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*APPLICATION NUMBER:*

**208564Orig1s000**

**CLINICAL REVIEW(S)**

Clinical Review

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

Resubmission NDA 208564

Imvexxy™ (estradiol vaginal inserts) 4 mcg and 10 mcg

**CLINICAL REVIEW**

<b>Application Type</b>	Class 2 Resubmission
<b>Application Number(s)</b>	NDA 208564
<b>Priority or Standard</b>	Standard
<b>Submit Date(s)</b>	November 29, 2017
<b>Received Date(s)</b>	November 29, 2017
<b>PDUFA Goal Date</b>	May 29, 2018
<b>Division/Office</b>	Division of Bone, Reproductive, and Urologic Products/Office of Drug Evaluation III
<b>Reviewer Name(s)</b>	Theresa H. van der Vlugt, M.D., M.P.H.
<b>Review Completion Date</b>	May 15, 2018
<b>Established/Proper Name</b>	Estradiol vaginal insert
<b>(Proposed) Trade Name</b>	Imvexxy™
<b>Applicant</b>	TherapeuticsMD
<b>Dosage Form(s)</b>	Intravaginal inserts
<b>Applicant Proposed Dosing Regimen(s)</b>	4 mcg insert administer intravaginally daily for 2 weeks, then 4 mcg insert administered intravaginally two times per week (approximately 3 to 4 days apart) 10 mcg insert administered intravaginally daily for 2 weeks, then 10 mcg insert administered intravaginally two times per week (approximately 3 to 4 days apart)
<b>Applicant Proposed Indication(s)/Population(s)</b>	Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Postmenopausal women

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## Glossary

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AC	advisory committee
AE	adverse event
BMI	Body Mass Index
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CE	conjugated estrogens
CMC	chemistry, manufacturing, and controls
CR	complete response
CRF	case report form
CRL	complete response letter
CSR	clinical study report
DCP-III	Division of Clinical Pharmacology-III
DEPI	Division of Epidemiology II
DMEPA	Division of Medication Error Prevention and Analysis
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
FDA	Food and Drug Administration
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
mITT	modified intent to treat
MBS	most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
MPA	medroxyprogesterone acetate
NAI	no action indicated
NDA	new drug application
NME	new molecular entity
OCP	Office of Clinical Pharmacology
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PI	prescribing information or package insert
PK	pharmacokinetics
PMR	postmarketing requirement

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PPI	patient package insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update Report
SAE	serious adverse event
TEAE	treatment emergent adverse event
VMS	vasomotor symptoms (hot flashes/flushes)
VTE	venous thromboembolism
VVA	vulvar and vaginal atrophy
WHI	Women's Health Initiative

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# 1. Executive Summary

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## 1.1. Product Introduction

Imvexxy™ (estradiol vaginal inserts) 4 mcg and 10 mcg is an estrogen (b) (4) estradiol (b) (4) proposed for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Imvexxy™, 4 mcg and 10 mcg inserts, are administered intravaginally daily for two weeks, then administered intravaginally two times per week, approximately 3-4 days apart. TherapeuticsMD originally submitted new drug application (NDA) 208564 for this indication on July 7, 2016.

On May 5, 2017, NDA 208564 for estradiol vaginal inserts 4 mcg, 10 mcg, (b) (4) received a Complete Response Letter (CRL) indicating “We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. Your application does not provide long-term endometrial safety data for the 4, 10, (b) (4) estradiol vaginal inserts. Sufficient assessment of endometrial histology to support chronic use is critical to the safety evaluation of unopposed estrogen and to ensure adequate labeling for the safe use of your product.” See the Primary Clinical Review, dated April 28, 2017, for complete information regarding the original NDA 208564 application. See the Agency’s CRL, dated May 5, 2017, for the issues identified in the original NDA application and, where possible, the Agency’s recommendations to address these issues.

The Agency recognized the challenge with conducting a sufficiently long and large enough clinical trial to adequately characterize endometrial safety of the Imvexxy™ estradiol vaginal inserts. The Agency recommended at the November 3, 2017 pre-NDA resubmission meeting that TherapeuticsMD conduct a class postmarketing requirement (PMR) long-term (3 to 5 years) observational study to identify the incidence of endometrial cancer associated use of unopposed low dose vaginal estrogen products in postmenopausal women as an acceptable approach to provide long-term endometrial safety data for the 4 mcg and 10 mcg estradiol vaginal inserts. TherapeuticsMD has committed to conduct the recommended PMR. See Section 3.2 of this review for a discussion of the regulatory activities prior to the resubmission of NDA 208564 on November 29, 2017.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

This clinical reviewer concludes that substantial evidence of efficacy for Imvexxy™ (estradiol vaginal inserts) 4 mcg and 10 mcg is demonstrated, based on successfully achieving the primary protocol-defined co-primary endpoints of 1) a statistically significant reduction versus placebo in moderate to severe dyspareunia, 2) a statistically significant increase in superficial epithelial cells and a corresponding statistically significant decrease in parabasal epithelial cells on a

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lateral vaginal wall smear, and 3) a statistically significant reduction in vaginal pH in the single, primary, phase 3 clinical Trial TXV14-01 submitted in the original NDA application. See the Primary Clinical Review, dated April 28, 2017, for complete information regarding the efficacy for Imvexxy™ (estradiol vaginal inserts) 4 mcg and 10 mcg demonstrated in the original NDA 208564 application.

