7. **Provide Patient Diary**: A diary with instructions will be provided to record date and time of dosing, AEs and concomitant medications. Patients will receive training on completing the diary.
8. **Dispense Study Product**: The Independent Dispenser will dispense study product to eligible patients with instructions.
9. Schedule Visit 3.

10.5.3 Visit 3 (Day 8 or Day 9): End of Study or Early Termination

1. **Concomitant Medication**: Review the patient's use of any new or ongoing concomitant medications since the last visit.
2. **Adverse Events**: Patients will be questioned about any health status changes/AEs since last visit. All AEs will be recorded.
3. **Vital Signs**: The patient's vital signs will be recorded (blood pressure, pulse, temperature and respiration rate).
4. **Signs and Symptoms**: Complete the Signs and Symptoms ratings. See Appendix B.
5. **Physical Exam**: Perform a general physical exam including pelvic exam and breast exam.
6. **Vaginal Cytology and pH**: Obtain samples for vaginal cytology and pH.
7. **Collect and Review Patient Diary**: Collect previously dispensed diary and review for compliance with the protocol.
8. **Collect Study Product**: Study product tubes will be collected.
9. Discharge from the study.

10.6 Study Procedures

10.6.1 Informed Consent

At Visit 1, before performing any study-related procedures the study patient must sign the IRB-approved ICF. The ICF will be reviewed and approved by an IRB before study commencement. No patient will be entered into the study without reading, understanding and signing an ICF. If any other language is required, translation will be performed by a certified translator and then approved by the IRB.

10.6.2 Medical History and Demographics

At Visit 1, each patient will be required to provide basic demographic information: date of birth, gender, ethnicity and race. Patients will also be questioned about medical history, including acute and chronic medical history and medical history relevant to their VVA.

10.6.3 Concomitant Medication

At Visit 1, patients will be questioned about current and prior medication use over the previous 6 months. At Visits 2 and 3 patients will be questioned about ongoing or any new concomitant medication use.

10.6.4 Adverse Events

At the end of Visit 1, patients will be questioned about any AEs that may have occurred during the visit. At Visits 2 and 3 patients will be questioned regarding any changes in their medical status since their previous visit. Any significant changes will be reported as AEs.

10.6.5 Vital Signs

The patient's vital signs will be recorded (pulse, blood pressure, temperature and respiration rate) at each visit. At Visits 1 and 2, systolic blood pressure reading cannot exceed 150 mmHg and diastolic blood pressure reading cannot exceed 90 mmHg.

10.6.6 Signs and Symptoms

At each visit, the blinded clinical staff or Investigator will question the patient regarding the severity of their symptoms. See Appendix B for rating scales. The following symptoms will be evaluated:

- Vaginal Dryness
- Vaginal/Vulvar irritation/itching
- Dysuria
- Vaginal Pain associated with Sexual Activity
- Vaginal Bleeding

The severity of each symptom will be recorded on the source documents. The patients will be asked to identify which symptom is considered to be the most bothersome symptom at each visit.

At Visits 1 and 2, the most bothersome symptom must have a score of moderate or severe (for vaginal dryness, vaginal/vulvar irritation/itching, dysuria, or vaginal pain associated with sexual activity) or present (for vaginal bleeding) to be eligible for inclusion in the study.

The worsening in severity of the Signs and Symptoms need not be additionally included as AEs unless the patient requires additional treatment or in the opinion of the Investigator

10.6.7 Physical Exam

At Visit 1, the Investigator will perform a general physical exam including pelvic exam and breast exam. The results of this exam should, in the Investigator's opinion, be consistent with a diagnosis of estradiol deficient vaginal/vulvar atrophy for the patient to be eligible for inclusion in the study. Additionally, this exam should exclude the possibility that the symptoms could be caused by any concurrent disease (e.g., bacterial vaginosis, candida infection). Any patient diagnosed with, or with any suspected concurrent vaginal infection or other vaginal disease will be excluded from the study. At Visit 3 the Investigator will perform a general physical exam including pelvic exam and breast exam. Any clinically significant abnormal findings on exam should be reported as AEs.

10.6.8 Vaginal Cytology and pH

At Visits 1 and 3, a vaginal cytology specimen will be collected [redacted]

The central laboratory will report the cytology results to the investigative site before randomization. To protect the study blind, the central laboratory will not release the results of any other cytology tests other than the Screening results to either the Investigator or [redacted] until the last patient has completed the study.

The patient's vaginal pH will be measured by inserting standardized pH paper into the vagina and comparing the color change result to the manufacturer's color chart. [redacted]

10.6.9 PAP Smear

At Visit 1, patients with an intact uterus, including patients who underwent a partial hysterectomy, will have a PAP smear completed during the pelvic exam if the Investigator does not have results from a PAP smear completed within the last 12 months. PAP smear samples will be sent to the central laboratory for testing.

10.6.10 Serum FSH and Fasting Triglycerides

All patients will have a blood sample taken for evaluation of serum FSH levels. Serum FSH will be evaluated by a central clinical laboratory. Patients must have a serum FSH > 40 mIU/mL to be eligible for participation in the study.

All patients will have a blood sample taken for fasting triglyceride testing. These samples will be sent to the central laboratory for testing. Patients with fasting triglyceride values > 350 mg/dL will not be eligible for inclusion in the study.

10.6.11 Mammogram

At Visit 1, patients > 40 years of age will have a mammogram scheduled if they do not have results from a mammogram in the last 9 months. Patients must have "Normal" Screening mammogram with no findings that, in the opinion of the Investigator, would indicate any suspicion of breast malignancy to be eligible for inclusion in the study.

10.6.12 Vaginal Ultrasound

All patients with an intact uterus will have a vaginal ultrasound performed as a part of their Screening evaluations which will be reviewed before randomization. Results should confirm an inactive endometrial lining, defined as endometrial thickness less than 4 mm. Patients with an endometrial thickness of 4 mm or more will be excluded from the study.

