Protocol [redacted] Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment 6	**07 December 2023**
Amendment 5	09 October 2023
Amendment 4	22 March 2023
Amendment 3	14 February 2023
Amendment 2	28 November 2022
Amendment 1	07 October 2022
Original	08 August 2022

Amendment 6 (07 December 2023)

Overall Rationale for the Amendment:

- Rationale for Amendment: Revised to update PV reconciliation address and clarification of reporting to the IRB and protocol deviations.

Section # Name	**Description of Change**	**Brief Rationale**
9.8.5 Reconciliation of SAEs & Pregnancy	Changed from: All communication regarding Safety Data Reconciliation should be directed to the [redacted] email address: [redacted] Changed to: All communication regarding Safety Data Reconciliation should be directed to the [redacted] email address: [redacted]	Email address changed

[redacted]
December 19, 2023
APPROVED

Amendment 5 (09 October 2023)

Overall Rationale for the Amendment:

- Rationale for Amendment: Revised to update instructions for sites outside of the US.

Section # Name	**Description of Change**	**Brief Rationale**
9.4.3 Investigational Medicinal Product Shipment, Storage and Retention	Added: If sites are instructed to maintain retention samples on-site, the site must ensure samples are maintained in a separate location (eg. can be stored in the same room as the investigational medicinal product for patient use, but must be placed in a separate area/container) so not to be confused with investigational medicinal product for patient use, and easily identifiable (eg. label or marking on the box to indicate as retention sample).	Sites outside US will maintain retention samples on site.
9.6.9 Serum FSH, Thyroid and Fasting Triglycerides	Changed from: central clinical laboratory Changed to: a clinical laboratory Added: US Sites will use a central clinical laboratory.	Sites outside US are able to use a local clinical laboratory for testing.
9.5.1	A minor variation in the screening window due to outstanding lab results may be acceptable in case-by-case basis as approved by the Sponsor.	Screening window allowance.

Amendment 4 (22 March 2023)

Overall Rationale for the Amendment:

- Rationale for Amendment: Revised to update Medical Monitor and adding clarification.

Section # Name	**Description of Change**	**Brief Rationale**
Medical Monitor	Change from: [redacted]	New Medical Monitor

	[redacted] Change to: [redacted]	
9.7 Adverse Events	Change from: Severity of each AE will be determined by the staff based on observation and questioning of the patients. Change to: Severity of each AE will be determined by an Investigator based on observation and questioning of the patients.	Revised to add clarification
Inclusion Criteria #9	Change from: Normal mammogram completed within 9 months before enrollment and a normal clinical breast examination prior to enrollment in the study. Change to: Normal mammogram completed within 9 months before randomization and a normal clinical breast examination prior to randomization in the study.	Revised to add clarification
Inclusion Criteria #10	Change from: 1. Patients who have underwent complete Hysterectomy, or in the case of patients with an intact uterus (including patients who underwent a partial hysterectomy), the later must have: a. A documented papanicolaou (PAP) smear conducted within 12 months before Screening with no findings that the Investigator believes	Revised to add clarification

	would contraindicate the use of topical vaginal estradiol. b. Documented vaginal ultrasonography results within 3 months before Screening to confirm an inactive endometrial lining, defined as endometrial thickness <4 mm. Change to: 1. Patients who have underwent complete Hysterectomy, or in the case of patients with an intact uterus (including patients who underwent a partial hysterectomy), the later must have: a. A documented papanicolaou (PAP) smear conducted within 12 months before randomization with no findings that the Investigator believes would contraindicate the use of topical vaginal estradiol. b. Documented vaginal ultrasonography results within 3 months before randomization to confirm an inactive endometrial lining, defined as endometrial thickness <4 mm.	

Amendment 3 (14 February 2023)

Overall Rationale for the Amendment:

- Rationale for Amendment: Revised to add guidance to patient restriction during the study. This is added to reduce drug exposure to your male sexual partner.

Section # Name	**Description of Change**	**Brief Rationale**
9.3.3 Restrictions During the Study	Added: If the sexual activity involves a male partner, patients should wait to have sexual intercourse with their male partner until 2-3 hours following administration of the study drug.	Revised to add restriction guidance

Amendment 2 (28 November 2022)

Overall Rationale for the Amendment:

- Rationale for Amendment: Revised to provide clarity on assessing IMP compliance and sexual intercourse if the Patient Diary is not returned and to provide clarity on Inclusion #10. Additional changes were made to correct typos and inconsistencies in the protocol.

Section # Name	**Description of Change**	**Brief Rationale**
9.4.6 Compliance	Added: If a subject does not return the patient diary at the final visit, every attempt will be made to retrieve it and have them share the patient diary at a later date (but complete the visit as planned). If the subject does not return the subject diary, but they return the IMP, the Independent Dispenser is allowed to assess IMP compliance based on patient interview and the quantity returned [redacted]	Revised to add clarification
Inclusion Criteria #10	Change from: Patients who have underwent complete Hysterectomy, or patients with an intact uterus (including patients who underwent a partial hysterectomy) must have: a. A documented papanicolaou (PAP) smear conducted within 12 months before Screening with no findings that the Investigator believes would contraindicate the use of topical vaginal estradiol. b. Documented vaginal ultrasonography results within 3 months before Screening to confirm an inactive endometrial lining, defined as endometrial thickness <4 mm. **Change to:**	Revised to add clarification

	Patients who have underwent complete Hysterectomy, or in the case of patients with an intact uterus (including patients who underwent a partial hysterectomy), the later must have: a. A documented papanicolaou (PAP) smear conducted within 12 months before Screening with no findings that the Investigator believes would contraindicate the use of topical vaginal estradiol. b. Documented vaginal ultrasonography results within 3 months before Screening to confirm an inactive endometrial lining, defined as endometrial thickness <4 mm.	

Amendment 1 (07 October 2022)

Overall Rationale for the Amendment:

- Rationale for Amendment: Revised inclusion/exclusion criteria based on FDA product Specific Guidance for Estradiol and protocol patient population. Additional changes were made to correct typos and inconsistencies in the protocol.

Section # Name	**Description of Change**	**Brief Rationale**
Inclusion Criteria #3	Change from: Have < 5% superficial cells on vaginal cytological smear. Change to: Have ≤ 5% superficial cells on vaginal cytological smear.	Revised base on FDA Product Specific Guidance for Estradiol
Inclusion Criteria #8	Change from: Baseline systolic blood pressure should be no greater than 140 mm Hg and diastolic blood pressure no greater than 80 mm Hg. Change to: Baseline systolic blood pressure should be no greater than 150 mm Hg and diastolic blood pressure no greater than 90 mm Hg.	Revised base on FDA Product Specific Guidance for Estradiol

Exclusion Criteria #4	Change from: History of cholestatic jaundice, hypertension, coronary heart disease or other serious heart problems, uncontrolled diabetes, hypercholesterolemia, hypercalcemia, hypoparathyroidism, hypertriglyceridemia, systemic lupus erythematosus, renal impairment, residual endometriosis post-hysterectomy, asthma, epilepsy, migraine, porphyria, hepatic hemangiomas. Change to: Significant history of cholestatic jaundice, hypertension, coronary heart disease or other serious heart problems, uncontrolled diabetes, hypercholesterolemia, hypercalcemia, hypoparathyroidism, hypertriglyceridemia, systemic lupus erythematosus, renal impairment, residual endometriosis post-hysterectomy, asthma, epilepsy, migraine, porphyria, hepatic hemangiomas 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.	Revised to add clarification
Exclusion Criteria #18	Change from: History or active presence of endocrine disease (except for controlled hypothyroidism or controlled non-insulin dependent diabetes mellitus). Patients who are on a stable thyroid medication prior to the study should have normal baseline thyroid function test results and expect not to have to change thyroid hormone regimen during the study. Change to: History or active presence of endocrine disease (except for controlled hypo- or hyper-thyroidism or controlled non-insulin dependent diabetes mellitus). Patients who are on a stable thyroid medication prior to the study should have normal baseline thyroid function test results and expect not to have to change thyroid hormone regimen during the study.	Revised to add clarification
Exclusion Criteria #26	Change from: Patients who have used vaginal hormonal products (rings, creams, gels) within the 4 weeks before Screening. Chante to:	Revised to add clarification

	Patients who have used vaginal hormonal products (i.e. rings, creams, gels) within the 4 weeks before Screening.	
Section 9.6.9	Changed from: At Visit 1, postmenopausal women with at least 12 months of spontaneous amenorrhea (women >55 years of age with history of hysterectomy without bilateral oophorectomy prior to natural menopause, or 6 months of spontaneous amenorrhea) will have serum FSH levels tested to confirm FSH levels >40 MIU/mL. Serum FSH will be evaluated by a central clinical laboratory. Changed to: At Visit 1, postmenopausal women aged 40-54 years with history of hysterectomy without bilateral oophorectomy prior to natural menopause with at least 12 months of spontaneous amenorrhea or postmenopausal women aged 40-75 years with at least 6 months of spontaneous amenorrhea will have serum FSH levels tested to confirm FSH levels >40 MIU/mL. Serum FSH will be evaluated by a central clinical laboratory.	Revised to provide clarity for FSH testing

1.0 Title Page

Drug Product	Estradiol 4 mcg vaginal insert
Study Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Inserts 4 mcg (Teva Pharmaceuticals, Inc.) with IMVEXXY® (estradiol vaginal inserts) (TherapeuticsMD, Inc.) in the Treatment of Dyspareunia in Women with Vulvar and Vaginal Atrophy
Population	Approximately 1026 postmenopausal females 40 to 75 years of age with moderate to severe dyspareunia with vulvar and vaginal atrophy (VVA).
Study Design	Randomized, double-blind, placebo-controlled, parallel-designed, multiple-site, bioequivalence study with clinical endpoints.
Sponsor	Teva Pharmaceuticals, Inc.
Protocol Number	[redacted]
[redacted]	[redacted]
Amendment No.	4
Protocol Date	22 March 2023

This document is a confidential communication of [redacted] and Teva Pharmaceuticals, Inc. Receipt of this document constitutes an agreement by the recipient that no unpublished information contained herein will be disclosed without written approval from [redacted] and Teva.

2.0 Key Study Personnel and Facilities

Sponsor:	Teva Pharmaceuticals, Inc. 400 Interpace Pkwy, Building A Parsippany, NJ 07054
CRO:	[redacted]
Sponsor's Representative:	[redacted]
CRO Representative:	[redacted]
Medical Monitor:	[redacted]
Biostatistician:	[redacted]

Drug Labeling, Packaging and Shipping:	[redacted]
Retention Sample Storage:	
Randomization Schedule	

3.0 Protocol Signature Page

We, the undersigned, have carefully read this protocol and agree that it contains all the necessary information required to conduct the study. The study will be performed according to this protocol, all applicable Food and Drug Administration (FDA) regulations, ICH guidelines and Good Clinical Practice standards.

[redacted]

Investigator Signature Page

I _____, agree to conduct protocol 71836003 in accordance with FDA regulations, ICH guidelines and Good Clinical Practice. I understand that no deviations from the protocol may be made without the prior permission of the Sponsor (Teva Pharmaceuticals, Inc.) or [redacted] the company managing the study.

_____ _____

Investigator (Sign) Date

_____

(Print)

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4.0 Synopsis

Protocol Number	71836003
Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Design, Multiple-Site Study to Evaluate the Therapeutic Equivalence of Estradiol Vaginal Inserts 4 mcg (Teva Pharmaceuticals, Inc.) with IMVEXXY® (estradiol vaginal inserts) (TherapeuticsMD, Inc.) in the Treatment of Dyspareunia in Women with Vulvar and Vaginal Atrophy
Objectives	The objectives of this study are to: 1. Evaluate the therapeutic equivalence of the Test product (estradiol vaginal inserts 4 mcg) from Teva Pharmaceuticals, Inc. to the marketed product IMVEXXY® (estradiol vaginal inserts 4 mcg) (TherapeuticsMD, Inc.) in the treatment of dyspareunia in women with vulvar and vaginal atrophy. 2. Demonstrate the superiority of the efficacy of the Test and Reference (active) products over that of Placebo (vehicle). 3. Compare the safety of Test, Reference and Placebo products.
Sponsor	Teva Pharmaceuticals, Inc.
Investigational Medicinal Products	Investigational Medicinal Products (IMP) include: • **Test**: Estradiol vaginal inserts 4 mcg [redacted] • **Reference**: IMVEXXY® (estradiol vaginal inserts) 4 mcg (TherapeuticsMD, Inc.) • **Placebo**: Placebo vaginal inserts [redacted] Study products will be supplied as soft gel capsules.
Dosage Regimen	Once daily for 14 days.
Route of Administration	Intravaginal
Randomization	1:1:1 (Test : Reference : Placebo)
Patient Population	Approximately 1026 postmenopausal females 40 to 75 years of age with moderate to severe dyspareunia with vulvar and vaginal atrophy (VVA).
Study Design	Randomized, double-blind, placebo-controlled, parallel-designed, multiple-site, bioequivalence study with clinical endpoints.
Study Conduct	Patients will administer IMP once daily, intravaginally, for 14 days and will visit the investigative site for a total of three scheduled visits. • **Visit 1**: Screening (Day -21 to -1)