### **1.3. Benefit-Risk Assessment**

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### Benefit-Risk Integrated Assessment

As endogenous estrogen serum levels decline during menopause, the genital tract and other estrogen-dependent tissues gradually undergo atrophic changes. Vulvar and vaginal atrophy (VVA) is characterized by a high ratio of parabasal to superficial epithelial cells, and an increase in vaginal pH (> 5.0), leading to an increased susceptibility to infection and symptoms of vulvar and vaginal atrophy. The loss of secretory superficial epithelial cells leads to a decrease in vaginal secretions (moisture), which may increase susceptibility to vaginal pain with intercourse or sexual activity (dyspareunia). Vulvar and vaginal atrophy symptoms are usually progressive, and unlikely to resolve spontaneously. It is estimated that up to 50% of postmenopausal women experience VVA.

Estrogen treatment has proven to be successful in controlling menopausal symptoms, including symptoms associated with VVA, through both systemic and local administration. Presently, approved local and systemic estrogen therapies for the treatment of VVA include natural or synthetic hormones administered in the form of oral tablet, topical gel/lotion, vaginal cream, vaginal ring, and vaginal inserts.

Imvexxy™ (estradiol vaginal inserts) 4 mcg and 10 mcg inserts, administered intravaginally daily for 2 weeks, then administered intravaginally two times per week (approximately 3 to 4 days apart), is demonstrated to be efficacious in the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy (see Section 1.2 above and Section 7 of this review and the original Primary Clinical and Statistical reviews, dated April 28, 2017 and April 4, 2017, respectively).

In the original review cycle, the applicant submitted 12-week safety data from Trial TXV14-01 to support the overall safety of the 4 mcg and 10 mcg estradiol vaginal inserts. Treatment of one or more moderate to severe symptoms (dyspareunia) of vulvar and vaginal atrophy is a chronic therapy indication. The data submitted from a 12-week trial is inadequate to assess long-term general and endometrial safety and chronic use drug exposure of Imvexxy™. An increased risk of endometrial hyperplasia/ cancer is a known major concern demonstrated with the use of estrogen-alone hormone therapy in a woman with a uterus. This risk is established in the literature of estrogen-alone products with systemic exposure, including products considered to have lower, moderate, and high dosage strengths.<sup>1,2,3</sup>

<sup>1</sup> Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med, 1975; 293(23):1167-1170

<sup>2</sup> Gambrell RD Jr. Estrogens, progestogens and endometrial cancer. J Reprod Med, 1977 Jun; 18(6):301-306.

<sup>3</sup> Sjögren LL, et al. Hormone replacement therapy and the risk of endometrial cancer: A systematic review. Maturitas, 2016 Sep; 91:25-35.

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TherapeuticsMD has now resubmitted NDA 208564 with a commitment and plan to conduct a class postmarketing requirement (PMR) for a long-term observational study, of 3 to 5 years of use/follow up information, to identify the incidence of endometrial cancer associated use of unopposed low dose vaginal estrogen products in non-hysterectomized postmenopausal women.

**Benefit-Risk Dimensions**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<a href="#">Analysis of Condition</a>	<ul style="list-style-type: none"><li>• Menopause is a natural biological process and marks the end of fertility because of permanent ovarian failure.</li><li>• Symptoms of menopause, such as vasomotor symptoms (VMS; hot flashes/hot flushes) and VVA symptoms [vaginal dryness, vaginal irritation/itching, and pain with sexual activity (dyspareunia)] can be debilitating with respect to a woman’s ability to accomplish her normal activities including sleep. However, menopause is not a life-threatening condition.</li><li>• In 2000, there were an estimated 45.6 million postmenopausal women in the United States (US). About 40 million of them were older than age 51, the average age of natural menopause in the Western world. By the year 2020, the number of US women older than age 51 is expected to be more than 50 million.<sup>4</sup></li></ul>	<ul style="list-style-type: none"><li>• Menopause symptoms, though not life-threatening, constitute a significant public health concern.</li></ul>