10.6.13 Inclusion/Exclusion Criteria Review

At Visit 1 and 2, inclusion/exclusion criteria will be reviewed to ensure patients' eligibility for participation in the study. At the Investigator's discretion, a urine pregnancy test may be done at study visits. At the Investigator's discretion, a urine pregnancy test may be done at study visits. The test has to be negative for the patient to be included in the study or for continued participation in the study.

10.6.14 Provide Patient Diary

At Visits 1 and 2, patients will be provided with a diary to record other concomitant medications and AEs. The patients will also receive on-site training on completing the diary. Date and time of dosing should be recorded in the diary dispensed at Visit 2.

10.6.15 Dispense Study Product

At Visit 2 after the Investigator has determined that the study participant meets the inclusion/exclusion criteria for the study the Independent Dispenser will dispense one 42.5 gram tube of study product to the patient using the lowest patient randomization number available at that investigative site.

10.6.16 Collect and Review Patient Diary

At Visits 2 and 3, patient diaries will be collected and reviewed for compliance with the protocol.

10.6.17 Collect Study Product

Tubes of study product will be collected at Visit 3 and checked for compliance or evidence of tampering with the blind.

10.7 Adverse Events

The patients will be monitored throughout the study for any AEs occurring after the patient has signed the ICF until the last study visit of the subject. AEs will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0 or higher AE Dictionary. The patients will be encouraged to report signs, symptoms, and any changes in health to the clinic staff. Severity of each AE will be determined by the staff based on observation and questioning of the patients. The Investigator will judge the relationship of the event to the study treatments. Adverse events should be followed up until they have resolved or stabilized. For any Serious adverse events (SAEs) still ongoing at the time of last visit, the Investigator should continue to follow up until the SAE has resolved or has stabilized / is judged permanent for SAEs considered to be related to study product (serious adverse drug reaction [SADRs]), and for up to 30 days after the last visit of subject for non-related SAEs.

10.7.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease, temporally associated with the use of a medicinal (investigational) product, whether or not related to this product. This includes events not seen at baseline, or worsened even if present at baseline.

Serious Adverse Event: An SAE is any untoward medical occurrence that at any dose results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing inpatient hospitalization, persistent or significant disability / incapacity, a congenital anomaly / birth defect (See Section 10.8.1).

Unexpected Adverse Event: An AE where the nature or severity of is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Adverse Drug Reaction: All noxious and unintended responses to a medical product related to any dose should be considered adverse drug reactions (ADRs). The response to a 'medical product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Suspected Unexpected Serious Adverse Reaction: An **Unexpected Adverse Reaction** is defined as an ADR, the nature or severity of which is not consistent with the Reference Safety Information. Suspected unexpected serious adverse reactions (SUSARs) are "unexpected" SAEs and SADRs in which the temporal relationship of the clinical event to study treatment administration **makes a causal relationship possible**, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

The Product Insert for Estrace® Cream is inserted in the Appendix (see Appendix C). This document will serve as the Reference Safety Information (RSI) as a basis for expectedness assessment.

10.7.2 Severity of Adverse Event

The severity of the AE will be graded by the Investigator using the following criteria as guidelines:

- MILD: Awareness of symptom but does not interfere with routine activities.
- MODERATE: Discomfort sufficient to interfere with routine activities. Prescription drug therapy may have been employed to treat the AE.
- SEVERE: Impossible to perform routine activities. Prescription drug therapy and/or hospitalization may have been employed to treat the AE

10.7.3 Relationship of Adverse Event

Causal relationship to the study product will be evaluated by the Investigator as follows:

- Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility, or the subject did not take the study product.
- Related: A causal relationship between the study treatment and the AE is a reasonable possibility, i.e. the relationship cannot be ruled out.

10.8 Serious Adverse Events

10.8.1 Definition of a Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose suggests a medically significant hazard, including any event that:

- Results in death: includes all deaths, even those that appear to be completely unrelated to study treatment (e.g., car accident where patient is a passenger).
- Is life-threatening: in the view of the Investigator, the patient is at immediate risk of death at the time of the event.
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Causes congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the serious outcomes listed above (e.g., intensive treatment in an emergency room, convulsions that do not result in hospitalizations).

Emergency Room visits that require medical or surgical intervention to prevent one of the other serious outcomes listed above are considered an SAE.

10.8.2 Reporting Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions

Investigator Reporting of SAEs

Adverse events which meet the above criteria for "Serious" will be reported to the Sponsor and IRB within 24 hours of notice whether or not they are considered expected or drug-related. All SAEs will be reported as per applicable regulations. All SAEs encountered during the study will be reported on the appropriate form and summarized in the final report.

Any SAEs should be reported to [redacted] within 24 hours after the Investigator's awareness.

Following is the contact information:

[redacted]

[redacted] will report any SAE to Sponsor.

Documentation of SAEs and follow-up information should be sent to the Sponsor within 24 hours from [redacted] being made aware of the SAE. Following is the contact information:

[redacted]

The Sponsor will be responsible for notifying the FDA of any SAEs. The Sponsor must notify FDA of fatal or life-threatening SUSARs as soon as possible, but no later than seven calendar days after knowledge by the sponsor and ensure that relevant follow-up information is

subsequently communicated within an additional eight calendar days. All other SUSARs not leading to death or a threat to life will be reported to the FDA as soon as possible but within a maximum of 15 calendar days of first knowledge by the Sponsor. Suspected unexpected serious adverse reaction reports do not need to be reported in an expedited manner to any other targets for submission besides FDA.

[redacted] will inform all the participating investigators of any SAEs and SUSARs reported at other study sites in a blinded manner. All relevant follow-up information concerning SUSARs will be reported by the Sponsor to the FDA as soon as possible but within a maximum of 15 calendar days of first knowledge by [redacted] on behalf of the Sponsor.

When an SAE is classified as SUSAR, the Sponsor as well as the [redacted] Medical Monitor must be contacted before breaking the blind for any patient. The blind should be broken by the Sponsor's Pharmacovigilance Department only for that specific patient (regulatory unblinding). A duplicate copy of the unblinding envelopes shall be retained by the Sponsor's Clinical Safety/ Pharmacovigilance department in order to be able to perform regulatory unblinding (peek blind) in case SUSAR reporting to Authorities needs to be performed. The blind will be maintained for persons responsible for the ongoing conduct of the study (such as the study management, monitors, and Investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometric personnel. Unblinded information will only be accessible to those who need to be involved in the safety reporting to relevant Competent Authority and Central Ethics Commitee.