	• **Visit 2**: Randomization (Day 1) • **Telephone Contact:** (Day 7 to 9) • **Visit 3:** End of Study (Day 15 ± 2) or Early Termination
Inclusion Criteria	1. Signed, IRB approved informed consent that meets all criteria of current FDA and local regulations. 2. Females aged 40-75 years inclusive who are postmenopausal, with at least: a. 12 months of spontaneous amenorrhea (women <55 year of age with history of hysterectomy without bilateral oophorectomy prior to natural menopause must have Serum follicle-stimulating hormone (FSH) level > 40 mIU/mL); or b. 6 months of spontaneous amenorrhea with FSH levels >40 mIU/mL; or c. At least 6 weeks postsurgical bilateral oophorectomy 3. Have ≤ 5% superficial cells on vaginal cytological smear. 4. Vaginal pH > 5.0. 5. Moderate to severe symptom of vaginal pain associated with sexual activity considered the most bothersome vaginal symptom (dyspareunia) of VVA by the patient at screening visit. (i.e., a VVA Symptom Self-Assessment Questionnaire score of 2 or 3) (Appendix B). 6. Women should be sexually active (for example, have sexual activity with vaginal penetration within approximately one month of screening visit). 7. [redacted] 8. Baseline systolic blood pressure should be no greater than 150 mm Hg and diastolic blood pressure no greater than 90 mm Hg. 9. Normal mammogram completed within 9 months before randomization and a normal clinical breast examination prior to randomization in the study. 10. Patients who have underwent complete Hysterectomy, or in the case of patients with an intact uterus (including patients who underwent a partial hysterectomy), the later must have: a. A documented papanicolaou (PAP) smear conducted within 12 months before randomization with no findings

	that the Investigator believes would contraindicate the use of topical vaginal estradiol. b. Documented vaginal ultrasonography results within 3 months before randomization to confirm an inactive endometrial lining, defined as endometrial thickness <4 mm. 11. In the opinion of the Investigator, the patient will comply with the protocol and has a high probability of completing the study.
Exclusion Criteria	1. Premenopausal, perimenopausal, pregnant or lactating patient or planning a pregnancy. 2. 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. 3. Any clinically significant laboratory finding that, in the Investigator's opinion, would contraindicate the use of estradiol or compromise patients' safety. 4. Significant history of cholestatic jaundice, hypertension, coronary heart disease or other serious heart problems, uncontrolled diabetes, hypercholesterolemia, hypercalcemia, hypoparathyroidism, hypertriglyceridemia, systemic lupus erythematosus, renal impairment, residual endometriosis post-hysterectomy, asthma, epilepsy, migraine, porphyria, hepatic hemangiomas 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. 5. History of Protein C, Protein S, or antithrombin deficiency, or other thrombophilic disorder. 6. Patients with known concurrent vaginal infections including but not limited to: Candida albicans, Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhea or Gardnerella vaginalis. 7. Patients with active vaginal herpes simplex infection or have had an outbreak within 40 days before Screening.

	8. History of sexual abuse that in the opinion of the investigator may interfere with the patient's assessment of vaginal pain with sexual activity. 9. Past or current diagnosis of endometrial hyperplasia. 10. Patients with known, suspected or current history of carcinoma of the breast. 11. Any patients with past or current undiagnosed vaginal bleeding or significant risk factors for endometrial cancer. 12. History of estrogen-dependent neoplasia (e.g., endometrial cancer). 13. Any patients with hypersensitivity to estrogens. 14. Liver impairment or disease or kidney dysfunction or disorder (e.g., chronic renal failure or hepatitis C). 15. History of thrombophlebitis, thrombosis, or thromboembolic disorders. 16. History of cerebrovascular accident, stroke, or transient ischemic attack. 17. History of Myocardial infarction or ischemic heart disease. 18. History or active presence of endocrine disease (except for controlled hypo- or hyper-thyroidism or controlled non-insulin [redacted] 19. Any clinically significant abnormalities on screening physical exam, assessments, ECG, or laboratory tests such as: a. Vulvar or vaginal inflammatory condition such as a contact or allergic dermatitis, lichen sclerosis, or other pathological findings. b. Presence of suspicious vulvar or vaginal lesions for dysplasia, malignancy, or other pathology other than atrophy. c. History of active or chronic pelvic pain. d. Painful genital warts or localized areas of ulceration. e. Interstitial cystitis. f. Unresolved findings suspicious for malignancy on the breast exam; incomplete mammogram result or unresolved findings suggestive of malignant changes or findings requiring follow-up on the pre-study mammogram.

	g. Patients with an intact uterus who have an endometrial thickness of 4mm or greater. 20. [redacted] 21. Taking inducers of CYP3A4 such as St. John's wort, anticonvulsants, phenylbutazone, rifampin, rifabutin, nevirapine and efavirenz. 22. Taking inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, nelfinavir and grapefruit juice. 23. Fasting triglyceride levels > 350 mg/dL. 24. History of radiation therapy or recent (within previous 6 weeks) surgical therapy to the vaginal or cervical areas. 25. Any known or suspected allergies that in the Investigator's opinion would compromise the safety of the patient. 26. Patients who have used vaginal hormonal products (i.e. rings, creams, gels) within the 4 weeks before Screening. 27. Patients who have used transdermal estrogen and/or progestin therapy within the 4 weeks before Screening. 28. Patients who have used oral estrogen, progestin, androgen or selective estrogen receptor modular (SERM) containing drug products within 8 weeks before Screening visit. 29. Intrauterine progestin therapy within 8 weeks before Screening. 30. Use of an intrauterine device within 12 weeks before screening visit. 31. Patients who have used estrogen pellet therapy or progestin implants/ injectable drug therapy within the 6 months before Screening. 32. [redacted] 33. Inability to understand the requirements of the study and the relative information or are unable or not willing to comply with the study protocol. 34. Patients who are unable or unwilling to give informed consent. 35. Current history of heavy smoking (more than 15 cigarettes per day) or use of e-cigarettes.

	36. Current use of marijuana. 37. Recent history of known alcohol or drug abuse, within one year start of the study. 38. Employees of the Investigator or research center or their immediate family members. 39. Receipt of any drug as part of a research study within 60 days before Screening. 40. Previous participation in this study.
Sample Size Determination	1026 eligible patients will be enrolled [redacted]
Efficacy Endpoints	The primary efficacy endpoints are: • % Responders in the Per Population for Responders (PPR), where a "Responder" is defined as a patient with: o At least a 25% reduction from baseline in the sum of % basal/parabasal + % intermediate cells on vaginal cytology o Vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5 • Mean change from baseline to Day 15 in dyspareunia score (the self-identified most bothersome symptom in women with VVA). 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 15. A "Treatment Success" is defined as a score of 0 or 1 on Day 15 for dyspareunia (the self-identified most bothersome symptom at baseline).
Statistical Analysis	<u>Therapeutic Equivalence:</u> Therapeutic equivalence of the Test product to the Reference product based on the primary endpoints will be evaluated in the PP population on Day 15 ± 2 (after 14 days of treatment). For the primary endpoint of response rate (cytology and pH), the 90% confidence interval will be calculated using Yates' correction on the

	absolute difference between the proportion of patients identified as Responders (primary endpoint) in the Test and Reference groups (p_T - p_R). Therapeutic equivalence of the Test product to the Reference product will be concluded if this confidence interval is contained within the range [-20%, +20%]. For the primary endpoint of change from baseline in dyspareunia score, the adjusted 90% confidence interval will be calculated for the Test/Reference ratio of the mean baseline-adjusted dyspareunia score using an ANCOVA model Therapeutic equivalence of the Test product to the Reference product will be concluded if the adjusted 90% confidence interval for the least-squares mean Test/Reference ratio is within 80.00-125.00% for the primary endpoint. <u>Superiority to Placebo</u> The superiority to Placebo will be evaluated for the primary endpoints in the mITT populations (mITTR and mITTD). The superiority of the Test and Reference products over Placebo for the primary endpoint of response rate (cytology and vaginal pH) is concluded if the proportion of Responders in the Test and the Reference product groups is superior to that of the Placebo at the 5% significance level ($p < 0.05$, two-sided) using a CMH test. The same statistical approach will be conducted for analysis of the secondary endpoint in the mITTD population. The superiority of the Test and Reference products over Placebo for the primary endpoint of mean change in dyspareunia score is concluded if the values for mean baseline-adjusted dyspareunia score are statistically superior to those respective values of the Placebo at the 5% significance level ($p < 0.05$, two-sided). The superiority of Test and Reference treatments over the Placebo will be evaluated in similar ANCOVA models for Test vs. Placebo and Reference vs. Placebo.
Safety Analysis	All patients who use IMP will be included in the comparative safety analysis. Adverse Events (AE) will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology and presented by treatment group. Summary tables listing the type, date of onset, date of resolution, incidence, severity, outcome, action taken, and Investigator's opinion of relationship to the study product will be presented by treatment group for AEs reported after randomization.

	Signs and symptoms of atrophic vaginitis 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 medications used during the study will be listed by patient.

5.0 Study Schematic

	Visit 1 Screening (Day -21 to Day -1)	**Visit 2** Randomization (Day 1)	**Telephone Contact** (Day 7-9)	**Visit 3** End of Study (Day 15 ± 2) or Early Termination
Informed Consent	X			
Baseline Demographics	X			
Medical History	X	X		
Vital Signs	X	X		X
VVA Signs and Symptoms*	X	X		X
Physical Exam (including breast and pelvic exam)	X			X
12-Lead ECG	X			
Vaginal Cytology	X			X
pH Testing	X			X
PAP Smear†	X			
Laboratory Sample Collection**	X			X

Mammogram‡	X			
Vaginal Ultrasound§	X			
Concomitant Medications	X	X		X
Inclusion/Exclusion Criteria Review	X	X		
Dispense Study Product		X		
Collect Study Product				X
Dispense Patient Diary		X		
Patient Reminder Regarding Study Compliance[α]		X	X	
Collect/Review Patient Diary				X
Adverse Events	X	X	X	X

* Please see Appendix B.

** Fasted blood sample should be collected for FSH, triglycerides [redacted] laboratory testing at Screening.
[redacted]

† Patients who do not have documentation of a PAP smear completed within the last 12 months.

‡ Patients who do not have documentation of a mammogram completed within the 9 months 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.

[redacted]

6.0 List of Abbreviations and Terms

ADaM	Analysis Dataset Model
AE	Adverse Event
ºC	Celsius
CDISC	Clinical Data Interchange Consortium
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
ºF	Fahrenheit
FDA	Food & Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practices

ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITTD	modified Intent-to-Treat Population for Dyspareunia
mITTR	modified Intent-to-Treat Population for Responders
NDA	New Drug Application
OTC	Over-the-Counter
PAP	Papanicolaou
PPD	Per-Protocol Population for Dyspareunia
PPR	Per-Protocol Population for Responders
RS	Reference Standard
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
[redacted]	[redacted]
USA	United States of America
VVA	Vulvar and Vaginal Atrophy

7.0 Introduction

7.1 Disease Being Treated

Female menopause is generally characterized by various signs and symptoms associated with the age-related decline in reproductive hormone levels. There are many indications associated with the reduction in circulating estrogen levels, one of the most common being atrophic changes in the vaginal mucosa.[1] Up to 40% of postmenopausal women have symptoms of vulvar and vaginal atrophy (VVA). Despite the prevalence of this condition, only 20-25% of symptomatic women seek medical help. Therefore, this condition presents a significant opportunity for improving the quality of life of a large patient population.[2-4]

Vaginal atrophy is thinning, drying and inflammation of the vaginal walls due to a long-term and significant decline in circulating estrogen levels (~18 pg/mL) in the body.[2] Menopause has been

shown to be the leading cause of this condition. However, in non-menopausal women, VVA can result from interruption of ovarian estrogen production by radiation therapy, chemotherapy, oophorectomy or immunologic disorders. Various medications can also cause or contribute to vaginal atrophy, including tamoxifen, danazol (Danocrine®), medroxyprogesterone acetate, leuprolide (Lupron®) and nafarelin acetate (Synarel®).[2]

Symptoms of VVA include vaginal dryness, burning, irritation and leukorrhoea. A cytologic examination of a vaginal smear is typically used to confirm atrophy. Patients with positive diagnosis exhibit a decreased proportion (< 5%) of superficial (mature, protective) cells, compared to 30-60% in healthy pre-menopausal females. There is also a corresponding increase in intermediate and basal/parabasal (immature, fragile) cells. Moreover, patients also exhibit an increase in vaginal pH from a usually acidic (pH 3.5-4.0) to neutral (pH 6.0-8.0). This environment is more favorable for the growth of vaginal infections, which potentially exacerbate symptoms of VVA.[2,4]

7.2 Availability and Efficacy of Already Approved Therapies

Over-the-counter (OTC) vaginal moisturizers and water-based lubricants are considered the first line of therapy for VVA. For the more advanced and chronic cases, topical (vaginal) or oral estrogen therapy is often considered. There are a number of prescribed estrogen replacement therapies, approved by the Food and Drug Administration (FDA) for the treatment of VVA, including oral tablets (Estrace®, Femtrace®), transdermal patches (Vivelle-Dot®), transvaginal rings (Estring®), vaginal tablets (Vagifem®) and vaginal creams (Estrace®, Premarin®).[1,2]

Systemic (oral/transdermal patch) estrogen therapies have been shown to effectively treat symptoms of VVA, but bear undesirable side effects including increased risk of heart attacks, stroke, endometrial cancer and breast cancer.[5,6] Topical therapies (creams, transvaginal delivery systems) provide low doses of estrogen to the vaginal mucosa to provide local relief for the symptoms of VVA, while reducing the unwanted side effects associated with systemic delivery systems.[7, 8]

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]

7.3 Scientific and Statistical Considerations

Estrogen therapy has been demonstrated to significantly increase the percentage of superficial cells in the vagina. This increase in the percentage of superficial cells along with a corresponding

decrease in parabasal and intermediate cells has been demonstrated to be an accurate and reliable indicator of the status of estrogen levels in the vaginal wall, hence a measure of therapeutic efficacy of estradiol cream in the treatment of VVA. Cytologic assessment of cell samples from the lateral vaginal wall can be used to calculate the number/proportion of superficial, intermediate and parabasal cells. Elevated vaginal pH (pH > 5), monitored by a pH strip in the vaginal cavity, has also been shown to be a reliable indicator of vaginal atrophy.[2,5,7-10]

[redacted]

7.4 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.[13-15]

Patients receiving Placebo would not be harmed by the lack of active treatment over the 14 day study period. Any patient whose condition worsens can be discontinued and provided with alternative therapy.