<sup>4</sup> US Census Bureau. Population survey: female population by age, sex, and race and Hispanic origin: March 2000. Available at: <https://www.census.gov/programs-surveys/decennial-census/decade.2010.html>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Current Treatment Options</a></p>	<ul style="list-style-type: none"> <li>Current treatment options for an indication for the treatment of moderate to severe dyspareunia (pain with intercourse/sexual activity) self-identified as most bothersome by the postmenopausal woman include: Premarin® (conjugated estrogens) Vaginal Cream (intravaginally applied estrogen cream); Enjuvia® (synthetic conjugated estrogens, B) Tablets (oral estrogen tablet); Osphena® (ospemifene) Tablets (oral estrogen agonist/antagonist tablet); and Intrarosa® (prasterone) Vaginal Inserts (intravaginally applied steroid insert).</li> </ul>	<ul style="list-style-type: none"> <li>Current treatment options for the general indication for the treatment of moderate to severe symptoms of VVA, involve multiple estrogen products, used alone in a woman without a uterus, or in combination with a progestogen in a woman with a uterus. Most of these products were approved under estrogen class labeling, and were not supported by clinical trial data demonstrating relief of one or more individual moderate to severe symptoms of vulvar and vaginal atrophy. These approved products offer a range of dosage strengths and different routes of administration including oral tablets, transdermal systems, topical gels, vaginal creams, and vaginal inserts.</li> <li>Estradiol is the active moiety in most of the Agency’s approved estrogen-alone and estrogen plus progestogen products with a general indication for the treatment of moderate to severe VVA symptoms due to menopause.</li> </ul>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><a href="#">Benefit</a></p>	<ul style="list-style-type: none"> <li>Imvexxy™ (estradiol vaginal inserts) is designed for insertion with no need for an applicator (manual administration intravaginally) which per the applicant, may mitigate pain from applicator insertion. Applicator insertion may also cause local abrasion, especially in women with severely atrophic vaginal mucosa.</li> <li>To allow healthcare providers the ability to tailor the dose to a woman’s individual needs, and to provide women the lowest dose appropriate for their symptoms, two dosage strengths of estradiol vaginal inserts (4 mcg and 10 mcg) are requested and recommended for approval.</li> <li>If approved, the 4 mcg estradiol insert dosage strength will be the lowest approved estrogen-alone dosage strength available to postmenopausal women for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.</li> </ul>	<ul style="list-style-type: none"> <li>Higher doses of vaginally administered estrogens, and oral and topically applied estrogens, are well studied and have been found to be safe and effective when used appropriately.</li> <li>The Agency’s draft 2005 FDA Guidance for Industry, “Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommended Prescribing Information for Health Care Providers and Patient Labeling” recommends that estrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.</li> </ul>
<p><a href="#">Risk and Risk Management</a></p>	<ul style="list-style-type: none"> <li>No long term general and endometrial safety data or chronic use drug exposure data, of at least 12-months duration, is available in the original NDA application or in the NDA resubmission for the 4 mcg and 10 mcg estradiol vaginal insert.</li> <li>The finding of proliferative endometrium and disordered proliferative endometrium at only 12-weeks of drug exposure in phase 3 Trial TXV14-01 confirm that long-term safety data was necessary to support the long-term general and endometrial safety and chronic use drug exposure of the 4 mcg and 10 mcg estradiol vaginal inserts for the treatment of moderate to</li> </ul>	<ul style="list-style-type: none"> <li>The Agency recommended at the November 3, 2017 pre-NDA resubmission meeting that TherapeuticsMD conduct a PMR long-term (3 to 5 years) observational study to identify the incidence of endometrial cancer associated use of unopposed low dose vaginal estrogen products in postmenopausal women.</li> </ul>

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.	<ul style="list-style-type: none"><li>• TherapeuticsMD has committed to conduct the recommended PMR.</li></ul>

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### 1.4. Patient Experience Data

The following clinical outcome assessment data (trial endpoints for phase 3, 12-week Trial TXV14-01), for the 4 mcg and 10 mcg estradiol vaginal inserts, was submitted in the original NDA 208564 application received July 17, 2016:

- Mean change in the severity of moderate to severe dyspareunia (pain with intercourse/sexual activity) compared with placebo at Week 12
- Mean change in the percentage of superficial epithelial cells on a lateral wall vaginal smear compared with placebo at Week 12
- Mean change in the percentage of parabasal epithelial cells on a lateral wall vaginal smear compared with placebo at Week 12
- Mean change in vaginal pH compared with placebo at Week 12.

In Trial TXV14-01, trial participants were asked to rate the acceptability of the product at Week 12 or Early Termination using a five-question questionnaire as follows:

1. Was the product easy to use?
2. How would you rate the ease of insertion of the capsule?
3. Level of satisfaction with the product.
4. How do you compare the treatment you received in this study to previous medication or therapies for your vulvar and vaginal atrophy symptoms?
5. Would you consider using this form of treatment again?

Overall, trial participants found this digitally administered product acceptable indicating they would definitely/probably consider using the estradiol vaginal inserts again (72.8% to 80.5% in active treatment groups compared with 62.5% in the placebo treatment group). Approximately 90% of treated women reported that the product was easy to use.

See the Primary Clinical Review, dated April 28, 2017, Section 5 Sources of Clinical Data, Subsection 5.3 Discussion of Individual Studies/Clinical Trials, Subsection 5.3.1 Trial TXV14-01 for a full discussion of trial design, primary and secondary efficacy analyses, responder analysis, and subpopulation analyses. See also the Statistical Review dated April 4, 2017.