11.0 STATISTICAL METHODS

11.1 Statistical Plan

A Statistical Analysis Plan (SAP), detailing the intended statistical analyses of the study data, will be prepared as a separate document and finalized before database lock. Any deviation from the original SAP will be described and justified in the final report, as appropriate. The procedure for accounting for missing, unused and spurious data will be included in the SAP.

All statistical analyses will be performed by [redacted] and conducted using the Statistical Analysis System (SAS®), Version 9.4 or higher. [redacted]

11.2 Determination of Sample Size

For the primary endpoint analysis (proportion of patients in the PP population that are identified as Responders at the end of the treatment period evaluated on Day 8 or Day 9), sample size is estimated for therapeutic equivalence of the Test to the Reference product and superiority of each of the active treatments groups over Placebo. [redacted]

[redacted]

[redacted]

[redacted]

11.3 Study Populations

11.3.1 Per-Protocol Population

The PP population will include all randomized patients who:

- Met the inclusion/exclusion criteria as defined in this protocol at Visit 1 and 2.
- Did not have any significant protocol deviations.
- Did not develop any concurrent vaginal infection or illness exhibiting symptoms similar to VVA, or symptoms that in the Investigator's opinion would interfere with primary and secondary endpoint assessments.
- Completed the last study visit (Visit 3) within window (Day 8 or Day 9).
- Were compliant with dosing between 75%-125% of the required doses.

Any patient who withdraws from the study because of lack of efficacy will be included in the PP population as a Non-Responder, provided they did not have any significant protocol deviations that would affect treatment evaluation.

11.3.2 Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population will include all randomized patients who:

- Administered at least one dose of randomized study product.
- Had a post-randomization evaluation.

11.3.3 Safety Population

The safety population will include all patients who are randomized and received study product.

11.4 Baseline Comparability

Baseline comparability of all treatment groups will be evaluated separately in the PP, mITT and Safety populations. The following baseline demographics (determined from their initial study visit) will be evaluated:

- Age (years)
- Gender (male/female)
- Ethnicity (Hispanic/non-Hispanic)
- Race (White, Black/African American, Native Hawaiian or Other Pacific Islander, Asian, American Indian or Alaska Native, Other)
- Natural or surgical menopause
- Duration of postmenopausal status
- Baseline signs and symptoms
- Baseline % of the three major vaginal wall cell types (basal/parabasal cells, intermediate cells and superficial cells)
- Vaginal pH

Summary tables by treatment group will be presented. Continuous variables will be summarized using descriptive statistics (number of observations, median, minimum, maximum, mean and standard deviation). Categorical variables will be summarized using frequencies and percentage. Baseline treatment comparisons will be presented using Chi-Square or Cochran-Mantel-Haenszel (CMH) tests for the categorical variables, and Analysis of Variance (ANOVA) for the continuous variables.

All data will be listed by treatment and patient.

11.5 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients in each treatment group that are identified as Responders at the end of the treatment period evaluated on Day 8 or Day 9.

A "Responder" is defined as a patient with at least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology AND vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5.

Secondary Efficacy Endpoint

The secondary efficacy endpoint is the proportion of patients in each treatment group that are considered a Treatment Success at the end of the treatment period evaluated on Day 8 or Day 9.

A "Treatment Success" is defined as a score of 0 or 1 on Day 8 or Day 9 for the symptom identified at baseline as the most bothersome. This evaluation will be based on (one) patient self-assessed symptom of VVA (vaginal dryness, vaginal and/or vulvar irritation/itching, dysuria, or vaginal pain associated with sexual activity) on a scale of 0 to 3 where 0 = none and 3 = severe. Evaluation of vaginal bleeding during sexual activity will be based on a Score of 1 (presence) if it is identified by the patient as the most bothersome symptom at baseline and a score of 0 (absent) on Day 8 or Day 9. Refer to Appendix B for rating scales.

11.6 Efficacy Analyses

Primary Endpoint Analysis

Therapeutic Equivalence:

Therapeutic equivalence will be evaluated for both primary and secondary endpoints in the PP population. If the 90% confidence interval (calculated using Yates' continuity correction) on the absolute difference between the proportion of patients identified as Responders in the Test and Reference groups (p_T - p_R) is contained within the range [-20%, +20%] then therapeutic equivalence of the Test product to the Reference product will be considered to have been demonstrated.

The same statistical approach will be conducted for analysis of the secondary endpoint in the PP population.

To declare therapeutic equivalence of the Test product to the Reference product, equivalence must be demonstrated for only the primary endpoints in the PP population.

Superiority to Placebo

Superiority of the Test and Reference products against the Placebo product for the primary endpoint will be evaluated in the mITT population using last observation carried forward (LOCF). If the proportion of Responders in the Test and the Reference product groups is numerically and statistically superior to that of the Placebo ($p < 0.05$; using a two-sided CMH test, stratified by clinical site) then superiority of the Test and Reference products over Placebo will be concluded.

The same statistical approach will be conducted for analysis of the secondary endpoint in the mITT population.

To declare superiority of the Test and Reference products over Placebo, their superiority must be demonstrated for only the primary endpoint in the mITT population.