7.5 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, 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.[16]

Qualified patients have a 33.3% chance they may be randomized to Placebo. Randomized patients will be enrolled in the study for 15 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.

8.0 Study Objectives

The objectives of this study are to:

1. Evaluate the therapeutic equivalence of the Test product (estradiol vaginal inserts 4 mcg) from Teva Pharmaceuticals, Inc. to the marketed product IMVEXXY® (estradiol) vaginal inserts 4 mcg from TherapeuticsMD, Inc. in the treatment of dyspareunia in women with vulvar and vaginal atrophy due to menopause.
2. Demonstrate the superiority of the efficacy of the Test and Reference (active) products over that of Placebo (vehicle).
3. Compare the safety of Test, Reference and Placebo products.

9.0 Investigational Plan

9.1 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 4 mcg vaginal insert (Teva Pharmaceuticals, Inc.) compared to IMVEXXY® (estradiol 4 mcg vaginal inserts (TherapeuticsMD, Inc.) in patients with moderate to severe dyspareunia, a symptom of VVA due to menopause. 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 1026 postmenopausal females 40 to 75 years of age with moderate to severe dyspareunia with VVA will be randomized to one of the three study products as follows:

- **Test**: Estradiol 4 mcg vaginal insert [redacted]
- **Reference**: IMVEXXY® 4 mcg estradiol vaginal inserts (TherapeuticsMD, Inc.)

- **Placebo**: Placebo (vehicle) vaginal insert [redacted]

Eligible patients will be randomized in a 1:1:1 (Test:Reference:Placebo) ratio and visit the investigative site for a total of three scheduled visits.

- **Visit 1**: Screening (Day -21 to -1)
- **Visit 2**: Randomization (Day 1)
- **Telephone Contact:** (Day 7 to 9)
- **Visit 3**: End of Study(Day 15 ± 2) or Early Termination

After randomization, patients will administer one vaginal insert once daily for 14 days. Evaluations will be performed in accordance with the study schematic. Safety assessments will include monitoring of adverse events (AEs), a physical examination, and vital sign measurements. Clinical assessments will include vaginal cytology, vaginal pH and VVA signs and symptoms scores.

9.2 Selection of Study Design

[redacted]

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Signed, IRB approved informed consent that meets all criteria of current FDA and local regulations.
2. Females aged 40-75 years inclusive who are postmenopausal, with at least:
   a. 12 months of spontaneous amenorrhea (women <55 year of age with history of hysterectomy without bilateral oophorectomy prior to natural menopause must have Serum follicle-stimulating hormone (FSH) level > 40 mIU/mL); or
   b. 6 months of spontaneous amenorrhea with FSH levels >40 mIU/mL; or
   c. At least 6 weeks postsurgical bilateral oophorectomy
3. Have ≤ 5% superficial cells on vaginal cytological smear.
4. Vaginal pH > 5.0.
5. Moderate to severe symptom of vaginal pain associated with sexual activity considered the most bothersome vaginal symptom (dyspareunia) of VVA by the patient at screening visit. (i.e., a VVA Symptom Self-Assessment Questionnaire score of 2 or 3) (Appendix B).
6. Women should be sexually active (for example, have sexual activity with vaginal penetration within approximately one month of screening visit).

7. [redacted]
8. Baseline systolic blood pressure should be no greater than 150 mm Hg and diastolic blood pressure no greater than 90 mm Hg.
9. Normal mammogram completed within 9 months before randomization and a normal clinical breast examination prior to randomization in the study.
10. Patients who have underwent complete Hysterectomy, or in the case of patients with an intact uterus (including patients who underwent a partial hysterectomy), the later must have:
    a. A documented papanicolaou (PAP) smear conducted within 12 months before randomization with no findings that the Investigator believes would contraindicate the use of topical vaginal estradiol.
    b. Documented vaginal ultrasonography results within 3 months before randomization to confirm an inactive endometrial lining, defined as endometrial thickness <4 mm.
11. In the opinion of the Investigator, the patient will comply with the protocol and has a high probability of completing the study.

9.3.2 Exclusion Criteria

1. Premenopasual, perimenopausal, pregnant or lactating patient or planning a pregnancy.
2. 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.
3. Any clinically significant laboratory finding that, in the Investigator's opinion would contraindicate the use of estradiol or compromise patients' safety.
4. Significant history of cholestatic jaundice, hypertension, coronary heart disease or other serious heart problems, uncontrolled diabetes, hypercholesterolemia, hypercalcemia, hypoparathyroidism, hypertriglyceridemia, systemic lupus erythematosus, renal impairment, residual endometriosis post-hysterectomy, asthma, epilepsy, migraine, porphyria, hepatic hemangiomas 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.
5. History of Protein C, Protein S, or antithrombin deficiency, or other thrombophilic disorder.

6. Patients with known concurrent vaginal infections including but not limited to: Candida albicans, Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhea or Gardnerella vaginalis.
7. Patients with active vaginal herpes simplex infection or have had an outbreak within 40 days before Screening.
8. History of sexual abuse that in the opinion of the investigator may interfere with the patient's assessment of vaginal pain with sexual activity.
9. Past or current diagnosis of endometrial hyperplasia.
10. Patients with known, suspected or current history of carcinoma of the breast.
11. Any patients with past or current undiagnosed vaginal bleeding or significant risk factors for endometrial cancer.
12. History of estrogen-dependent neoplasia (e.g., endometrial cancer).
13. Any patients with hypersensitivity to estrogens.
14. Liver impairment or disease or kidney dysfunction or disorder (e.g., chronic renal failure or hepatitis C).
15. History of thrombophlebitis, thrombosis, or thromboembolic disorders.
16. History of cerebrovascular accident, stroke, or transient ischemic attack.
17. History of Myocardial infarction or ischemic heart disease.
18. History or active presence of endocrine disease (except for controlled hypo- or hyper-thyroidism or controlled non-insulin dependent diabetes mellitus). [redacted]
19. Any clinically significant abnormalities on screening physical exam, assessments, ECG, or laboratory tests such as:
    a. Vulvar or vaginal inflammatory condition such as a contact or allergic dermatitis, lichen sclerosis, or other pathological findings. b. Presence of suspicious vulvar or vaginal lesions for dysplasia, malignancy, or other pathology other than atrophy.
    c. History of active or chronic pelvic pain.
    d. Painful genital warts or localized areas of ulceration.
    e. Interstitial cystitis.
    f. Unresolved findings suspicious for malignancy on the breast exam; incomplete mammogram result or unresolved findings suggestive of malignant changes or findings requiring follow-up on the pre-study mammogram.
    g. Patients with an intact uterus who have an endometrial thickness of 4mm or greater.
20. [redacted]

21. Taking inducers of CYP3A4 such as St. John's wort, anticonvulsants, phenylbutazone, rifampin, rifabutin, nevirapine and efavirenz.
22. Taking inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, nelfinavir and grapefruit juice.
23. Fasting triglyceride levels > 350 mg/dL.
24. History of radiation therapy or recent (within previous 6 weeks) surgical therapy to the vaginal or cervical areas.
25. Any known or suspected allergies that in the Investigator's opinion would compromise the safety of the patient.
26. Patients who have used vaginal hormonal products (i.e. rings, creams, gels) within the 4 weeks before Screening.
27. Patients who have used transdermal estrogen and/or progestin therapy within the 4 weeks before Screening.
28. Patients who have used oral estrogen, progestin, androgen or selective estrogen receptor modular (SERM) containing drug products within 8 weeks before Screening visit.
29. Intrauterine progestin therapy within 8 weeks before Screening.
30. Use of an intrauterine device within 12 weeks before screening visit.
31. Patients who have used estrogen pellet therapy or progestin implants/ injectable drug therapy within the 6 months before Screening.
32. [redacted]
33. Inability to understand the requirements of the study and the relative information or are unable or not willing to comply with the study protocol.
34. Patients who are unable or unwilling to give informed consent.
35. Current history of heavy smoking (more than 15 cigarettes per day) or use of e-cigarettes.
36. Current use of marijuana.
37. Recent history of known alcohol or drug abuse, within one year start of the study.
38. Employees of the Investigator or research center or their immediate family members.
39. Receipt of any drug as part of a research study within 60 days before Screening.
40. Previous participation in this study.

9.3.3 Restrictions During the Study

Patients will be instructed to restrict use of the following treatments/products 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 of known strong CYP3A4 inducers or inhibitors that, in the opinion of the Investigator, may affect estrogen metabolism. Examples of strong CYP3A4 inhibitors include erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice; strong CYP3A4 inducers include St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine and rifampin.
- [redacted]

[redacted]

9.3.4 Removal of Patients from the Study

Patients will be informed that they are free to withdraw from the study at any time for any reason. If necessary, the Investigator may withdraw a patient from the study to protect the health of that patient. If a patient terminates from the study early, all efforts will be made to complete Visit 3 study procedures. For early termination, the Investigator will fully document the reason for early termination. 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 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)
- Non-compliance with investigational medication product (eg. missing more than 2 consecutive doses)
- Pregnancy
- Patient drug code is unblinded
- 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
- Concomitant therapy is reported or required which is liable to interfere with the results of the study
- Patient is lost to follow up
- Participant enrolls in another clinical trial, or is found to have previously enrolled in this clinical trial

- Any other reason that may affect the outcome of the study or the safety of Patients
- Termination of the study by the Sponsor.

Patients who withdraw or are removed from the study will not be replaced.

In the case of those patients that have significant worsening of VVA, if the Principal Investigator determines that the Patient's condition has worsened to the degree that it is unsafe for the Patient to continue in the study, the Patient may be discontinued from the study as a treatment failure (non-responder) and the patient may be treated using the standard care if there is exacerbation of their VVA. Patients discontinued early for other reasons should be excluded from the PP populations, but included in the mITT populations, using LOCF.

Before a patient is considered to be lost to follow-up, the Principal Investigator will document all attempts to reach the Patient twice by telephone and will send a certified follow-up letter.

In the event that a patient discontinues from the study at any time due to an adverse event (AE), the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a patient, the Principal Investigator must strive to follow the patient until the adverse event has resolved, becomes clinically insignificant, is stabilized or the patient is lost to follow-up. In case of any serious adverse events, procedures for reporting must be followed.

If a patient contracts COVID-19 after enrollment into the study, she may continue in the study following local guidelines and procedures. Any concomitant medications should be documented. If the patient terminates early due to COVID-19, this should be documented as the early termination reason.

9.4 Treatments

9.4.1 Identity of the Investigational Medicinal Product

Investigational Medicinal Products include:

- **Test**: Estradiol 4 mcg vaginal insert [redacted]
- **Reference**: IMVEXXY® 4 mcg estradiol vaginal inserts (TherapeuticsMD, Inc.)
- **Placebo**: Placebo (vehicle) vaginal insert [redacted]

[redacted]

9.4.2 Treatment Administration

Eligible patients will be provided with verbal and written instructions on how to administer the study medication and receive IMP at Visit 2: Randomization, dispensed by the Independent Dispenser.

Patients will be required to self-administer one vaginal insert intravaginally once daily, at approximately the same time of day, for 14 consecutive days.

Patients should wash their hands prior to handling the study medication. The insert is to be administered intravaginally, inserted with the smaller end up for a depth of about two inches into the vaginal canal. Patients should administer 1 insert daily at approximately the same time daily. Patients should wash their hands following administration of the vaginal insert.

Patients will record daily application within the Sponsor provided diary. The patient's last dose should occur the day before visit 3. The patient should not dose on the day of visit 3.

9.4.3 Investigational Medicinal Product Shipment, Storage and Retention

The IMP will be randomized, packaged and blinded by an independent packaging team [redacted]. The labeling and packaging scheme will be outlined in a separate document by the Sponsor. The label content of IMP products will meet the requirements of ICH GCP guidelines, country specific guidelines and study protocol.

The IMP will be shipped to each Investigator's site from a central location. The 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 IMP will be maintained in accordance with federal regulations.

Storage Conditions

IMP will be stored in a secure, limited access location at 20-25°C (68-77°F), excursions permitted to 15-30°C (59-86°F). Any temperature excursions should be reported to [redacted] as soon as possible. [redacted] will in turn notify the Sponsor.