## 2. Therapeutic Context

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### 2.1. Analysis of Condition

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

During the reproductive years, estradiol in women is produced primarily by the granulosa cells of the ovaries by the aromatization of  $\Delta^4$ -androstenedione (produced in the theca folliculi cells) to estrone, followed by conversion of estrone to estradiol by 17 $\beta$ -hydroxysteroid dehydrogenase. Smaller amounts of estradiol are also produced by the adrenal cortex in women. In postmenopausal women, fat cells produce active precursors to estradiol. Estradiol is conjugated in the liver to form estrogen conjugates (estradiol sulfate, estradiol glucuronide) and, as such, is excreted via the kidneys. Some of the water-soluble conjugates are excreted via the bile duct, and partly reabsorbed after hydrolysis from the intestinal tract. This enterohepatic circulation contributes to maintaining estradiol levels.

## 2.2. Analysis of Current Treatment Options

Current treatment options for the general indication for the treatment of moderate to severe symptoms of VVA, involve multiple estrogen products, including estradiol products, used alone in a woman without a uterus, or in combination with a progestogen in a woman with a uterus. Most of these products were approved under estrogen class labeling, and were not required to be supported by clinical trial data demonstrating relief of one or more individual moderate to severe symptoms of vulvar and vaginal atrophy. These approved products offer a range of dosage strengths and different routes of administration including oral tablets, transdermal systems, topical gels, vaginal creams, and vaginal inserts. Estradiol is the active moiety in most of the Agency's approved estrogen-alone and estrogen plus progestogen products with a general indication for the treatment of moderate to severe VVA symptoms due to menopause.

Table 1 shows the number of drug products approved for the treatment of moderate to severe dyspareunia (or pain with sexual activity), an individual symptom of vulvar and vaginal atrophy, due to menopause.

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

Vaginal Cream Product	Available Dosage Strength/Dosing Regimens
Premarin® (conjugated estrogens) Vaginal Cream	Cyclic Administration: 0.5 g intravaginally daily for 21 days then off for 7 days  Twice Weekly Administration: 0.5 g intravaginally twice weekly (for example, Monday and Thursday)
Vaginal Insert Product	Available Dosage Strength/Dosing Regimens
Intrarosa® (prasterone) Vaginal Insert	6.5 mg insert administered intravaginally once daily at bedtime
Oral Estrogen-alone Product	Available Dosage Strength/Dosing Regimens
Enjuvia® (synthetic conjugated estrogens, B) Tablets*	0.3 mg taken orally once daily
Oral Estrogen Agonist/Antagonist Product	Available Dosage Strength/Dosing Regimens
Osphena® (ospemifene) Tablet	60 mg tablet taken orally once daily with food

\* Teva Women's Health, Inc. no longer manufactures or distributes Enjuvia® (synthetic conjugated estrogens, B) tablets under NDA 21443. NDA 21443 for Enjuvia® remains active. The last approved Enjuvia® (synthetic conjugated estrogens, B) tablets labeling is dated November 1, 2017.

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

See the Primary Clinical Review of NDA 208564, dated April 28, 2017, Section 9 Appendices, for detailed information on currently approved estrogen-alone and estrogen plus progestogen products with a general indication for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, due to menopause.

## 3. Regulatory Background

### 3.1. U.S. Regulatory Actions and Marketing History

Estradiol, the active moiety in estradiol vaginal inserts, 4 mcg and 10 mcg, has been used via multiple routes of administration and dosage strengths for various indications in women and men for several decades. Estradiol is approved for treatment of moderate to severe VMS and treatment of moderate to severe VVA, each due to menopause in postmenopausal women. Estradiol-alone products approved for VVA include: oral formulations, transdermal applications, and vaginal preparations in both branded and generic versions, with extensive nonclinical pharmacology and toxicology existing in the literature and previously reviewed by the Agency:

- Oral products: Menest® (esterified estrogens) tablets, various generic estradiol tablets
- Transdermal products: Alora® (estradiol matrix transdermal system), Climara® (estradiol matrix transdermal system), Estraderm® (estradiol reservoir transdermal system), VivelleDot® (estradiol matrix transdermal system), and various generic estradiol matrix transdermal systems

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- Topical products: EstroGel® 0.06% (estradiol gel) for topical use
- Vaginal cream products: Estrace® Cream (estradiol vaginal cream) and generic estradiol vaginal cream
- Vaginal ring products: Estring® (estradiol vaginal ring), Femring® (estradiol acetate vaginal ring)
- Vaginal insert products: Vagifem® (estradiol vaginal insert), and generic vaginal inserts

Estradiol plus progestin products approved for VVA include:

- Oral products: Angeliq® (drospirinone plus estradiol) tablets, for oral use; Prefest® (estradiol/norgestimate) tablets
- Transdermal products: CombiPatch® (estradiol/norethindrone acetate transdermal system)

### 3.2. Summary of Presubmission/Submission Regulatory Activity

See the Primary Clinical Review, dated April 28, 2017, Section 2 Introduction and Regulatory Background, and Subsection 2.5 Summary of Presubmission Regulatory Activity Related to Submission for a summary of presubmission and submission regulatory activity for the original NDA 208564 application received July 7, 2016.