Treatment-by-Site Interaction and Pooling of Clinical Sites

As this is a multiple-site study, the interaction of treatment-by-site may be evaluated for the primary efficacy endpoint in the PP population for equivalence testing. The treatment-by-site interaction will be evaluated by the Breslow-Day test for homogeneity of the odds ratio at the 5% significance level ($p < 0.05$, 2-sided). A site(s) with a low enrollment rate(s) may be pooled with its geographically closest site, so as to avoid bias in the stratification of the sites in the CMH test and in the estimation of a treatment-by-site interaction effect. The pooling will be done for low enrolling sites that account for less than 4-7% of the total number of patients in the PP population at the site with the highest

enrolling rate in the PP population. If the treatment-by-site interaction term is found to be statistically significant ($p < 0.05$) for the primary endpoint, then the interaction term will also be assessed for clinical relevance before pooling the data across sites. This will include examination of "Responder" rates at each site where sample sizes per treatment may be influential in the assessment of the interaction

11.7 Safety Analysis

Adverse events will be classified using standard MedDRA terminology Version 20.0 or higher and summarized by treatment group. Summary tables comparing the type, incidence, date of onset, date of resolution, severity, action taken, outcome and Investigator's opinion of relationship to the study product will be prepared by treatment group. If sufficient data exist, AE frequencies will be compared between treatments using Fisher's exact test or a similar test.

Signs and symptoms of VVA will not be considered AEs, unless in the Investigator's opinion, they have increased in frequency and/or severity to such an extent that the Investigator/patient considers that it is in the patient's best interest to be dropped from continued participation in the study and given alternative therapy for their condition.

Concomitant medication use during the study will be tabulated by patient.

12.0 REGULATORY OBLIGATIONS

12.1 Institutional Review Board

The study protocol, ICF, Investigator's Brochure, or package insert (as applicable), and any specific advertising will be submitted to, and approved by, an IRB before the start of the study. A form must be signed by the chairman or designee of the IRB noting the approvals. This notification of the board's approval along with a description by profession and gender of the board's composition will be provided to the Sponsor.

12.2 Study Documentation

This study will be conducted in compliance with the protocol; Good Clinical Practices and all applicable regulations, including the Federal Food, Drug and Cosmetics Act, US applicable Code of Federal Regulations (title 21), parts 50, 56, 312, 320, and any IRB requirements relative to clinical studies; and the Declaration of Helsinki, June 1964, as modified by the 64th World Medical Association General Assembly, October 2013.[16,20-22] The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

12.2.1 Protocol

The Investigator indicated on FDA Form 1572 will act as the Principal Investigator at each study site. Protocols will be noted as approved by placement of the [redacted] Representative's signature on the cover page. The Sponsor of the study will also approve the protocol by having a study-responsible individual sign the protocol cover page. The Principal Investigator will sign the protocol signature page indicating their agreement to conduct the study according to the protocol.

12.2.2 Informed Consent

An ICF that includes all of the relevant elements currently required by FDA and local state regulations will be provided to each prospective study patient before enrollment into the study. The type and method of study, tests to be administered, any potential or possible hazards, and the patient's right to withdraw from the study at any time will be explained to the patients by the Investigator or designee. Once the Investigator or designee is assured that an individual candidate understands the implications of participating in this study, the patient will be asked to give consent by signing and dating in the appropriate areas of the ICF. The Investigator or designee will also sign and date the form, along with a staff member who will sign the ICF as a witness to verify that the patient has indeed received information. If any other language is required, translation will be performed by a certified translator. A copy of the ICF will be provided to the patient.

12.2.3 Protocol and Informed Consent Changes

Sponsor approved changes to the protocol or the ICF will be implemented as revisions to the original documents and will require additional review and approval by the IRB. Revisions to the original protocol will be documented in amendments, incorporated as a preface to the new version. Any revision that substantially alters the study design or increases potential risk to the patient requires the patient’s consent to continue in the study. The approvals will be processed in accordance with the established IRB procedures. Copies of all protocol and ICF amendments/revisions, along with letters noting IRB approval, will be submitted to the Sponsor.

12.2.4 Source Documents and Electronic Case Report Forms

All patients will be identified by initials, date of birth and a unique patient number. Source documents will be used to record all study-related data. Source document entries will be used to complete electronic case report forms (eCRFs). A set of eCRFs will be completed for each patient randomiazed in the study. All data and eCRFs will be reviewed, evaluated and signed by the Investigator.

The original source documents and a copy of the corresponding eCRFs will be retained by the Investigator. Patients who terminate early from the study will have the Visit 3 (End of Study) source/eCRF completed.

12.2.5 Drug Accountability

All study product receipt, inventory, dispensing, dosing and reconciliation records will be maintained in compliance with federal regulations. The study product will be dispensed to qualified study patients according to established procedures. At the end of the study (after the database has been locked) all used and unused study product will be returned to Sponsor or designee.

12.2.6 Drug Storage

Study product will be stored at controlled room temperature protected from temperatures in excess of 40 ºC (104 ºF) in a secure place with access by authorized individuals only. The Investigator will be responsible for maintaining accurate records of drug receipt, dispensing, and return. At the end of the study, all partially used and unused study product will be returned to Sponsor's designee.

Retention of Reserve Samples

Each Investigator will randomly remove at least one block of study product and keep for retention. [redacted]

12.2.7 Pregnancies

If following initiation of study participation, it is subsequently discovered that a study patient is pregnant or may have been pregnant since the initiation of study participation (i.e. since the signing of ICF), the study product will be permanently discontinued. The Principal Investigator or designee must immediately notify the Medical Monitor of this event. Reporting timelines and [redacted]/Sponsor contact will be consistent with SAE reporting guidelines (i.e., pregnancies will be reported to the Sponsor/[redacted] within 24 hours to the contacts listed in section 10.8.2).

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient. Other appropriate pregnancy follow-up procedures should be considered if indicated. All follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome will be communicated as per the above guidelines. Infants should be followed for a minimum of eight weeks after birth.

12.2.8 Reporting Safety Information to the IRB

The Investigator must promptly report to the Investigator's IRB all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs occurring during the study, regardless of the assessed causality.[23]

12.2.9 Record Retention

All drug accountability records, eCRFs, source data and related regulatory documents must be retained for at least two years following completion of the study or Test product approval for marketing by the FDA.

12.2.10 Study Monitoring and Auditing

[redacted] will be responsible for monitoring the study according to Good Clinical Practice and applicable regulations. Monitoring visits are for the purpose of confirming adherence to the protocol and to verify complete and accurate data collection. The clinical site will make all

records associated with the study available to [redacted] representative during such visits and audits.