Retention

For every IMP shipment received at the site, the Investigator ([redacted] IMP from each shipment prior to dispensing to patients and documented accordingly. [redacted]. The number of kits in each block kept for retention will be noted on the study product accountability form, as a retention sample, in addition to the retention sample log. The selection process will ensure a sufficient amount of retention samples are retained as per Sponsor requirement. Each block selected for retention will be labeled as a retention sample and should not be dispensed to study patients. To ensure samples are not confused with investigational medicinal product for patient use and to ease the storage burden at a site, the randomly selected retention samples of investigational medicinal product may be transferred by the sites to an independent biorepository vendor, an independent third-party storage facility for long term storage. If sites are instructed to maintain retention samples in their site's pharmacy, the site must ensure samples are maintained in a separate location location (eg. can be stored in the same room as the investigational medicinal product for patient use, but must be placed in a separate area/container) so not to be confused with investigational medicinal product for patient use, and easily identifiable (eg. label or marking on the box to indicate as retention sample). The selected retention samples will be retained by the biorepository vendor under FDA regulations for a minimum of five years post approval or if not approved, 5 years after study completion.[19]

The site will return IMP, other than the randomly selected retention samples, to the central depot once notified by [redacted]. It is important that retention samples not be returned to [redacted], the Sponsor or the packaging company during or after completion of the study.

9.4.4 Method of Assigning Patients to Treatment Groups

All patients who sign an ICF will be assigned a patient number. The patient number will consist of the two-digit country number, followed by three-digit site number and three-digit screening number, beginning with 001 and continuing in ascending order at each investigative site (e.g. 10-101-001, 10-101-002, etc.). Randomization will be pre-planned according to a computer-generated randomization schedule, generated by an independent third-party. The packaging list taking into account this randomization will be shared with the independent packaging site [redacted] for appropriate randomizing, packaging and blinding. The randomization will be generated in "blocks", each containing three patients worth of study product (1 Test, 1 Reference, and 1 Placebo). Each of these study products (test/reference/placebo) will be [redacted]

At Visit 2, eligible patients will receive a randomized kit number (based on the treatment assigned), which will be recorded in the CRF. [redacted]

At the end of the study, after all the clinical data has been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician.

9.4.5 Study Blind

This is a double-blind clinical endpoint bioequivalence study. The Investigational Medicinal Product will be labeled and packaged such that neither the patient nor any Investigator or study personnel can identify the treatment. The Investigator, staff at the study site, study monitors, and data analysis/management personnel will be blinded to the trea [redacted]

In order to ensure the study blind the clinical packaging company [redacted] will hold the randomization scheme until database lock.

[redacted] The label will include at least the following fields: Protocol number, patient number, kit number, space for patient's initials, statement that the study product is for Investigational Use only, space for dispensing date, storage information, general directions and the Sponsor's name. Each shipment of investigational product will include an envelope which will contain individual kit randomization (unblinding) cards describing the actual treatment. The envelope should only be accessed and the unblinded card opened in case of medical emergency and should be kept at the site with the study documents when the study is completed. In addition, all patients will be provided with written instructions on how to use the study product.

Whenever possible, the [redacted] Medical Monitor must be contacted before breaking the blind for any patient. The unblinding envelopes should be stored in a secure location at all times and maintained at the site for all randomized patients after the completion of the study.

At the end of the study, after all the clinical data has been entered and the study database has been locked, a copy of the randomization schedule will be sent to the statistician by [redacted]. In addition, after the database has been locked, the packaging site will send each Investigative Site a sealed envelope containing the full study randomization scheme that should be retained with the study documents in the event of an FDA Inspection.

9.4.6 Compliance

Patients will be provided with a diary to record the time and date of dosing, concomitant medications and AEs. Patients who dose less than 75% or more than 125% of the intended doses, or miss more than two consecutive doses will be considered noncompliant with dosing. For example:

	Range	
Intended Doses	75%	125%
14	11	18

If a subject does not return the patient diary at the final visit, every attempt will be made to retrieve it and have them share the patient diary at a later date (but complete the visit as planned).

[redacted]

9.5 Study Conduct

Each site will follow their individual site policies and procedures regarding COVID-19 testing and symptoms to ensure the safety of clinical trial participants.

9.5.1 Visit 1: Screening (Day -21 to Day -1)

[redacted]

1. **Informed Consent:** patients willing to enter the study will read, ask any questions and sign the ICF.
2. **Medical History and Demographics:** review and record the patient's demographic and medical history, including acute, chronic, conditions related to the indication being studied, and general history within the last year.
3. **Concomitant Medications:** review and record the use of any current and past medications within the last six months.
4. **Vital Signs:** the patient's vital signs will be recorded (sitting blood pressure, pulse, temperature and respiration). Patients must remain in a seated position for at least 5 minutes before vital signs are obtained.
5. **Signs and Symptoms of VVA:** complete signs and symptoms of VVA rating scale (Appendix B).
6. **Physical Exam:** perform a general physical exam, including breast and pelvic exam.
7. **ECG:** perform a 12-lead screening ECG.
8. **Vaginal Cytology and pH:** obtain samples for vaginal cytology and pH. [redacted]
9. **PAP Smear:** obtain 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 a partial hysterectomy).
10. **Mammogram:** obtain results from a mammogram performed within the last nine months or schedule a mammogram.
11. **Fasted Screening Sample:** collect a fasted blood sample for FSH, [redacted] and triglyceride testing (Appendix A).
12. **Vaginal Ultrasound:** perform or schedule a vaginal ultrasound for patients with an intact uterus to review prior to randomization.
13. **Inclusion and Exclusion Review:** review of inclusion and exclusion criteria
14. **Adverse Events:** review and record any AEs since signing ICF.
15. **Schedule Next Visit**

9.5.2 Visit 2: Randomization (Day 1)

1. **Concomitant Medications:** review and record the use of any medications since the last visit.
2. **Medical History:** confirm and record the patient's medical history.
3. **Adverse Events:** review and record any AEs since signing ICF.
4. **Vital Signs:** the patient's vital signs will be recorded (sitting blood pressure, pulse, temperature and respiration).

5. **Signs and Symptoms of VVA:** complete Baseline signs and symptoms of VVA rating scale (Appendix B).
6. **Inclusion and Exclusion Review:** review of inclusion and exclusion criteria, and confirmation of eligibility.
7. **Dispense Patient Diary:** review and dispense patient dosing diary.
8. **Dispense Investigational Medicinal Product:** [redacted] review, provide instructions and dispense IMP to eligible patients.
9. [redacted]

9.5.3Telephone Contact

1. A telephone reminder should be made once between Day 7-9 [redacted] Patient compliance regarding dosing and restricted medications should also be reviewed and any changes in health discussed and recorded. [redacted]

9.5.4 Visit 3: End of Study (Day 15 ± 2)/Early Termination

1. **Concomitant Medications:** review and record the use of any medications since last visit.
2. **Adverse Events:** review and record any AEs since the last visit.
3. **Vital Signs:** the patient's vital signs will be recorded (sitting blood pressure, pulse, temperature and respiration).
4. **Signs and Symptoms of VVA:** complete signs and symptoms of VVA rating scale (Appendix B).
5. **Physical Exam:** perform a general physical exam, including breast and pelvic exam.
6. **Vaginal Cytology and pH:** obtain samples for vaginal cytology a [redacted]
7. **Lab Sample:** obtain sample for thyroid analysis, if applicable.
8. **Review and Collect Patient Diary:** review and collect patient diary for safety and compliance with the protocol.
9. **Collect Investigational Medicinal Product:** IMP will be reviewed and collected.

9.5.5 Unscheduled Visit

Unscheduled Visits are allowed at any time, for any reason, if in the Principal Investigator's opinion, it is warranted. If the Unscheduled Visit is due to an adverse event (AE), the Principal Investigator will determine whether additional visits are needed. If a Patient is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Termination Visit and all procedures scheduled for the Early Termination Visit will be performed. If the Unscheduled Visit is not an Early Termination Visit (i.e., the patient will continue to take part in the study), then the reason for unscheduled visit is documented and required procedures at the discretion of Investigator considering the reason for visit, will be performed with the exception of the collection of IMP and patient diaries from patients.

9.6 Study Procedures

9.6.1 Informed Consent

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 the IRB approved ICF. If any other language is required, translation will be performed by a certified translator and then approved by the IRB.

9.6.2 Medical History and Demographics

At Visit 1 patients will be asked to provide basic demographic information including: date of birth, gender, ethnicity and race. Patients will also be questioned about their overall medical history and medical history relevant to their VVA. Medical history should be collected including acute, chronic, and general history within the last year. Medications taken within the previous 6 months and ongoing should be recorded.

9.6.3 Vital Signs

The patient's vital signs will be recorded at each visit including sitting blood pressure, pulse, temperature and respiration.

Blood pressure (millimeters of mercury [mmHg]) and heart rate (beats per minute [bpm]) will be measured during the physical examination after 5 minutes rest in sitting position. Blood pressure and heart rate will be obtained preferably using the same arm and same equipment each time. If one arm has higher blood pressure than the other, that arm should be used for further blood pressure measurements (all further blood pressure measurements should be done on the same arm).
Body temperature will be measured using thermometer with digital display and recorded in degree Celsius (°C). Preferably the same method will be used each time.

Vital signs may be repeated at an individual study visit at the discretion of Site staff and according to Site standard procedures. All collected vital signs should be recorded in Source documents, with the final values recorded in the eCRF.

9.6.4 Signs and Symptoms of VVA

At each visit the Investigator or designee will question the patient regarding their symptoms of VVA, using the scale in Appendix B. The following patient self-assessed symptoms of vulvar and vaginal atrophy should be evaluated on a scale of 0 to 3 where 0 = none, 1=mild, 2=moderate and 3 = severe:

- Vaginal dryness
- Vaginal/ vulvar irritation and itching
- Dysuria
- Dyspareunia
- Vaginal bleeding (absent or present)

The severity of each symptom will be recorded on the source documents. The patients will be asked to identify their most bothersome symptom at Visit 1 and Visit 2. For inclusion in the study the most bothersome symptom at both Visit 1 and Visit 2 (Baseline) must be dyspareunia with a score of moderate (2) or severe (3). Signs and symptoms of atrophic vaginitis 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 prescribed an alternative treatment for their condition.

9.6.5 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 suspected or diagnosed with a 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 if they differ from the patient's baseline at Visit 1.

At a minimum, the physical examination will include the following: assessment of general appearance, skin, Head, Eyes, Ears, Nose and Throat (HEENT), heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. Height (measured in inches, only at Screening) and weight (measured in pounds), will also be recorded.

9.6.6 Vaginal Cytology and pH

At Visits 1 and 3, a vaginal cytology specimen will be collected by scraping the right and left lateral vaginal walls (mid-way between the fornix and introitus) with a spatula. The cells and mucus will be mixed and fixed according to the instructions provided by the central laboratory. Samples will be sent to the central laboratory for cytology testing.

The central laboratory will report the Visit 1 cytology results to the investigative site before randomization. The Visit 3 cytology reports will be received by the investigative site from the central laboratory following completion of the patient.

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. All Investigators will use the same type of provided pH paper.

9.6.7 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.

9.6.8 Mammogram

At Visit 1 Patients 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.

9.6.9 Serum FSH, [redacted] and Fasting Triglycerides

At Visit 1, postmenopausal women aged 40-54 years with history of hysterectomy without bilateral oophorectomy prior to natural menopause with at least 12 months of spontaneous amenorrhea or postmenopausal women aged 40-75 years with at least 6 months of spontaneous amenorrhea will have serum FSH levels tested to confirm FSH levels >40 MIU/mL. Serum FSH will be evaluated by a clinical laboratory US Sites will use a central clinical laboratory.

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

[redacted]

9.6.10 ECG

All patients will have a Screening ECG performed and interpreted locally by Investigator. Patients should have no clinically significant abnormalities as per the Investigator review to be eligible for inclusion in the study.

9.6.11 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.

9.6.12 Inclusion and Exclusion Criteria Review

At Visit 1 and 2, inclusion/exclusion criteria will be reviewed to ensure patients' eligibility for participation in the study.

[redacted]

9.6.13 Dispense Patient Diary

At Visit 2 the patient will be provided with a dosing diary to record IMP use, concomitant medications use and any adverse events experienced.

9.6.14 Dispense Investigational Medicinal Product

At Visit 2 after the Investigator has determined that the patient meets inclusion and exclusion criteria they can be randomized into the study. [redacted]

9.6.15 Adverse Events

Adverse events will be reviewed with the patient and recorded in the source documents.

9.6.16 Collect and Review Patient Diary

The patient diary will be collected at Visit 3/EOS and reviewed for completeness and accuracy with the patient. The patient diary will be reviewed for patient compliance with the IMP, AEs experienced, any concomitant medication, [redacted].

9.6.17 Collect and Review Investigational Medicinal Product

The IMP will be collected at Visit 3/EOS and reviewed for compliance and evidence the blind remains intact.

9.7 Adverse Events

The patients will be monitored throughout the study for any AEs after signing of Informed Consent. Adverse events will be collected through both solicited and unsolicited means and subsequently coded in tabular form using the MedDRA (Version 22.0 or higher). 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 an Investigator 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.

9.7.1 Adverse Event Definition

Any untoward medical occurrence in a patient or clinical investigation patient, regardless of whether it has a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of this study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an adverse event. Stable chronic conditions (such as arthritis) that are present before study entry and do not worsen during this study will not be considered adverse events.