A summary of the regulatory activity prior to the resubmission of NDA 208564 follows:

**May 5, 2017** - NDA 208564 received a CRL because long-term endometrial safety data and chronic use drug exposure data was absent. The Agency determined that sufficient assessment of endometrial histology to support chronic use was critical to the safety evaluation of unopposed estrogen in a woman with a uterus, and to ensure adequate labeling for safe use of the estradiol vaginal insert product.

**May 15, 2017** - TherapeuticsMD requested a Type A meeting to “gain clarification regarding the Agency’s Complete Response Letter and the recommendation to provide additional endometrial and general safety data.” The Type A meeting package contained the applicant’s plan for the resubmission of NDA 208564 as follows:

- Proposal to resubmit the application for approval of the 4 mcg and 10 mcg estradiol vaginal inserts (b) (4)
- (b) (4)
- Adopt labeling consistent with the Agency’s draft 2005 labeling Guidance for Industry
- Include in labeling: (b) (4)
- Include all changes to the product label and cartons as described in the CRL
- Commitment to assess long-term (b) (4) endometrial and general safety PMR study, of the 4 mcg and 10 mcg dosage strengths, which is designed in agreement with

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the Division. The applicant proposes [REDACTED] (b) (4)

- A request for a separate meeting with Chemistry, Manufacturing and Controls (CMC) to address issues identified in the CRL
- Submit a proprietary name for review

**May 24, 2017** - TherapeuticsMD submits a General Correspondence: Addendum to the Type A Meeting Request and Briefing Materials, Questions by Discipline.

**June 14, 2017** – Type A meeting held with TherapeuticsMD. Selected comments from the July 5, 2017 Meeting Minutes include:

*Question 1:* Does the Division agree that, consistent with the draft 2005 Labeling Guidance, the current estrogen class labeling comprehensively communicates the long-term safety of estrogen drug products, including vaginal estradiol products with higher systemic absorption than TX-004HR? TX-004HR is the code name for the estradiol vaginal inserts.

### **FDA Response:**

The Agency's recommended estrogen-alone and estrogen plus progestin (progestogen) class labeling communicates in the BOXED WARNINGS and WARNINGS and PRECAUTIONS sections, long-term endometrial and general safety findings and recommendations based on data obtained with approved estrogen-alone and estrogen plus progestin drug products. In the absence of adequate and sufficient data to advise otherwise, estrogen-alone and estrogen plus progestin class labeling has been applied to all estrogen-alone and estrogen plus progestin (progestogen) products, irrespective of dosage strength or route of administration, which are approved for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause and/or treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause. Additional non-class efficacy and safety findings may be included in the labeling for each individual product based on their respective clinical trial(s) conducted to support the indication(s).

However, we have become aware that prevailing clinical guidelines for the treatment of signs and symptoms of vulvar vaginal atrophy due to menopause have recommended, inconsistent with the Boxed Warning, that administration of a progestogen is not necessary for women treated with certain vaginally-administered "low" dose estrogen-alone products. These recommendations appear to be based largely on pharmacokinetic data (serum estrogen concentrations) and with one exception, short-term clinical trials, but, importantly, do not take into account the potential for adverse endometrial effects from local exposure to vaginally-applied estrogens. Because clinical guidelines are influential in guiding patient care, there is compelling reason to believe that health care providers follow their recommendations of not generally administering a progestogen for endometrial protection,

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despite the information and advice provided in class labeling. Therefore, class labeling for certain vaginally-administered “low” dose estrogen-alone products alone may not provide adequate risk communication about and risk mitigation against endometrial cancer in real world clinical practice. Given this circumstance, it is essential to have long-term endometrial safety data with your product in labeling, at the time of approval, to adequately guide prescribers’ decisions concerning endometrial surveillance and the need for progestogen therapy.

Question 2: Does the Division agree that the current class labeling would be appropriate for the 4 µg and 10 µg strengths of TX-004HR?

### **FDA Response:**

The current class labeling will not be sufficient to support approval of your product with only 12 weeks of endometrial data for the reasons explained in our response to Question 1.

### **Clinical Reviewer’s Comments:**

A study synopsis for a proposed long-term study was provided in the Type A Meeting Request and Briefing Document. TherapeuticsMD proposed that long-term safety of the 4 mcg and 10 mcg estradiol vaginal inserts could be confirmed in a (b) (4) postmarketing clinical safety trial.

Question 3: Does the Division agree that the proposed clinical study is properly designed to provide the requested long-term endometrial and general safety of TX-004HR?

### **FDA Response:**

To address the deficiencies precluding approval, you will need to conduct a pre-approval endometrial and general safety trial with TX-004HR of a minimum of one year duration, for the reasons outlined in our May 5, 2017, Complete Response letter. Based on the context of use of these products in the real-world, generally without a progestogen, data of sufficient duration of use with locally administered “low” dose estrogen-alone products are important to ensuring the safe use of these products. Be advised that we are deliberating the adequate duration of endometrial safety evaluation for these approved and investigational estrogen-alone products, which would include your product; such safety evaluation may span multiple years.