The study may be subject to audit by the Sponsor, Sponsor Representative or by regulatory authorities. If such an audit occurs the Investigator must agree to allow access to required patient records. By signing this protocol, the Investigator grants permission to personnel from the Sponsor, its representatives and appropriate regulatory authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of study procedures.

12.2.11 End of the Trial

The end of the trial is defined as the time at which the last patient has completed their last visit in the study. Upon completion of the study, the study product will no longer be available to the patient but the Investigator can, at their discretion, discuss alternative treatments with the patient.

12.2.12 Clinical Study Report

At the end of the study a full report per requirements of Sponsor and regulatory authorities will be prepared which will include a narrative of the clinical conduct and results of the study, a statistical report including a description of the analysis performed, and other documentation as may be appropriate. The report will be in electronic format according to eCTD and International Conference on Harmonisation formatting standards and guidelines.[24]

13.0 REFERENCES

1 [redacted]

20 FDA. 21CFR Part 50 Protection of Human Subjects. *Department of Health and Human Services,*

[redacted]

14.0 APPENDICES

14.1 APPENDIX A: Clinical Laboratory Testing

CLINICAL LABORATORY TESTING

As part of the Screening Procedures the blood and cytology samples will be obtained for the following laboratory evaluations:

Serum FSH

Fasting Triglycerides

Vaginal Cytology

PAP Smear (as appropriate)

All samples will be sent to the central laboratory:

14.2 APPENDIX B: Definitions and Severity ratings for Signs and Symptoms

Vaginal Dryness		
No lubrication or secretions noted on perineum or after wiping; if sexually active loss of lubrication during coitus.		
Score	Severity	Description
0	None	No noticeable lack of vaginal lubrication or secretions reported or observed
1	Mild	Episodic loss of lubrication/secretions or noticed some reduction in general secretions, does not interfere with daily activities
2	Moderate	Symptom present most of the time, and noticeable but overall is tolerable and does not interfere with daily activities
3	Severe	Very minimal or no natural vaginal lubrication/secretions almost all of the time and interferes with normal activities

Vaginal/Vulvar Irritation/Itching		
Scratching or sand paper type feeling in vaginal/vulvar area. May feel uncomfortable with clothing or undergarments touching the perineum.		
Score	Severity	Description
0	None	No irritation or itching reported.
1	Mild	Occasional irritation/itching but does not interfere with daily activities
2	Moderate	Frequent irritation/itching that can be uncomfortable but generally does not interfere with daily activities
3	Severe	Very frequent or continuous irritation/itching of the vaginal area, may interfere with daily activities.

Dysuria		
Pain or discomfort during urination		
Score	Severity	Description
0	None	No pain or discomfort during urination reported.
1	Mild	Occasional or slight discomfort during urination but tolerable
2	Moderate	Some discomfort during urination at least 50% of the time which can be painful but overall tolerable.
3	Severe	Urination nearly always painful, usually intolerable and causing disruption to daily activities

Vaginal Pain during Sexual Activity		
Suffers discomfort or pain during sexual activity that may be restrictive.		
Score	Severity	Description
0	None	No discomfort or pain
1	Mild	Some feeling of vaginal soreness or pain, during or after sexual activity. Does restrict frequency of or type of sexual activity.
2	Moderate	Vaginal pain during sexual activity such that frequency and type of sexual activity have been disrupted. Lubrication may be needed for penetration
3	Severe	Vaginal penetration very painful and impossible without vaginal lubrication. Discomfort such that frequency of sexual activity significantly reduced.

Vaginal bleeding during or after sexual activity		
Score	Severity	Description
0	Absent	No vaginal bleeding observed
1	Present	Bleeding observed during or soon after vaginal activity

At each visit each patient must also clearly identify which is the most bothersome sign/symptom to her, even if she rates two or more symptoms the same severity rating.

14.3 APPENDIX C: Product Insert for Estrace®

ESTRACE® Cream
(estradiol vaginal cream, USP, 0.01%)

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

Estrogen-Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see **WARNINGS, Malignant Neoplasms, Endometrial Cancer**].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**, and **Probable Dementia**].

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [see **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**].

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg) -alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**, and **Probable Dementia**].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [see **CLINICAL STUDIES** and **WARNINGS, Cardiovascular Disorders**].

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see **CLINICAL STUDIES** and **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**].

Breast Cancer

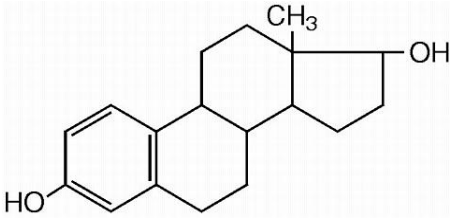
The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see **CLINICAL STUDIES** and **WARNINGS, Malignant Neoplasms, Breast Cancer**].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

DESCRIPTION

Each gram of ESTRACE (estradiol vaginal cream, USP, 0.01%) contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and di-glycerides, hypromellose 2208 (4000 cps), sodium lauryl sulfate, methylparaben, edetate di-sodium and *tertiary*-butylhydroquinone. Estradiol is chemically described as estra-1,3,5(10)-triene-3, 17(beta)-diol. It has an empirical formula of $C_{18}H_{24}O_2$ and molecular weight of 272.37. The structural formula is:



CLINICAL PHARMACOLOGY

Endogenous estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens

exist in a dynamic equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level.

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

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

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

Pharmacokinetics

Absorption

Estrogen drug products are absorbed through the skin, mucous membranes, and the gastrointestinal tract after release from the drug formulation.

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Metabolism

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

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Special Populations

No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

Drug Interactions

In vitro and in vivo studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4 such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

CLINICAL STUDIES

Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other cause. These substudies did not evaluate the effects of CE or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI estrogen-alone substudy was stopped early because an increased risk of stroke was observed, and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints.
Results of the estrogen-alone substudy, which included 10,739 women (average 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other), after an average follow-up of 7.1 years are presented in Table 1.