Accordingly, an adverse event can include any of the following:

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other preexisting conditions
- events occurring during diagnostic procedures or during any washout phase of this study
- laboratory or diagnostic test abnormalities that result in the withdrawal of the patient from the study, are associated with clinical signs and symptoms or a serious adverse event, or require medical treatment or further diagnostic work up, or are considered by the investigator to be clinically significant (Note: Abnormal laboratory test results at the screening visit that preclude a patient from entering the study or receiving study treatment are not considered adverse events).
- side effects caused by drug interaction

Worsening of the disease under study will be measured by patient signs and symptoms scale and should be recorded as an adverse event only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

In this study, any adverse event occurring after the patient has signed the informed consent form until the end of follow-up period should be recorded and reported as an adverse event.

A treatment-emergent AE is any AE that occurs after initiation of study medication, or any event already present that worsens in either intensity or frequency following exposure to study medication.

9.7.2 Adverse Event Severity

The severity of the AE must be recorded as one of the choices on the following scales:

- Mild: Awareness of symptom but does not interfere with routine activities.
- Moderate: Discomfort sufficient to interfere with routine activities.
- Severe: Impossible to perform routine activities.

9.7.3 Adverse Event Relationship

Adverse events will be assessed for the relationship to the study drug (causality) according to the following scale:

TERM	DEFINITION	CLARIFICATION

No Reasonable Possibility (not related)	This category applies to those adverse events which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those adverse events, which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the test drug.	An adverse experience may be considered No Reasonable Possibility if it is clearly due to extraneous causes or when (must have two): • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.
Reasonable Possibility (related)	This category applies to those adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty or felt with a high degree of certainty to be related to the test drug.	An adverse experience may be considered Reasonable Possibility related if or when (at least two of the following): • It follows a reasonable temporal sequence from administration of the drug. • It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. • It follows a known pattern of response to the test drug.

9.8 Serious Adverse Events

9.8.1 Serious Adverse Event Definition

A serious adverse event (SAE) is any untoward medical occurrence that at any dose that results in any of the following outcomes or actions:

- 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 (ie, the patient was at risk of death at the time of the event); it does not refer to an event which hypothetically might have caused death if it were more severe.
- 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: meaning that hospital inpatient admission and/or prolongation of hospital stay were required for

treatment of an adverse event, or that they occurred as a consequence of the event. Hospitalizations scheduled prior to study entry will not be considered serious adverse events, unless there was worsening of the preexisting condition during the patient's participation in this study.

- Is a congenital anomaly or birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent one of the outcomes listed in this definition.
- Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

An adverse event that does not meet any of the criteria for seriousness listed above will be regarded as a non-serious adverse event.

9.8.2 Expectedness

The Sponsor's Pharmacovigilance Department will determine the expectedness for all serious adverse events. CRO and Investigators will not determine the expectedness.

An AE which is not included in the adverse events section of the relevant Safety Information Reference by its specificity, severity, outcome or frequency is considered an unexpected adverse event.

The reference safety information for this study is included in the attached prescribing information for IMVEXXY® (estradiol vaginal inserts) (TherapeuticsMD, Inc.) to use as reference for safety information is to be found in Appendix C.

9.8.3 Reporting of Serious Adverse Events

For adverse event recording, the study period is defined for each patient as that time period from signature of the informed consent form through the end of the study (including the follow up period).

All adverse events that occur during the defined study period must be recorded on the source documentation and CRF, regardless of the severity of the event or judged relationship to the study

drug. For serious adverse events, the Serious Adverse Event Form must also be completed and the serious adverse event must be reported immediately.

At each contact with the patient, the Investigator or designee must question the patient about adverse events by asking an open ended question such as, "Have you had any unusual symptoms or medical problems since the last visit? If yes, please describe." All reported or observed signs and symptoms will be recorded individually, except when considered manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and any test findings may be recorded collectively as a single diagnosis on the CRF and, if it is a serious adverse event, also on the Serious Adverse Event Form.

The onset and end dates and times, action taken regarding study drug, treatment administered, and outcome for each adverse event must be recorded on the source documentation.

The relationship of each adverse event to study drug treatment, and the severity and seriousness of each adverse event, as judged by the investigator, must be recorded as described below.

The clinical course of each adverse event will be monitored at suitable intervals until resolved or stabilized or returned to baseline, until the patient is referred for continued care to a health care professional or until a determination of a cause unrelated to the study drug or study procedure is made.

Adverse events will be coded according to MedDRA (Medical Dictionary for Regulatory Activities) and reported with respect to severity, duration, relationship to study medication(s), seriousness, outcome and action taken.

To satisfy regulatory requirements, all serious adverse events (as described in Section 10.8.1) that occur during the study period (including the protocol defined follow up period) regardless of judged relationship to treatment with the study drug, must be reported to Teva's Lead Safety Officer (LSO) on their PV team and CRO in parallel, by the Investigator. The event must be reported within 24 hours of when the Investigator learns about it. Completing the serious adverse event form (preferably in English) and reporting the event must not be delayed, even if not all the information is available. Subsequently, the CRO will communicate this information with the Teva Clinical Manager (Sponsor) and Medical monitor (MM) in parallel (and any other contacts identified in the Safety and Medical Monitoring Plan) within 1 business day (in some studies an SAE email distribution list may be used). If there is no LSO, then according to the SMMP.

If the SAE form is written in a local language, the LSO or CRO has to translate it into English. It is the responsibility of the CRO to translate to English if there is no LSO, and every effort should be made to perform this within 24 hours.
It should be considered that Day 0 is the day a Teva employee, or an employee of a company which Teva has a contractual arrangement with, becomes aware of a case which fulfils the minimum criteria for reporting. Note: If the Investigator calls a Teva representative or CRO representative, this will count as Day 0 and the contacted person must inform Teva immediately.
PLEASE NOTE THAT EMAIL IS THE PREFERRED MEANS OF COMMUNICATION.
All SAEs must be reported in parallel to the following persons:

- Appropriate Pharmacovigilance (PhV) unit:

[redacted]

&

[redacted]

Or

[redacted]

SAE reports should be scanned and sent to [redacted] for processing within 24 hours of the site becoming aware along with the above referenced phone call. [redacted] will be responsible for notifying the Sponsor of any SAEs.

- Sponsor's Contact person for this study (copy of the SAE details for information purposes only)

[redacted]

[redacted] must notify FDA of fatal or life-threatening SAE as soon as possible, but no later than seven calendar days from reporting the event by the Investigator. [redacted] will inform all the participating Investigators of any SAEs reported at other study sites within 15 days from the initial report.

For studies conducted in USA: It is the responsibility of the CRO to report a Serious Adverse Event (SAE) to the FDA within proper time constraints as per the Guidance for Industry and Investigators Safety Reporting Requirements for INDs and BA/BE Studies – *please refer to the most current version*. Confirmation of submission of this report must then be provided to Teva's study representative as well as their Pharmacovigilance department.

The timeliness for submission of expedite reports should be 15 days or 7 days (death cases) or as otherwise specified in local regulations.

These SAE reports must contain the following information, preferably using the template provided by the Sponsor:

A. Study name/number
B. Study Drug
C. Investigator details (name, phone, fax, e-mail)
D. Patient Number
E. Patient Initials when appropriate
F. Patient Demographics
G. Clinical Event
    1) Description
    2) Date of onset
    3) Treatment (drug, dose, dosage form)
    4) AE Relationship to study drug
    5) Action taken regarding study drug in direct relationship to the AE
H. If the AE was Fatal:
    1) Cause of death (whether or not the death was related to study drug)
    2) Autopsy findings (if available)

The SAE form and supportive documents should be typed (not hand-written) in English. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact. Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded within 24 hours of the information becoming available to the same address as the initial report. Patients who have had an SAE during the study must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Each report of a serious adverse event will be reviewed and evaluated by the investigator and the sponsor pharmacovigilance to assess the nature of the event and the relationship of the event to the study drug, study procedures, and to underlying disease.

Any serious adverse event will be reported to competent authority and ethics committee according to the country specific requirements and the responsibilities defined above. All AEs will be reported in the Clinical Study Report with the complete information named above according to the requirements of the Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).

Any administration of study drug that is not in accordance with the study protocol should be reported in the patient's source documents, regardless of whether or not an adverse event occurs as a result.

9.8.4 Medication Errors and Special Situations

The following are types of medication errors and special situations:

1. Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.
2. Overdose: Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information. Clinical judgment should always be applied.
3. Misuse: Situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information or the study protocol.
4. Abuse: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
5. Occupational exposure: Exposure to a medicinal product, as a result of one’s professional or non-professional occupation.
6. Lack of efficacy.

9.8.5 Reconciliation of SAEs & Pregnancy

It is the CRO responsibility throughout the course of the study, to maintain a listing of all SAEs and pregnancy reports. At the conclusion of the study, in the case that NO SAE/pregnancy occurred, the CRO should send an email to Teva Global PV to indicate that no SAE/pregnancy occurred during the study. In the case that a SAE/pregnancy did occur, the CRO should send an email to PV requesting the reconciliation line listing. The CRO should perform a reconciliation of the SAEs in the study with those in the Teva Global PV database.

All communication regarding Safety Data Reconciliation should be directed to the Teva Global PV email address: [redacted]

10.0 Statistical Methods

10.1 Statistical Analysis 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.

All statistical analyses will be managed by [redacted] and conducted using the Statistical Analysis System (SAS®), Version 9.4 or higher. Datasets will be prepared using headings from Clinical Data Interchange Consortium (CDISC) Study Data Tabulation Model (SDTM) implementation for human clinical trials and Analysis Dataset Model (ADaM).

10.2 Determination of Sample Size

1026 eligible patients will be enrolled [redacted]

10.3 Study Populations

10.3.1 Per-protocol Population (Responder)

The Per-protocol Population for Responders (PPR) will include patients who:

- [redacted]

- [redacted]

10.3.2 Per-protocol Population (Dyspareunia)

The Per-protocol Population for Dyspareunia (PPD) will include all patients who:

- [redacted]

10.3.3 Modified Intent to Treat Population (Responder)

The modified intent-to-treat population for Responders (mITTR) will include all patients who use at least one dose of IMP and who:

- [redacted]

10.3.4 Modified Intent to Treat Population (Dyspareunia)

[redacted]

10.3.5 Safety Population

The Safety population will include all patients who use at least one dose of IMP.

10.4 Baseline Demographics

Demographics and Baseline Characteristics will be summarized using descriptive statistics by treatment group. 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.

All data will be listed by treatment and patient.

10.5 Efficacy Endpoints

The primary efficacy endpoints are:

- % Responders in the Per Population for Responders (PPR), where 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
    - Vaginal pH < 5.0 with a change from baseline vaginal pH of at least 0.5
- Mean change from baseline to Day 15 in dyspareunia score (the self-identified most bothersome symptom in women with VVA).

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 15. A "Treatment Success" is defined as a score of 0 or 1 on Day 15 for dyspareunia (the self-identified most bothersome symptom at baseline).

10.6 Efficacy Analysis

Therapeutic Equivalence:

Therapeutic equivalence of the Test product to the Reference product based on the primary endpoints will be evaluated on Day 15 ± 2 (after 14 days of treatment). Therapeutic equivalence will be evaluated for the primary endpoint of response rate (cytology and vaginal pH) in the PPR population. If the 90% confidence interval calculated using Yates' correction on the absolute difference between the proportion of patients identified as Responders (primary endpoint) in the Test and Reference groups (pT - pR) 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.

Therapeutic equivalence will be evaluated for the primary endpoint of dyspareunia in the PPD population. The baseline dyspareunia score will be subtracted from the post-dose score to obtain

the baseline-corrected score on Day 15. The statistical analyses for dyspareunia score will use Analysis of Covariance (ANCOVA) with terms for treatment and site as fixed effects and using baseline score as a covariate in the model. The adjusted 90% confidence interval will be calculated for the Test/Reference ratio of the mean baseline-adjusted dyspareunia score using an iterative procedure. The mean baseline value for use in the iterative procedure will be determined from the baseline score of all patients receiving active treatment in the PPD population, without regard to the treatment received. If the adjusted 90% confidence interval for the least-squares mean Test/Reference ratio is within 80.00-125.00% for the primary endpoint, then therapeutic equivalence of the Test to Reference product will be considered to have been demonstrated.

The treatment-by-site and treatment-by-baseline interactions will be evaluated in separate models before performing the final ANCOVA. This Baseline score covariate will be patient-specific. The interactions of treatment-by-site and treatment-by-baseline will be investigated and removed from the final model if they are not statistically significant at the alpha=5% level. If the treatment-by-baseline interaction is found to be statistically significant at the 5% level, this would suggest that using an ANCOVA is not appropriate and that an ANOVA should be considered instead. If the treatment-by-site interaction is found to be statistically significant at the 5% level, it will be examined for clinical relevance prior to pooling the data across sites. To declare therapeutic equivalence of the Test product to the Reference product, equivalence must be demonstrated for only the primary endpoints in the PPD and PPR populations. The secondary endpoint of success rate will also be evaluated in the PPD population using the same procedure as used for the primary endpoint of response rate, and presented for informational purposes.

Superiority to Placebo

The superiority to Placebo will be evaluated for the primary endpoints in the mITT populations (mITTR and mITTD).