### **Clinical Reviewer’s Comments:**

DBRUP provided comments and recommendations on the proposed (b) (4) and requested that TherapeuticsMD submit a final protocol for review and comment.

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### Question 4:

(b) (4)

does the Division agree that only safety data needs to be collected in the proposed postmarketing long-term safety study?

### **FDA Response:**

No. See our response to Question 3.

Question 5: Does the Division agree with TherapeuticsMD's proposal for resubmission of NDA 208564?

### **FDA Response:**

No, we do not agree. Refer to our responses to Questions 3 and 4. We do not agree with your proposed postmarketing clinical trial for the 4 mcg and 10 mcg estradiol vaginal inserts.

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

An overall discussion occurred between the Agency and TherapeuticsMD in the Type A meeting. TherapeuticsMD noted that the Women's Health Initiative (WHI) Observational Sub-trial has collected data on real-world use of vaginal estradiol products and may be able to provide safety data to better understand and support the safe use of estrogen-alone products administered vaginally.

TherapeuticsMD discussed the research of one of its consultants, (b) (4), which concluded that TX-004HR, which is administered to the lower third of the vagina, will not appreciably result in uptake and effect on the endometrium.

**July 7, 2017-** Office of Surveillance and Epidemiology (OSE) was consulted to review manuscript of the WHI Observational Sub-trial and provide assessment of data.

**July 19, 2017-** TherapeuticsMD submitted a Dispute Resolution/ Request for Resolution above the Division Level because:

- "DBRUP never advised TherapeuticsMD that the 505(b)(2) application would be deficient without endometrial and general safety data from a long-term (e.g., 12-month) study of TX-004HR, though the Division knew that the Company's clinical development program did not include a long-term endometrial and general safety study of TX-004HR.
- TherapeuticsMD's 505(b)(2) application for TX-004HR is not deficient because it provides or references all of the long-term endometrial and general safety data that is required.
- Based on its numerous communications and interactions with DBRUP and the 2003 Clinical Evaluation Guidance, TherapeuticsMD conducted a 12-week, phase 3 clinical trial (Trial TXV14-01) of TX-004HR that evaluated efficacy and safety, including

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endometrial biopsies at Baseline and Week 12. There were no cases of endometrial hyperplasia or endometrial cancer and no signal of exogenous endometrial stimulation in the 12-week clinical trial.

- The current estrogen class labeling proposed for TX-004HR adequately communicates the long-term safety of the product and therefore supports approval of TherapeuticsMD's 505(b)(2) application. All currently approved estrogen products have labeling based on this guidance. The proposed labeling for TX-004HR likewise is based on and is consistent with the 2005 Labeling Guidance.
- There were no cases of endometrial hyperplasia or endometrial cancer in the 12-week clinical trial. Twelve weeks is a valid and reliable measurement for endometrial evaluation based on the dosing regimen for TX-004HR that includes a daily loading phase for two weeks at the start of treatment (when the estradiol level will ostensibly be highest), followed by a maintenance phase of one insert administered vaginally twice weekly thereafter.
  - Endometrial proliferation was only reported in one subject in the 10 µg arm (1/91) with no reported proliferation in the 4 µg arm. This incidence rate is well within background rates of the general postmenopausal population and lower than the rates reported in the placebo groups of other studies in a similar population (ranging from 3.2% to 10.7%). One case of endometrial proliferation is not suggestive of a signal for endometrial stimulation and, in any event, endometrial proliferation is not a signal for endometrial cancer.
- The 4 µg dose of TX-004HR, when approved, will be the lowest dose available for postmenopausal women with VVA who may seek treatment for moderate to severe dyspareunia."

**July 21, 2017** – TherapeuticsMD submitted a Formal Dispute Resolution Request – Withdrawal Without Prejudice after discussion with representatives from the Center for Drug Evaluation and Research's Dispute Resolution Team.

**July 27, 2017** – TherapeuticsMD request Type B Chemistry, Manufacturing, and Controls meeting to discuss propose analysis of estradiol-related compounds and degradation impurities by HPLC-MS identified in the CRL as not approvability issues. Type B meeting scheduled for September 19, 2017.

**August 3, 2017** - Agency sends General Advice letter to TherapeuticsMD: "We are currently conducting a comprehensive review of the published literature regarding the use of vaginal estrogen products and the risk of endometrial hyperplasia or cancer. Our review will include the findings from the WHI-Observational Study; we are working with the study's investigators to gain a full understanding of its strengths and limitations in assessing the risk of endometrial cancer in users of vaginal estrogen products relative to non-users.

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- To aid in our review, we request that you submit, by September 18, 2017, all literature references that provide an evaluation of vaginal estrogen use and risk of endometrial hyperplasia or cancer, regardless of positive or negative findings, to your NDA. In this submission, also provide your critical review and interpretation of the body of literature overall and by dose, if the information is available. The findings of the 2016 Morch et al. publication identified below should be discussed in your review:
  - Morch LS, Kjaer SK, Keiding N, Lokkegaard E, Lidegaard O. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. *Int J Cancer*. 2016; 138(6):1506-15.
- We propose a meeting with you in November 2017 to provide you a status update of our review of the published literature and discuss potential next steps for your application.” A November 3, 2017 meeting was scheduled.