TABLE 1 -Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[b])	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events[c]	0.95 (0.78-1.16)	54	57
Non-fatal MI[c]	*0.91 (0.73-1.14)*	*40*	*43*
CHD death[c]	*1.01 (0.71-1.43)*	*16*	*16*
All Stroke[c]	1.33 (1.15-1.68)	45	33
Ischemic stroke[c]	1.55 (1.19-2.01)	38	25
Deep vein thrombosis[c,d]	1.47 (1.06-2.06)	23	15
Pulmonary embolism[c]	1.37 (0.90-2.07)	14	10
Invasive breast cancer[c]	0.80 (0.62-1.04)	28	34
Colorectal cancer[c]	1.08 (0.75-1.55)	17	16
Hip fracture[c]	0.65 (0.45-0.94)	12	19
Vertebral fractures[c,d]	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures[c,d]	0.58 (0.47-0.72)	35	59
Total fractures[c,d]	0.71 (0.64-0.80)	144	197
Death due to other causes[e,f]	1.08 (0.88-1.32)	53	50
Overall mortality[c,d]	1.04 (0.88-1.22)	79	75
Global index[g]	1.02 (0.92-1.13)	206	201

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[c] Results are based on centrally adjudicated data for an average follow-up of 7.1 years.
[d] Not included in "global index".
[e] Results are based on an average follow-up of 6.8 years.
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a "global index" defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes.

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE-alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 7 fewer hip fractures[1]. The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

No overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE-alone compared with placebo was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow-up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant differences in distribution of stroke subtypes or severity, including fatal strokes, in women receiving CE-alone compared to

placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined[2].

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy stratified by age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD *[hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)]* and overall mortality *[HR 0.71 (95 percent CI, 0.46–1.11)]*.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was also stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years.

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women-years in the group treated with CE plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 6.8 percent Black, 5.4 percent Hispanic, 3.9 percent Other), are presented in Table 2. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

TABLE 2 -Relative and Absolute Risk Seen in the Estrogen Plus Progestin Substudy of WHI at an Average of 5.6 Years[a,b]

Event	Relative Risk CE/MPA vs. Placebo (95% nCI[c])	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99–1.53)	41	34
Non-fatal MI	*1.28 (1.00–1.63)*	*31*	*25*
CHD death	*1.10 (0.70–1.75)*	*8*	*8*
All Strokes	1.31 (1.03–1.68)	33	25
Ischemic stroke	*1.44 (1.09–1.90)*	*26*	*18*
Deep vein thrombosis[d]	1.95 (1.43–2.67)	26	13
Pulmonary embolism	2.13 (1.45–3.11)	18	8
Invasive breast cancer[e]	1.24 (1.01–1.54)	41	33
Colorectal cancer	0.61 (0.42–0.87)	10	16
Endometrial cancer[d]	0.81 (0.48–1.36)	6	7
Cervical cancer[d]	1.44 (0.47–4.42)	2	1
Hip fracture	0.67 (0.47–0.96)	11	16
Vertebral fractures[d]	0.65 (0.46–0.92)	11	17
Lower arm/wrist fractures[d]	0.71 (0.59–0.85)	44	62
Total fractures[d]	0.76 (0.69–0.83)	152	199
Overall Mortality[f]	1.00 (0.83–1.19)	52	52
Global Index[g]	1.13 (1.02–1.25)	184	165

[a] Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
[b] Results are based on centrally adjudicated data.
[c] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[d] Not included in "global index."
[e] Includes metastatic and non-metastatic breast cancer, with the exception of *in situ* cancer.
[f] All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
[g] A subset of the events was combined in a "global index" defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified by age showed in women 50 to 59 years of age, a non-significant trend toward reduced risk for overall mortality *[HR 0.69 (95 percent CI, 0.44-1.07)]*.

Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg)-alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was

conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see **BOXED WARNINGS, WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**].

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47 percent were 65 to 69 years of age; 35 percent were 70 to 74 years; 18 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) plus MPA (2.5 mg) on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed types (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**].

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women [see **WARNINGS, Probable Dementia** and **PRECAUTIONS, Geriatric Use**].

INDICATIONS AND USAGE

ESTRACE (estradiol vaginal cream, USP, 0.01%) is indicated in the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

CONTRAINDICATIONS

ESTRACE (estradiol vaginal cream, USP, 0.01%) should not be used in women with any of the following conditions:

1. Undiagnosed abnormal genital bleeding.
2. Known, suspected, or history of cancer of the breast.
3. Known or suspected estrogen-dependent neoplasia.
4. Active DVT, PE or history of these conditions.
5. Active arterial thromboembolic disease (for example, stroke, MI) or a history of these conditions.
6. Known anaphylactic reaction or angioedema to ESTRACE (estradiol vaginal cream, USP, 0.01%).
7. Known liver dysfunction or disease.
8. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.
9. Known or suspected pregnancy.

WARNINGS

See **BOXED WARNINGS.**

Systemic absorption may occur with the use of ESTRACE (estradiol vaginal cream, USP, 0.01%). The warnings, precautions, and adverse reactions associated with oral estrogen treatment should be taken into account.

1. Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen-alone therapy. An increased risk of PE, DVT, stroke and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (e.g., hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (e.g., personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

a. Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year one and persisted [see **CLINICAL STUDIES].** Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years)[3].

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) [see **CLINICAL STUDIES]**. The increase in risk was demonstrated after the first year and persisted[3]. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

b. Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI and CHD death) was reported in women receiving estrogen-alone compared to placebo[4] [see **CLINICAL STUDIES**].

Subgroup analyses of women 50 to 59 years of age suggest a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years)[3].

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years)[3]. An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [see **CLINICAL STUDIES**].

In postmenopausal women with documented heart disease (n = 2,763), average age 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study; HERS), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty one (2,321) women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

c. Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to women receiving placebo (30 versus 22 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years[5] [see **CLINICAL STUDIES**]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was observed during the first year and persisted [6][see **CLINICAL STUDIES**]. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

2. Malignant Neoplasms

a. Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

b. Breast Cancer

The most important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE (0.625 mg)-alone was not associated with an increased risk of invasive breast cancer (relative risk [RR] 0.80) [7] [see **CLINICAL STUDIES**].

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years, for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups[8] [see **CLINICAL STUDIES**].