The superiority of the Test and Reference products over Placebo for the primary endpoint of response rate (cytology and vaginal pH) is concluded if the proportion of Responders in the Test and the Reference product groups is superior to that of the Placebo at the 5% significance level ($p < 0.05$, two-sided) using a CMH test. The same statistical approach will be conducted for analysis of the secondary endpoint in the mITTD population.

The superiority of the Test and Reference products over Placebo for the primary endpoint of mean change in dyspareunia score is concluded if the values for mean baseline-adjusted dyspareunia score are statistically superior to those respective values of the Placebo at the 5% significance level

($p < 0.05$, two-sided). The superiority of Test and Reference treatments over the Placebo will be evaluated in similar ANCOVA models for Test vs. Placebo and Reference vs. Placebo.

To declare superiority of the Test and Reference products over Placebo, superiority needs only be demonstrated for the primary endpoints in the mITTD and mITTR populations. Secondary endpoint results are presented for informational purposes. The purpose of the superiority test is not to demonstrate the efficacy of the Reference product (which has already been established), but rather to determine whether the present study can detect a difference between treatment groups, thereby validating the equivalence test between Test and Reference products. Therefore, if superiority over Placebo cannot be shown for the Test and Reference products separately, the two active treatments (Test and Reference) may be pooled into a single treatment group and compared to the Placebo group. If superiority can be demonstrated in this comparison, these results may be presented to support the equivalence assessment.

10.7 Safety Analysis

All patients who use IMP will be included in the comparative safety analysis. Adverse Events (AE) will be classified using standard Medical Dictionary for Regulatory Activities (MedDRA) terminology and presented by treatment group. The type, date of onset, date of resolution, incidence, severity, outcome, action taken, and Investigator's opinion of relationship to the study product will be presented by treatment group for AEs reported after randomization.

Signs and symptoms of atrophic vaginitis 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 medications used during the study will be listed by patient.

11.0 Regulatory Obligations

11.1 Institutional Review Board

The study protocol, ICF, Investigator's Brochure, or prescribing information (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.

11.2 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.[20-24]. The Investigator will permit trial-related monitoring, audits, IRB review and regulatory inspections providing direct access to source data/documents.

11.2.1 Protocol

The Investigator indicated on FDA Form 1572 will act as the Investigator at each study site. Protocols will be noted as approved by placement of the [redacted] and Sponsor representative's signatures on the Protocol Signature Page. The Investigator will sign the Investigator Signature Page indicating their agreement to conduct the study according to the protocol.

11.2.2 Informed Consent

An ICF that includes all of the relevant elements currently required by FDA and other applicable 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 appropriately delegated Sub-Investigator will sign and date the form, along with the staff member who conducted the informed consent to verify that the patient has indeed received information and all questions and concerns have been addressed. 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.

11.2.3 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. Changes to the protocol will be documented in amendments or revisions in subsequent versions. 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.

11.2.4 Source Documents and Case Report Forms

All patients will be identified by 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 (CRFs). A set of CRFs will be completed for each patient randomized in the study. All data and CRFs will be reviewed, evaluated and signed by the Investigator.

The Principal Investigator must maintain primary source documents supporting significant data for each Patient's medical notes. These documents, which are considered "source data", should include documentation of:

1. Demographic information
2. Evidence supporting the diagnosis/condition for which the Patient is being studied
3. General information supporting the Patient's participation in the study
4. General history and physical findings
5. Hospitalization or Emergency Room records (if applicable)
6. Each study visits by date, including any evaluations, relevant findings/notes by the Principal Investigator(s), occurrence (or lack) of adverse events and changes in medication usage, including the date the study drug commenced and completed.
7. Any additional visits during the study
8. Any relevant telephone conversations with the Patient regarding the study or possible adverse events
9. An original, signed informed consent form/assent form (as applicable) for study participation
10. Patient Diary

The Principal Investigator must also retain all Patient specific printouts/reports of tests/procedures performed as a requirement of the study. During monitoring visits, the monitor will need to validate data in the eCRFs against these sources of data.

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

11.2.5 Investigational Medicinal Product 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 they are instructed to do so the Investigator may return used and unused IMP to [redacted] or their designee. Retention samples should not be stored at the site, rather shipped to an independent storage facility (as in section 9.4.3) under limited access temperature controlled conditions per FDA regulations for a minimum of five years post approval or if not approved, 5 years after study completion.

11.2.6 Investigational Medicinal Product Storage

Study product will be stored at controlled room temperature 20-25°C (68-77°F) with excursions permitted between 15-30°C (59-86°F) 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.

11.2.7 Pregnancies

All pregnancies of women participating in the study that occur during the study, or within at least 5 half-lives, or 30 days for unknown half-lives days of completion of the study, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the Investigator must provide the Sponsor with the completed pregnancy form. The process for reporting a pregnancy to the Sponsor is the same as that for reporting a serious adverse event but using the pregnancy form as provided by the Sponsor.

Any female patient becoming pregnant during the screening period (i.e. before study drug administration) will be considered a screen failure and will not be allowed to rescreen. The Investigator is not required to report such pregnancies, provided no protocol-related procedures with known risk on pregnancy were applied.

Any female patient becoming pregnant during the study will discontinue treatment. All patients who become pregnant will be monitored for the outcome of the pregnancy (including spontaneous or voluntary termination). If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including details of birth and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to the Sponsor. Any complication of pregnancy during the study and any complication of pregnancy that the Investigator becomes aware of after termination from the study will be reported as an adverse event or serious adverse event, as appropriate.

The Investigator or designee must immediately notify the [redacted] contact consistent with SAE reporting guidelines. (i.e., pregnancies will be reported to [redacted] within 24 hours to the contacts listed in section 10.8.2). Protocol required procedures for study discontinuation and follow-up should 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.

11.2.8 Reporting Safety Information to the IRB

The Investigator must promptly report to the IRB all unanticipated problems involving risks to patients including but not limited to protocol deviations that affect patient safety or SAEs.

11.2.9 Protocol Deviations

The Investigator should not implement any deviation from the protocol without Sponsor and IRB approval except where necessary to prevent an immediate hazard to trial patients. Any protocol deviations should be clearly documented and explained by the Investigator (or designee) in the source documents and reported on the CRF. Patients with protocol deviations are not required to be discontinued from the study unless, in the Investigator's opinion, continuation in the study could be harmful to the health or wellbeing of the patient. Protocol deviations which occur due to circumstances surrounding the COVID-19 pandemic should be identified.

11.2.10 Record Retention

Institution will retain all records related to the Study until [redacted] or Sponsor notifies Institution in writing that records may be destroyed. If, after ten (10) years (unless a longer period is stated in the Study Protocol or in an applicable federal, state, local law, rules, and regulations) from Study completion, or earlier in the case of Institution closing or going out of business, Institution reasonably determines that Study record retention has become unduly burdensome, and [redacted] has not provided written notification of destruction, then Institution may submit a written request to [redacted] at least sixty (60) days before any planned disposition of Study records. Upon receipt of such request, Sponsor may make arrangements for appropriate archival or disposition, including requiring that Institution deliver such records to Sponsor at Sponsor's reasonable expense. Institution shall notify [redacted] of any accidental loss or destruction of Study records.

11.2.11 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.

11.2.12 Early Termination

A patient may terminate from the study early for any reason at any time without any disadvantages. In this case, the Investigator should make every effort to have the patient return to the next scheduled visit to perform all required End of Study / Study Completion / Early Termination visit activities and to collect and reconcile all test articles. If the patient does not return for the End of Study / Study Completion / Early Termination visit, the site should fully document the reason for early termination. All data, including the date and primary reason for termination, must be recorded on the End of Study / Study Completion / Early Termination case report form (CRF), and source document.

Any patient who experiences an adverse event may be terminated from the study or from study treatment at any time at the discretion of the investigator. In this case, the patient should be followed at the discretion of the investigator until the resolution or stabilization of the AE. All applicable data should be recorded in the adverse events section of the case report form (CRF). If a patient terminates from the study early for multiple reasons that include adverse events, the End of Study / Study Completion / Early Termination case report form should indicate that early termination was related to an adverse event.

An exception to this requirement will be the occurrence of an adverse event that in the opinion of the investigator is not severe enough to warrant early termination but that requires the use of a prohibited medication, thereby requiring discontinuation of the patient. In such a case, the reason for discontinuation would be need to take a prohibited medication, not the adverse event.

The investigator must inform the clinical project physician/clinical leader/Principal Investigator as soon as possible of all patients who are being considered for early termination due to adverse events. Additional reports must be provided when requested.

The Sponsor reserves the right to terminate the study at any time for administrative reasons. The study may also be terminated by regulatory authorities or by the investigator for his/her site following consultation with the Sponsor. Following a decision to discontinue the trial, the investigator will immediately inform both the study patients and the IEC responsible for this trial within 10 working days, stating the reasons for discontinuation of the study and, furthermore, advise them in writing of any potential risks to the health of study patients or other persons. It is Sponsor's responsibility to report the premature termination of the study to the regulatory agencies within 15 days providing them with the reasons for the trial discontinuation and advising them in

writing of any potential risks to the health of study patients or other persons. The CRO may notify the regulatory agency on behalf of the Sponsor.

The CRO should inform PhV if the whole study is early discontinued due to safety reasons and should provide PhV with the Early Termination Report.

11.2.13 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 Harmonization formatting standards and guidelines.[19]

12.0 References

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APPENDICES

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 (Visit 1)

Fasting Triglycerides (Visit 1)

[redacted]

Vaginal Cytology (Visit 1 and Visit 3, or early termination)

PAP Smear (Visit 1, as appropriate)

US samples are sent to the central laboratory:

[redacted]

[redacted]

[redacted]

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

For inclusion in the study, the most bothersome symptom reported by patient must be Dyspareunia with a score of Moderate or Severe.

APPENDIX C Prescribing Information for Imvexxy®

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use IMVEXXY safely and effectively. See full prescribing information for IMVEXXY.

IMVEXXY® (estradiol vaginal inserts)
Initial U.S. Approval: 1975

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

See full prescribing information for complete boxed warning.

Estrogen-Alone Therapy

- **There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)**
- **The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)**
- **The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)**
- **Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia (5.2, 5.4)**

Estrogen Plus Progestin Therapy

- **The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE) and myocardial infarction (MI) (5.2)**
- **The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)**
- **The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)**
- **Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia (5.2, 5.4)**

RECENT MAJOR CHANGES

Boxed Warning	11/2021

INDICATIONS AND USAGE

IMVEXXY is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. (1)

DOSAGE AND ADMINISTRATION

Administer IMVEXXY intravaginally: 1 vaginal insert daily for 2 weeks, followed by 1 insert twice weekly (for example, Monday and Thursday). (2.1)

DOSAGE FORMS AND STRENGTHS

Vaginal inserts: 4 mcg or 10 mcg estradiol. (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4, 5.3)
- Breast cancer or a history of breast cancer (4, 5.3)
- Estrogen-dependent neoplasia (4, 5.3)
- Active DVT, PE, or history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.2)
- Known anaphylactic reaction, angioedema, or hypersensitivity to IMVEXXY (4)
- Hepatic impairment or disease (4, 5.11)
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders (4)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia, or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- Monitor thyroid function in women on thyroid replacement hormone therapy (5.12, 5.19)

ADVERSE REACTIONS

The most common adverse reaction with IMVEXXY (incidence ≥ 3% and greater than placebo) is headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact TherapeuticsMD, Inc. at 1-888-228-0150 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism and decrease or increase the estrogen plasma concentration. (7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

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

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 progestogen to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding *[see Warnings and Precautions (5.3)]*.

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 Warnings and Precautions (5.2), and Clinical Studies (14.2)]*.

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 and 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 Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestogens 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

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 Warnings and Precautions (5.2), and Clinical Studies (14.2)]*.

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 and 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 Warnings and Precautions (5.4), Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

Do not use estrogen plus progestogen therapy for the prevention of cardiovascular disease or dementia *[see Warnings and Precautions (5.2, 5.4), and Clinical Studies (14.2, 14.3)]*.

Breast Cancer

The WHI estrogen plus progestin substudy demonstrated an increased risk of invasive breast cancer *[see Warnings and Precautions (5.3), and Clinical Studies (14.2)]*.

Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestogen therapy, taking into account her individual risk profile.

Prescribe estrogens with or without progestogens at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

1 INDICATIONS AND USAGE

1.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, Due to Menopause

2 DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, consider addition of a progestogen to reduce the risk of endometrial cancer.

Generally, a woman without a uterus does not need to use a progestogen in addition to her estrogen therapy. In some cases, however, hysterectomized women with a history of endometriosis may need a progestogen *[see Warnings and Precautions (5.3, 5.15)]*.

Use estrogen-alone, or in combination with a progestogen, at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Re-evaluate postmenopausal women periodically as clinically appropriate to determine if treatment is still necessary.

2.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, Due to Menopause

Generally, start therapy with the IMVEXXY 4 mcg dosage strength administered intravaginally; insert with the smaller end up for a depth of about two inches into the vaginal canal. Administer 1 insert daily at approximately the same time for 2 weeks, followed by 1 insert twice weekly, every three to four days (for example, Monday and Thursday). Make dosage adjustment based on the clinical response.