**September 14, 2017** – TherapeuticsMD submitted a Clinical Information Amendment: Response to the General Advice Letter dated August 3, 2017 Request for a Literature Review.

### **Clinical Reviewer’s Comments:**

See Subsection 8.2 Review of the Safety Database in this review for a summary of the quality of evidence provided by TherapeuticsMD in the September 14 Clinical Information Amendment.

See also the Memorandum to the File, dated November 14, 2017, for a full discussion of the information submitted in the September 14, 2017 Clinical Information Amendment.

**September 19, 2017** – Type B CMC meeting with TherapeuticsMD. Meeting Minutes (provided to the applicant on October 16, 2017) presented the following Agency discussion:

- We acknowledge the challenges encountered with developing robust analytical procedures for the determination of assay, impurities and dissolution of your drug product. Although we find the current tests and acceptance criteria adequate for quality control purposes, the methods do not appear to be suitably robust for regulatory use, i.e., they cannot be readily replicated in another laboratory.
- We also acknowledge that the current USP monograph for Estradiol Vaginal Inserts, which is based on a tablet-like formulation, may not be suitable for your liquid-filled soft gelation capsule-based formulation. The Agency expects that robust analytical procedures will be established, and that you will work with the USP to revise the monograph.
- While we recommend that these issues be addressed prior to resubmission of the NDA, we understand that resolution of the problems will require some time. Depending on the planned timing of the NDA submission, we would consider accepting the development and validation of robust analytical procedures as post-marketing commitments. We recommend that you propose a timeline for completing the

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necessary activities. In any case, the relevant sections of Module 3 should be updated to reflect any changes to the analytical procedures and (re)validation activities.

**November 3, 2017** – The following items of discussion were provided to the applicant in the meeting minutes dated November 28, 2017:

Question 1: Given the supplemental information provided to the NDA since issuance of the CRL, does the Division agree that TherapeuticsMD's proposal for resubmission of NDA 208564 adequately addresses the CRL?

### **FDA Response:**

At this time, we understand that you propose to resubmit NDA 208564 to support approval of estradiol vaginal inserts 4 mcg and 10 mcg with non-contraceptive estrogen class labeling, and to conduct a post-marketing (b) (4) endometrial safety trial.

We have reviewed in detail the Crandall et al. and the Morch et al. papers, conducted a thorough review of the literature, and considered your summary of that literature. At this time, we find that the available information does not support definitive conclusions regarding the endometrial safety of long-term use of unopposed vaginal estrogen products in postmenopausal women for the treatment of a moderate to severe symptom of vulvar and vaginal atrophy due to menopause.

The objective of this meeting is to engage in discussion regarding the types of information that would support resubmission of NDA 208564. Listed below are the two deficiencies identified in the May 2017 Complete Response (CR) letter. Also provided are examples of the types of information that you may submit to address these deficiencies as stated in the CR letter, as well as alternative approaches that we would like to discuss with you. We remind you that the adequacy of your resubmission will be a review issue.

1. Your application does not provide long-term endometrial safety data for the 4, 10, (b) (4) mcg estradiol vaginal inserts. Sufficient assessment of endometrial histology to support chronic use is critical to the safety evaluation of unopposed estrogen and to ensure adequate labeling for safe use of your product.

The CR letter indicates that to address this deficiency, you will need to conduct and provide data from a long-term endometrial trial of sufficient size and duration to adequately characterize endometrial safety with your product. We recognize the challenges with conducting a sufficiently long and large enough clinical trial to address this concern, as well as the fact that there are uncertainties with regard to the long-term endometrial safety of approved low-dose vaginal estrogen products. Therefore, an alternative approach could be to conduct a required post-marketing, observational

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study to identify the incidence of endometrial cancer associated with long-term use of unopposed low dose vaginal estrogen products in postmenopausal women for the indication of treatment of a moderate to severe symptom (dyspareunia or vaginal atrophy) of vulvar and vaginal atrophy due to menopause. We are considering a post-marketing required study (PMR) for such an observational study with these products. The proposed study data source(s), domestic or international, should 1) include vaginal estrogen users across the entire postmenopausal age range, and 2) have linkage to national cancer registries to identify confirmed endometrial cancer cases. The median duration of study follow up should be 3 to 5 years or longer after first use of an unopposed vaginal estrogen product, with adequate numbers of long-term users to assess the risk in this population, and adequate post-exposure follow-up to capture the outcome. Appropriate comparison groups are needed to allow risk estimates for endometrial cancer, such as non-users and users of combined low dose vaginal estrogen plus progestogen. Key baseline covariates, such as body weight, should be measured and controlled to reduce confounding. (b) (4)

Should you decide to pursue this option; final details of the PMR should be agreed-to by the Agency.