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-

alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline in about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

c. Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA was 4 versus 3 cases per 10,000 women-years [9]. In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

3. Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83-2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years [10] [see **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**].

In the WHIMS estrogen plus progestin ancillary study, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo.

After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. The relative risk of probable dementia for CE plus MPA versus placebo was 2.05 (95 percent CI, 1.21-3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years [10] [see **CLINICAL STUDIES** and **PRECAUTIONS, Geriatric Use**].

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progestin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [10] [see **PRECAUTIONS, Geriatric Use**].

4. Gallbladder Disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.

5. Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual Abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

7. Anaphylactic Reaction and Angioedema

Cases of anaphylaxis, which develop within minutes to hours after taking orally-administered estrogen and require emergency medical management, have been reported in the postmarketing setting. Skin (hives, pruritis, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) involvement has been noted.

Angioedema involving the tongue, larynx, face, hands and feet requiring medical intervention has occurred postmarketing in patients taking orally-administered estrogen. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop an anaphylactic reaction with or without angioedema after treatment with oral estrogen should not receive oral estrogen again.

8. Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema**.**

PRECAUTIONS

A. General

1. Addition of a Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestins with estrogens compared to estrogen-alone regimens. These include a possible increased risk of breast cancer.

2. Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

3. Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. Consider discontinuation of treatment if pancreatitis occurs.

4. Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in patients with impaired liver function. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

5. Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

6. Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogen- alone is prescribed.

7. Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

8. Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometrial implants have been reported in women treated post-hysterectomy with estrogen alone therapy. For patients known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

9. Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.

B. Patient Information

Physicians are advised to discuss the PATIENT INFORMATION leaflet with women for whom they prescribe ESTRACE (estradiol vaginal cream, USP, 0.01%).

C. Laboratory Tests

Serum FSH and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.

D. Drug-Laboratory Test Interactions

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone levels, as measured by protein-bound iodine (PBI), T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered. Women on thyroid replacement therapy may require higher dose of thyroid hormone.
3. Other binding proteins may be elevated in serum, i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).
4. Increased plasma high-density lipoprotein (HDL) and HDL_2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentration, increased triglycerides levels.

5. Impaired glucose tolerance.

E. Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer. (See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.)

Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

F. Pregnancy

ESTRACE should not be used during pregnancy [see **CONTRAINDICATIONS**].

There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

G. Nursing Mothers

ESTRACE should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the milk of women receiving estrogen therapy. Caution should be exercised when ESTRACE is administered to a nursing woman.

H. Pediatric Use

ESTRACE Vaginal Cream is not indicated in children. Clinical studies have not been conducted in the pediatric population.

I. Geriatric Use

There have not been sufficient numbers of geriatric patients involved in studies utilizing ESTRACE to determine whether those over 65 years of age differ from younger subjects in their response to ESTRACE.

The Women's Health Initiative Study

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age [see **CLINICAL STUDIES** and **WARNINGS].**

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast

cancer in women greater than 65 years of age [see **CLINICAL STUDIES** and **WARNINGS].**

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo [see **CLINICAL STUDIES** and **WARNINGS].**

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [10] [see **CLINICAL STUDIES** and **WARNINGS].**

ADVERSE REACTIONS

See **BOXED WARNINGS, WARNINGS** and **PRECAUTIONS**.

Systemic absorption may occur with the use of ESTRACE. The warnings, precautions, and adverse reactions associated with oral estrogen treatment should be taken into account.

The following adverse reactions have been reported with estrogen and/or progestin therapy.

1. Genitourinary System

Abnormal uterine bleeding or spotting; dysmenorrhea or pelvic pain, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in cervical secretion; cystitis-like syndrome; application site reactions of vulvovaginal discomfort including burning and irritation; genital pruritus; ovarian cancer; endometrial hyperplasia; endometrial cancer.

2. Breasts

Tenderness, enlargement, pain, nipple discharge, fibrocystic breast changes; breast cancer.

3. Cardiovascular

Deep and superficial venous thrombosis; pulmonary embolism; myocardial infarction; stroke; increase in blood pressure.

4. Gastrointestinal

Nausea, vomiting; abdominal cramps, bloating; increased incidence of gallbladder disease.

5. Skin

Chloasma that may persist when drug is discontinued; loss of scalp hair; hirsutism; rash.

6. Eyes

Retinal vascular thrombosis, intolerance to contact lenses.

7. Central Nervous System

Headache; migraine; dizziness; mental depression; nervousness; mood disturbances; irritability; dementia.

8. Miscellaneous

Increase or decrease in weight; glucose intolerance; edema; arthralgias; leg cramps; changes in libido; urticaria; exacerbation of asthma; increased triglycerides; hypersensitivity (including erythema multiforme).

OVERDOSAGE

Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of ESTRACE therapy together with institution of appropriate symptomatic care.

DOSAGE AND ADMINISTRATION

Use of ESTRACE alone or in combination with a progestin, should be limited to the shortest duration consistent with treatment goals and risks for the individual woman. Postmenopausal women should reevaluate periodically as clinically appropriate to determine if treatment is still necessary. For treatment of vulvar and vaginal atrophy associated with the menopause, the lowest dose and regimen that will control symptoms should be chosen and medication should be discontinued as promptly as possible. For women who have a uterus, adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal genital bleeding.

Usual Dosage: The usual dosage range is 2 to 4 g (marked on the applicator) daily for one or two weeks, then gradually reduced to one half initial dosage for a similar period. A maintenance dosage of 1 g, one to three times a week, may be used after restoration of the vaginal mucosa has been achieved.

NOTE: The number of doses per tube will vary with dosage requirements and patient handling.

HOW SUPPLIED

ESTRACE (estradiol vaginal cream, USP, 0.01%).
N 0430-3754-14: Tube containing 1 ½ oz (42.5 g) with a calibrated plastic applicator for delivery of 1, 2, 3, or 4 g.

Store at room temperature 20° to 25°C (59° to 77°F). Protect from temperatures in excess of 40°C (104° F).

Keep ESTRACE Vaginal Cream out of the reach of children.

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Allergan USA, Inc.