3 DOSAGE FORMS AND STRENGTHS

IMVEXXY are small, light pink, tear-shaped, vaginal inserts for manual placement into the vagina. IMVEXXY inserts contain 4 mcg or 10 mcg of estradiol. Each insert is imprinted in white ink on one side with “04” or “10” corresponding to the insert’s dosage strength.

4 CONTRAINDICATIONS

IMVEXXY is contraindicated in women with any of the following conditions:

- Undiagnosed abnormal genital bleeding *[see Warning and Precautions (5.3).*
- Breast cancer or a history of breast cancer *[see Warnings and Precautions (5.3)]*.
- Estrogen-dependent neoplasia *[see Warnings and Precautions (5.3)]*.
- Active DVT, PE, or history of these conditions *[see Warnings and Precautions (5.2)]*.
- Active arterial thromboembolic disease (for example, stroke or MI), or a history of these conditions *[see Warnings and Precautions (5.2)]*.
- Known anaphylactic reaction, angioedema, or hypersensitivity to IMVEXXY.

- Hepatic impairment or disease.
- Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders.

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Systemic Absorption

IMVEXXY is intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY *[see Pharmacokinetics (12.3)]*. The warnings, precautions, and adverse reactions associated with the use of systemic estrogen-alone therapy should be taken into account.

5.2 Cardiovascular Disorders

Increased risks of stroke and DVT are reported with estrogen-alone therapy. Increased risks of PE, DVT, stroke, and MI are reported with estrogen plus progestin therapy. Immediately discontinue estrogen with or without progestogen therapy if any of these occur or are suspected.

Manage appropriately any risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and/or venous thromboembolism (VTE) (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus).

Stroke

The WHI estrogen-alone substudy reported a statistically significant increased risk of stroke 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, respectively). The increase in risk was demonstrated in year 1 and persisted *[see Clinical Studies (14.2)]*. Immediately discontinue estrogen-alone therapy if a stroke occurs or is suspected.

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).[1]

The WHI estrogen plus progestin substudy reported a statistically significant increased risk of stroke 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, respectively) *[see Clinical Studies (14.2)]*. The increase in risk was demonstrated after the first year and persisted.[1] Immediately discontinue estrogen with or without progestogen therapy if a stroke occurs or is suspected.

Coronary Heart Disease

The WHI estrogen-alone substudy reported no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or CHD death) in women receiving estrogen-alone compared to placebo[2] *[see Clinical Studies (14.2)]*.

Subgroup analysis of women 50 to 59 years of age, who were less than 10 years since menopause, suggests a reduction (not statistically significant) of CHD events in those women

receiving daily CE (0.625 mg)-alone compared to placebo (8 versus 16 per 10,000 women-years).[1]

The WHI estrogen plus progestin substudy reported an increased risk (not statistically significant) of CHD events 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).[1] 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 (14.2)]*.

In postmenopausal women with documented heart disease (N = 2,763), average 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 CHD. 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 the original 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.

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 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[3] *[see Clinical Studies (14.2)]*. Immediately discontinue estrogen-alone therapy if a VTE occurs or is suspected.

The WHI estrogen plus progestin substudy reported a statistically significant 2-fold greater rate of VTE 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 demonstrated during the first year and persisted[4] *[see Clinical Studies (14.2)]*. Immediately discontinue estrogen plus progestogen therapy if a VTE occurs or is suspected.

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

5.3 Malignant Neoplasms

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-fold 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 1 year. The greatest risk appears associated with prolonged

use, with an increased risk of 15- to 24-fold for 5 to 10 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 progestogen therapy is important. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, 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 progestogen to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The WHI substudy of daily CE (0.625 mg)-alone provided information about breast cancer in estrogen-alone users. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80][5] *[see Clinical Studies (14.2)]*.

After a mean follow-up of 5.6 years, the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg) reported an increased risk of invasive breast cancer in women who took daily CE plus MPA compared to placebo. In this substudy, prior use of estrogen-alone or estrogen plus progestin therapy was reported by 26% 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[6] *[see Clinical Studies (14.2)]*.

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 over 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. 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.

Ovarian Cancer

The CE plus MPA substudy of WHI reported that estrogen plus progestin increased the 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% confidence interval [CI], 0.77 to 3.24), but it was not statistically significant. The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.[7]

A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The primary analysis, using case-control comparisons, included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% CI 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [median of 3 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI, 1.27 to 1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progestin products. The exact duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

5.4 Probable Dementia

In the WHI Memory Study (WHIMS) estrogen-alone ancillary study, 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% CI, 0.83 to 2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

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% CI, 1.21 to 3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 cases per 10,000 women-years[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

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% CI, 1.19 to 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[8] *[see Use in Specific Populations (8.5), and Clinical Studies (14.3)]*.

5.5 Gallbladder Disease

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

5.6 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. Discontinue estrogens, including IMVEXXY, if hypercalcemia occurs and take appropriate measures to reduce the serum calcium level.

5.7 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue IMVEXXY pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. Permanently discontinue estrogens, including IMVEXXY, if examination reveals papilledema or retinal vascular lesions.

5.8 Addition of a Progestogen When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestogen 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 progestogens with estrogens compared to estrogen-alone regimens. These include an increased risk of breast cancer.

5.9 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.

5.10 Exacerbation of Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis. Discontinue IMVEXXY if pancreatitis occurs.

5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with hepatic impairment. Exercise caution in any woman with a history of cholestatic jaundice associated with past estrogen use or with pregnancy. In the case of recurrence of cholestatic jaundice, discontinue IMVEXXY.

5.12 Exacerbation of 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 T4 and T3 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. Monitor thyroid function in these

women during treatment with IMVEXXY to maintain their free thyroid hormone levels in an acceptable range.

5.13 Fluid Retention

Estrogens may cause some degree of fluid retention. Monitor any woman with a condition(s) that might predispose her to fluid retention, such as cardiac or renal impairment. Discontinue estrogen-alone therapy, including IMVEXXY, with evidence of medically concerning fluid retention.

5.14 Hypocalcemia

Estrogen-induced hypocalcemia may occur in women with hypoparathyroidism. Consider whether the benefits of estrogen therapy, including IMVEXXY, outweigh the risks in such women.

5.15 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. Consider the addition of progestogen therapy for women known to have residual endometriosis post-hysterectomy.

5.16 Hereditary Angioedema

Exogenous estrogens may exacerbate symptoms of angioedema in women with hereditary angioedema. Consider whether the benefits of estrogen therapy, including IMVEXXY, outweigh the risks in such women.

5.17 Exacerbation of Other Conditions

Estrogen therapy, including IMVEXXY, may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas. Consider whether the benefits of estrogen therapy outweigh the risks in women with these conditions.

5.18 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of postmenopausal women with moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

5.19 Drug Laboratory Test Interactions

- 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 antifactor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

- Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T4 levels (by column or by radioimmunoassay) or T3 levels by radioimmunoassay. T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.
- Other binding proteins may be elevated in serum, for example, 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).
- Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels.
- Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Cardiovascular Disorders *[see Boxed Warning, Warnings and Precautions (5.2)]*.
- Malignant Neoplasms *[see Boxed Warning, Warnings and Precautions (5.3)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of IMVEXXY 4 mcg and 10 mcg was assessed in a single, double-blind, parallel-group, placebo-controlled trial (N = 382). The duration of treatment in this trial was 12 weeks (dosing occurred every day for 14 days and then twice weekly thereafter for maintenance).

Adverse reactions with an incidence of ≥ 3% in any IMVEXXY group and numerically greater than those reported in the placebo group are listed in Table 1.

Table 1: Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥ 3% and Numerically More Common in Women Receiving IMVEXXY

Preferred Term	IMVEXXY 4 mcg (N = 191)	IMVEXXY 10 mcg (N = 191)	Placebo (N = 192)
Nervous system disorders, n (%)			
Headache	7 (3.7)	5 (2.6)	6 (3.1)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of IMVEXXY 4 and 10 mcg. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Genitourinary system

Vaginal discharge.

7 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 (Hypericum perforatum) preparations, 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

IMVEXXY is not indicated for use in pregnancy. There are no data with the use of IMVEXXY in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives (estrogens and progestins) before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

Estrogens are present in human milk and can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for IMVEXXY and any potential adverse effects on the breastfed child from IMVEXXY or from the underlying maternal condition.

8.4 Pediatric Use

IMVEXXY is not indicated for use in pediatric patients. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

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

The Women's Health Initiative Studies

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 (14.2)]*.

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 (14.2)]*.

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 Warnings and Precautions (5.4), and Clinical Studies (14.3)]*.

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[8] *[see Warnings and Precautions (5.4), and Clinical Studies (14.3)]*.

10 OVERDOSAGE

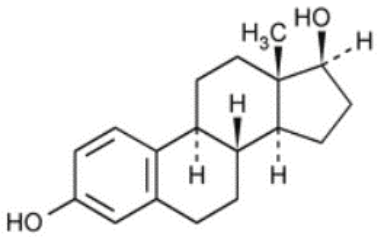
Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of IMVEXXY therapy with institution of appropriate symptomatic care.

11 DESCRIPTION

IMVEXXY (estradiol vaginal inserts) are small, light pink, tear-shaped, vaginal inserts for manual placement into the vagina. Inserts contain 4 mcg or 10 mcg of estradiol, an estrogen. Each insert is imprinted in white ink on one side with "04" or "10" corresponding to the insert's dosage strength. IMVEXXY vaginal inserts are used intravaginally. When the insert comes in contact with the vaginal mucosa, estradiol is released into the vagina.

Estradiol is chemically described as estra-1,3,5 (10)-triene-3,17β-diol. The chemical formula is $C_{18}H_{24}O_2$ with a molecular weight of 272.38.

The structural formula is:



IMVEXXY (estradiol vaginal inserts) contain the following inactive ingredients: ammonium hydroxide, ethanol, ethyl acetate, ethylene glycol palmitostearate, FD&C Red #40, gelatin, glycerin, isopropyl alcohol, lecithin, medium chain triglycerides, polyethylene glycol, polyethylene glycol stearates, polyvinyl acetate phthalate, propylene glycol, purified water, sorbitol-sorbitan solution, and titanium dioxide. FDA approved acceptance criteria for assay, organic impurities, and dissolution tolerances differ from the USP test.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 in the 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 FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

Generally, a serum estrogen concentration does not predict an individual woman’s therapeutic response to IMVEXXY nor her risk for adverse outcomes. Likewise, exposure comparisons across different estrogen products to infer efficacy or safety for the individual woman may not be valid.

12.3 Pharmacokinetics

Absorption

Estrogen drug products are well absorbed through the skin, mucous membranes, and the gastrointestinal tract. The vaginal delivery of estrogens circumvents first-pass metabolism.

In a multicenter, double-blind placebo-controlled study of 574 postmenopausal women randomized to placebo, or 4 and 10 mcg of IMVEXXY, a subset of 54 women participated in a pharmacokinetics substudy. Women received 1 vaginal insert daily for the first 2 weeks, followed by 1 insert twice weekly for the following 10 weeks.

Mean (±SD) serum estradiol and estrone following 14 days of once daily administration of IMVEXXY are shown in Figure 1. Administration of the 4 mcg and 10 mcg IMVEXXY vaginal inserts and placebo once daily for 14 days resulted in a mean estradiol $C_{avg\ (0\text{-}24)}$ of 3.6, 4.6, and 4.3 pg/mL, respectively, Table 2.

Figure 1: Mean (±SD) Serum Concentration of Estradiol and Estrone on Day 14 Following Daily Administration of IMVEXXY 4 mcg, IMVEXXY 10 mcg, and Placebo

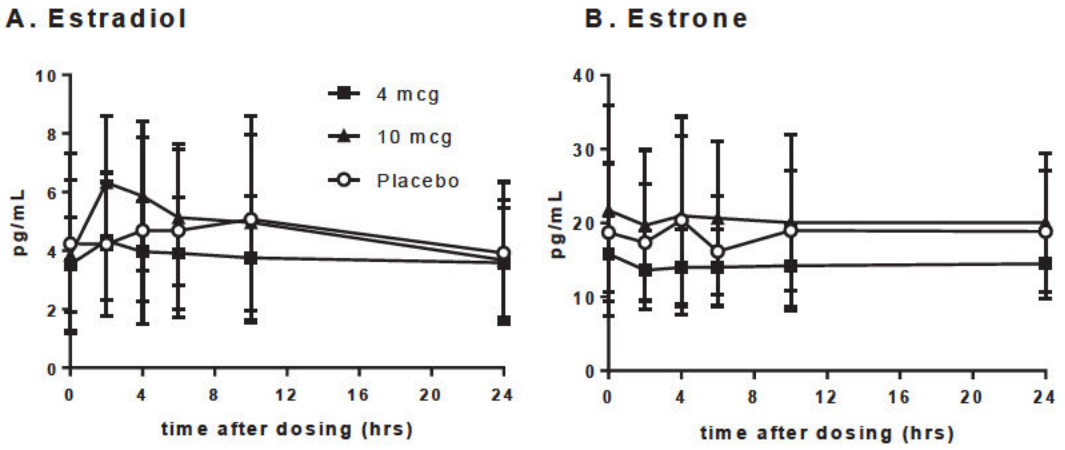


Table 2: Arithmetic Mean (SD) of Estradiol and Estrone Pharmacokinetic Parameters Following 14 Daily Doses – Unadjusted for Baseline

	Estradiol		Estrone	
	C_{max} (pg/mL)	$C_{avg\ (0\text{-}24)}$ (pg/mL)	C_{max} (pg/mL)	$C_{avg\ (0\text{-}24)}$ (pg/mL)
4 mcg	4.8 (2.3)	3.6 (1.8)	16.0 (5.5)	13.6 (4.8)
10 mcg	7.3 (2.4)	4.6 (2.3)	23.9 (13.5)	19.3 (10.2)
Placebo	5.5 (3.4)	4.3 (2.8)	22.8 (10.9)	17.8 (7.5)

At Day 84, estradiol concentrations compared to Baseline concentrations were: 4.3 vs 3.9 pg/mL for 4 mcg; 4.8 vs 5.0 pg/mL for 10 mcg; and 4.4 vs 4.5 pg/mL for placebo.

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 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 intestine followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

14 CLINICAL STUDIES

14.1 Effects on Moderate to Severe Dyspareunia in Postmenopausal Women

The effectiveness and safety of IMVEXXY on moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause were examined in one placebo-controlled clinical trial.

This 12-week, randomized, double-blind, placebo-controlled, parallel-group trial enrolled 574 generally healthy postmenopausal women between 40 to 75 years of age (mean 59 years of age) who at baseline assessment had ≤ 5% superficial cells on a vaginal smear, a vaginal pH > 5.0, and also identified, at baseline, moderate to severe dyspareunia as the most bothersome symptom to her. Greater than 90% of women also reported moderate to severe vaginal dryness at baseline. Treatment groups included 4 mcg IMVEXXY (N = 191), 10 mcg IMVEXXY (N = 191), and placebo (N = 192). All women were assessed for improvement in the mean change from Baseline to Week 12 for the co-primary efficacy variables of: most bothersome moderate to severe symptom of dyspareunia, percentage of vaginal superficial and percentage of vaginal parabasal cells on a vaginal smear, and vaginal pH.

IMVEXXY 4 mcg and 10 mcg inserts were statistically superior to placebo in reducing the severity of moderate to severe dyspareunia at Week 12 (see Table 3). A statistically significant increase in the percentage of superficial cells and a corresponding statistically significant decrease in the percentage of parabasal cells on a vaginal smear was also demonstrated for IMVEXXY 4 and 10 mcg inserts ($p < 0.0001$). The mean reduction in vaginal pH between Baseline and Week 12 was also statistically significant for IMVEXXY 4 and 10 mcg inserts ($p < 0.0001$).

Table 3: Efficacy of Dyspareunia Associated with Postmenopausal Vulvar and Vaginal Atrophy (Least Square Mean Change from Baseline to Week 12 in Severity of Woman's Self-Identified Most Bothersome Moderate to Severe Symptom of Vulvar and Vaginal Atrophy)

Most Bothersome Moderate to Severe Symptom at Baseline	IMVEXXY 4 mcg (N = 151)	IMVEXXY 10 mcg (N = 154)	Placebo (N = 163)
Dyspareunia			
Baseline Mean (SD)	2.7 (0.48)	2.6 (0.48)	2.7 (0.46)
LS Mean Change from Baseline (SE)	-1.52 (0.071)	-1.69 (0.071)	-1.28 (0.070)
p-value vs placebo	0.0149	<0.0001	------

The modified intent-to-treat population (MITT) included only women in the ITT population who at baseline met the inclusion criteria of ≤ 5% superficial cells on a vaginal smear, a vaginal pH > 5.0, and who identified moderate or severe dyspareunia as her most bothersome vaginal symptom.
Definitions: SD – standard deviation; SE – standard error; LS – least square

14.2 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 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 causes. These substudies did not evaluate the effects of CE-alone 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% White, 15.1% Black, 6.1% Hispanic, 3.6% Other) after an average follow-up of 7.1 years, are presented in Table 4.

Table 4: 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 Strokes[c]	1.33 (1.05-1.68)	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, 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.[9] 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 difference in distribution of stroke subtype 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.[10]

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 50-59 years of age a non-significant trend toward reduced risk for CHD *[hazard ratio (HR) 0.63 (95% CI, 0.36 to 1.09)]* and overall mortality *[HR 0.71 (95% CI, 0.46 to 1.11)]*.

WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive 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% White, 6.8% Black, 5.4% Hispanic, 3.9% Other) are presented in Table 5. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

Table 5: 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

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	
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[e,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, PE, 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 50-59 years of age, a non-significant trend toward reduced risk for overall mortality *[HR 0.69 (95% CI, 0.44 to 1.07)]*.

14.3 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominately healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45% were 65 to 69 years of age; 36% were 70 to 74 years of age; 19% 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% CI, 0.83 to 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 Warnings and Precautions (5.4), and Use in Specific Populations (8.5)]*.

The WHIMS estrogen plus progestin ancillary study of WHI enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were 65 to 69 years of age; 35% were 70 to 74 years; 18% 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% CI, 1.21 to 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 and Precautions (5.4), and Use in Specific Populations (8.5)]*.

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% CI, 1.19 to 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 and Precautions (5.4), and Use in Specific Populations (8.5)]*.

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10. Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. Circulation. 2006; 113:2425-2434.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

IMVEXXY (estradiol vaginal inserts) are small, light pink, tear-shaped inserts for manual placement into the vagina. Inserts contain 4 mcg or 10 mcg of estradiol. Each insert is imprinted in white ink on one side with “04” or “10” corresponding to the insert’s dosage strengths.

IMVEXXY (estradiol vaginal inserts), 4 mcg and 10 mcg, are provided in opaque push-through blisters and are packaged in cartons containing either 18 inserts for the starter pack or 8 inserts for the maintenance pack.

IMVEXXY 4 mcg	8 inserts	NDC 50261-104-08
IMVEXXY 4 mcg	18 inserts	NDC 50261-104-18
IMVEXXY 10 mcg	8 inserts	NDC 50261-110-08
IMVEXXY 10 mcg	18 inserts	NDC 50261-110-18

Keep out of reach of children. Packages are not child-resistant.

16.2 Storage and Handling

Store at 20°C to 25ºC (68°F to 77ºF), excursions permitted to 15ºC to 30ºC (59ºF to 86ºF). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

Advise women to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible *[see Warnings and Precautions (5.3)]*.

Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia *[see Warnings and Precautions (5.2, 5.3, 5.4)]*.

Possible Common Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

PATIENT INFORMATION

IMVEXXY® (ĭm vex' ee)

(estradiol vaginal inserts)

Read this Patient Information before you start using IMVEXXY and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

What is the most important information I should know about IMVEXXY (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 IMVEXXY. 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 of 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 65 years of age and older.
- Do not use estrogens with progestogens to prevent heart disease, heart attacks, strokes or dementia.
- Using estrogens with progestogens may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots.
- Using estrogens with progestogens may increase your chance of getting dementia, based on a study of women 65 years of age and older.
- Only one estrogen-alone product and dose have been shown to increase your chances of getting strokes, blood clots, and dementia. Only one estrogen with progestogen product and dose have been shown to increase your chances of getting heart attacks, strokes, breast cancer, blood clots, and dementia. Because other products and doses have not been studied in the same way, it is not known how the use of IMVEXXY will affect your chances of having these conditions.
- You and your healthcare provider should talk regularly about whether you still need treatment with IMVEXXY.

What is IMVEXXY?

IMVEXXY is a prescription medicine that contains an estrogen hormone in a vaginal insert.

What is IMVEXXY used for?

IMVEXXY is used after menopause to treat moderate to severe painful intercourse, a symptom of changes in and around your vagina, due to menopause.

Who should not use IMVEXXY?

Do not start using IMVEXXY 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.
- **have been diagnosed with a bleeding disorder.**
- **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 (womb). If you have or have had cancer, talk with your healthcare provider about whether you should use IMVEXXY.
- **currently have or have had blood clots.**
- **had a stroke or heart attack.**
- **currently have or have had liver problems.**
- **are allergic to IMVEXXY or any of its ingredients.** See the list of ingredients in IMVEXXY at the end of this leaflet.

Before you use IMVEXXY, tell your healthcare provider about all of your medical conditions, including if you:

- **have any 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 or spotting to find out the cause.
- **have any other medical conditions that may become worse while you are using IMVEXXY.** Your healthcare provider may need to check you more carefully if you have certain medical conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, angioedema (swelling of face and tongue), problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.
- **are going to have surgery or will be on bed rest.** You may need to stop using IMVEXXY.
- **are pregnant or think you may be pregnant.** Imvexxy is not for pregnant women.
- **are breast feeding.** The hormone in IMVEXXY can pass into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some medicines may affect how IMVEXXY works.

IMVEXXY may also affect how other medicines work. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get new medicine.

How should I use IMVEXXY?

For detailed instructions, see the step-by-step instructions for using IMVEXXY at the end of this Patient Information.

- Use IMVEXXY exactly as your healthcare provider tells you to use it.
- IMVEXXY is a vaginal insert that you place in your vagina.
- IMVEXXY is only for use in the vagina. **Do not** take IMVEXXY by mouth (orally).
- Estrogens should be used at the lowest dose possible for your treatment and for only as long as needed.
- Put 1 IMVEXXY insert inside your vagina, 1 time a day at about the same time for the first two weeks.
- Then put 1 IMVEXXY insert into your vagina two times a week, every three to four days (for example, Monday and Thursday), for as long as you use IMVEXXY.
- 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 IMVEXXY.

What are the possible side effects of IMVEXXY?

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

Serious, but less common side effects could include:

- heart attack
- breast cancer
- dementia
- gallbladder disease
- high levels of fat (triglyceride) in your blood
- enlargement of benign tumors of the uterus (“fibroids”)
- stroke
- cancer of the lining of the uterus (womb)
- high or low blood calcium
- visual abnormalities
- liver problems
- worsening of swelling of face and tongue (angioedema) in women with a history of angioedema
- blood clots
- cancer of the ovary
- high blood pressure
- changes in your thyroid hormone levels

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

Common side effects of IMVEXXY include:

- headache
- breast tenderness or pain
- nausea and vomiting

These are not all of the possible side effects of IMVEXXY. For more information, ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effects that bother you or that do not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to TherapeuticsMD® at 1-888-228-0150.

What can I do to lower my chances of a serious side effect with IMVEXXY?

- Talk with your healthcare provider regularly about whether you should continue using IMVEXXY.
- If you have a uterus (womb), talk with your healthcare provider about whether the addition of a progestogen is right for you. In general, the addition of a progestogen is 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 IMVEXXY.
- 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 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 a higher chance of getting heart disease. Ask your healthcare provider for ways to lower your chances of getting heart disease.

General information about the safe and effective use of IMVEXXY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use IMVEXXY for a condition for which it was not prescribed. Do not give IMVEXXY to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about IMVEXXY that is written for health professionals.

What are the ingredients in IMVEXXY?

Active ingredient: IMVEXXY (estradiol vaginal inserts) are small, light pink, tear-shaped inserts that contain estradiol.

Inactive ingredients: Each insert also contains ammonium hydroxide, ethanol, ethyl acetate, ethylene glycol palmitostearate, FD&C Red #40, gelatin, glycerin, isopropyl alcohol, lecithin, medium chain triglycerides, polyethylene glycol, polyethylene glycol stearates, polyvinyl acetate phthalate, propylene glycol, purified water, sorbitol-sorbitan solution, and titanium dioxide. IMVEXXY is supplied in blister cartons of 18 or 8 vaginal inserts.

Instructions for Use
IMVEXXY® (ĭm vex' ee)
(estradiol vaginal inserts)

Read this Instructions for Use before you start using IMVEXXY and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

How should I use IMVEXXY?

- IMVEXXY is an insert only for use in the vagina. Do not take by mouth.
- Put 1 IMVEXXY insert inside your vagina, 1 time a day at about the same time for the first two weeks, then put 1 IMVEXXY insert into your vagina two times a week, every three to four days (for example, Monday and Thursday), for as long as you use IMVEXXY.
- Write down the days you will put in your IMVEXXY insert.
- Wash and dry your hands before handling the IMVEXXY insert.

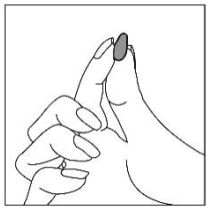
Step 1: Push 1 IMVEXXY insert through the foil of the blister package.

Figure A



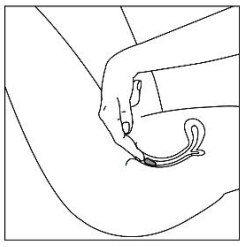
Step 2: Hold the IMVEXXY insert with the larger end between your fingers.

Figure B



Step 3: Select the best position for vaginal insertion that is most comfortable for you to put in the IMVEXXY insert. See Figure C for suggested insertion in the lying down position or Figure D for suggested insertion in the standing position. With the smaller end up, put the insert about two inches into your vagina using your finger.

Figure C **or** **Figure D**





If you have any questions, please ask your healthcare provider or pharmacist.

How should I store IMVEXXY?

- Store IMVEXXY at room temperature between 68°F to 77°F (20°C to 25°C).
- IMVEXXY packaging is not child-resistant.

Keep IMVEXXY and all medicines out of the reach of children.

For information, go to TherapeuticsMD.com or call TherapeuticsMD, Inc. at 1-877-833-0176

Manufactured for: TherapeuticsMD, Inc., Boca Raton, FL 33431

For patent information, go to TherapeuticsMD.com/patents
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The Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

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