Irvine, CA 92612

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ESTRACE® CREAM **Rx only**
(estradiol vaginal cream, USP, 0.01%)

INFORMATION FOR THE PATIENT

Read this PATIENT INFORMATION before you start using ESTRACE Vaginal Cream and read what you get each time you refill your ESTRACE Vaginal Cream prescription. There may be new information. This information does not take the place of talking with your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about ESTRACE Vaginal Cream (an estrogen hormone)?

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb). Report any unusual vaginal bleeding right away while you are using ESTRACE Vaginal Cream. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline in brain function)
- Using estrogen-alone may increase your chances of getting strokes or blood clots
- Using estrogen-alone may increase your chance of getting dementia, based on a study of women age 65 years of age or older
- Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia
- Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots
- Using estrogens with progestins may increase your chance of getting dementia, based on a study of women age 65 years of age or older
- You and your healthcare provider should talk regularly about whether you still need treatment with ESTRACE Vaginal Cream

What is ESTRACE Vaginal Cream?

ESTRACE Vaginal Cream is a medicine that contains an estrogen hormone.

What is ESTRACE Vaginal Cream used for?

ESTRACE Vaginal Cream is used after menopause to:

- **Treat moderate to severe menopausal changes in and around the vagina**
  You and your healthcare provider should talk regularly about whether you still need treatment with ESTRACE Vaginal Cream to control these problems.

Who should not use ESTRACE Vaginal Cream?

Do not start using ESTRACE Vaginal Cream if you:

- **Have unusual vaginal bleeding**
- **Currently have or have had certain cancers**
  Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use ESTRACE Vaginal Cream.
- **Had a stroke or heart attack**
- **Currently have or have had blood clots**
- **Currently have or have had liver problems**
- **Have been diagnosed with a bleeding disorder**
- **Are allergic to ESTRACE Vaginal Cream or any of its ingredients**
  See the list of ingredients in ESTRACE Vaginal Cream at the end of this leaflet.
- **Think you may be pregnant**

Tell your healthcare provider:

- **If you have unusual vaginal bleeding**
  Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.
- **About all of your medical problems**
  Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **About all the medicines you take**
  This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how ESTRACE Vaginal Cream works. ESTRACE Vaginal Cream may also affect how your other medicines work.
- **If you are going to have surgery or will be on bed rest.**
  You may need to stop using ESTRACE Vaginal Cream.

- **If you are breastfeeding**
  The estrogen hormone in ESTRACE Vaginal Cream can pass into your breast milk.

How should I use ESTRACE Vaginal Cream?

ESTRACE Vaginal Cream is a cream that you place in your vagina with the applicator provided with the cream.

- Take the dose recommended by your healthcare provider and talk to him or her about how well that dose is working for you
- Estrogens should be used at the lowest dose possible for your treatment only as long as needed. You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are using and whether you still need treatment with ESTRACE Vaginal Cream
- Step 1. Remove the cap from the tube. (There is no seal on tube)
- Step 2. Do not separate plunger from applicator.
- Step 3. Screw threaded end of applicator onto the open tube until secure.
- Step 4. Position upright in order to view the calibrated gram amounts.
- Step 5. Gently squeeze tube from the bottom to expel the prescribed amount of ESTRACE Vaginal cream into the applicator. As cream is squeezed out, plunger will rise to indicate amount of grams.
- Step 6. Unscrew applicator from tube.
- Step 7. Replace cap on tube.
- Step 8. Lie on back with knees drawn up. To deliver medication, gently insert applicator deeply into vagina and press plunger downward to its original position.
- Step 9. To cleanse applicator: Pull plunger to remove it from barrel. Wash with mild soap and warm water (DO NOT BOIL OR USE HOT WATER)

What are the possible side effects of ESTRACE Vaginal Cream?

Although ESTRACE Vaginal Cream is only used in and around the vagina, the risks associated with oral estrogens should be taken into account.

Side effects are grouped by how serious they are and how often they happen when you are treated.

Serious, but less common side effects include:

- Heart attack
- Stroke
- Blood clots
- Dementia
- Breast cancer
- Cancer of the lining of the uterus (womb)
- Cancer of the ovary
- High blood pressure
- High blood sugar
- Gallbladder disease
- Liver problems
- Enlargement of benign tumors of the uterus ("fibroids")
- Severe allergic reaction

Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:

- New breast lumps
- Unusual vaginal bleeding
- Changes in vision or speech
- Sudden new severe headaches
- Severe pains in your chest or legs with or without shortness of breath, weakness and fatigue
- Swollen lips, tongue or face

Less serious, but common side effects include:

- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach or abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection
- Reactions from inserting ESTRACE Vaginal Cream, such as vaginal burning, irritation, and itching

These are not all the possible side effects of ESTRACE Vaginal Cream. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

What can I do to lower my chances of a serious side effect with ESTRACE Vaginal Cream?

- Talk with your healthcare provider regularly about whether you should continue using

ESTRACE Vaginal Cream.

- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you. The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus.
- See your healthcare provider right away if you get vaginal bleeding while using ESTRACE Vaginal Cream.
- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else. If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.
- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease. Ask your healthcare provider for ways to lower your chances for getting heart disease.

General information about safe and effective use of ESTRACE Vaginal Cream

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use ESTRACE Vaginal Cream for conditions for which it was not prescribed. Do not give ESTRACE Vaginal Cream to other people, even if they have the same symptoms you have. It may harm them.

Keep ESTRACE Vaginal Cream out of the reach of children.

This leaflet provides a summary of the most important information about ESTRACE Vaginal Cream. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about ESTRACE Vaginal Cream that is written for health professionals. You can get more information by calling the toll free number 1-800-678-1605.

What are the ingredients in ESTRACE Vaginal Cream?

Each gram of ESTRACE Vaginal Cream contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and di-glycerides, hypromellose 2208 (4000 cps), sodium lauryl sulfate, methylparaben, edetate di-sodium and *tertiary*-butylhydroquinone.

HOW SUPPLIED

ESTRACE® (estradiol vaginal cream, USP, 0.01%).
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