### **Discussion:**

A PMR long-term observational study to identify the incidence of endometrial cancer associated use of unopposed low dose vaginal estrogen products in postmenopausal women for the indication of treatment of a moderate to severe symptom (dyspareunia or vaginal atrophy) of vulvar and vaginal atrophy due to menopause is an acceptable approach to provide long-term endometrial safety data for your estradiol vaginal inserts. The Food and Drug Administration (FDA) indicated that it was premature to discuss the PMR in detail. TherapeuticsMD acknowledged the need for a PMR and stated their intention to work closely with the Agency on protocol development.

To address the CRL deficiency for endometrial safety, FDA recommended that TherapeuticsMD provide a synopsis of their proposal for the required post-marketing study in the resubmission; TherapeuticsMD committed to do so. FDA reiterated that the data sources selected for the PMR study should be able to support a hypothesis testing safety study, with the capability of capturing and confirming cancer cases. Drug exposure should reflect the real-world user experience. The study should be sufficiently powered and provide follow-up of at least 3 years.

2. The safety evaluation of your product is expected to quantify and characterize the general safety of the drug over a reasonable duration consistent with its intended chronic use. Such extended duration of exposure is needed to adequately characterize

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the pattern of drug-related adverse reactions over time or to detect adverse reactions that may occur only with a longer duration of treatment.

The CR letter indicates that the long-term endometrial trial that would satisfy Deficiency #1 above could adequately characterize the general safety of your product. An alternative approach could be reliance on published literature via the 505(b)(2) regulatory pathway to support general safety and chronic use drug exposure for estradiol vaginal inserts 4 mcg and 10 mcg (the existing literature, however, will not be able to adequately characterize endometrial safety – see our comments above). Reliance on the published literature requires that you provide a “bridge” to the published literature. Such a bridge can be a scientific-supported rationale that the literature is scientifically sound and relevant to the proposed product, thereby supporting that reliance on the literature is scientifically appropriate. If the published literature describes a brand name product(s), then your application will rely on FDA’s finding of safety and effectiveness for that listed drug(s), and you will also have to provide any necessary patent certifications or statements to address such reliance. Refer to the 505 (b)(2) Regulatory Pathway section below.

In summary, if estradiol vaginal inserts 4 mcg and 10 mcg were to be approved based on reliance on the published literature to support general safety and chronic use drug exposure, you would receive non-contraceptive estrogen class labeling for general safety information, and a requirement for a post-marketing study to adequately characterize endometrial safety with long-term use of your product.

### ***Discussion:***

TherapeuticsMD indicated that the published literature that will be submitted to support general safety of their proposed product is largely non-product specific. FDA reiterated that if the published literature describes a listed drug(s), that is considered reliance on FDA’s finding of safety for that listed drug(s) and TherapeuticsMD should provide an appropriate patent certification or statement for each listed drug relied upon. FDA also reiterated that the “bridge” to the published literature is a scientific rationale establishing that reliance on the studies described in the literature is scientifically appropriate.

FDA explained that TherapeuticsMD’s proposal to provide data from cross-study comparisons between their proposed product and listed drugs to demonstrate similar or lower exposure is generally not acceptable for establishing relative bioavailability between products, but may be included as part of their scientific rationale to rely on the published literature to support general safety of the proposed product.

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FDA emphasized that comparison of estrogen exposure through cross-study comparisons should not be the sole source of evidence to address the lack of long-term general safety information as outlined in the Complete Response Letter. The cross-study comparison will only provide a broad qualitative overview of the relative systemic exposure of the proposed product and other estrogen products used in the literature and may be considered as part of the Sponsor's scientific bridge to the literature. A cross-study comparison will not provide a precise comparison of systemic estrogen exposures.

TherapeuticsMD acknowledged the Agency's advice and committed to submitting a full overview of studies in the literature that will be used to support the general safety of their product, as well as their scientific justification for reliance on such literature. The NDA resubmission will include a mapping table.

### 3.3. Foreign Regulatory Actions and Marketing History

Imvexxy™ (estradiol vaginal inserts) is not marketed in the United States or internationally.

## 4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

The mandatory Biomedical Research Information requested by the OSI was presented and reviewed in the original NDA 208564 application. OSI clinical inspections were conducted at four sites: 1) Site 400, Dr. David Portman; 2) Site 454, Dr. Robin Kroll; 3) Site 454, Dr. William Kolton; and 4) Site 484, Dr. Christ-Ann Magloire. Form FDA 483 was not issued to any of the sites inspected. All sites inspected received a NAI classification.

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

See the Primary Clinical Review, dated April 28, 2017, Section 3 Ethics and Good Clinical Practice, Subsection 3.1 Submission Quality and Integrity for a full discussion. See also the archived OSI Clinical Inspection Summary, dated March 23, 2017.

### 4.2. Product Quality

See the Quality Assessment Review, dated April 17, 2017, for a full discussion of the Chemistry, Manufacturing, Controls (CMC) issues identified in the original NDA application and conveyed to TherapeuticsMD in the CRL dated May 5, 2017 as follows:

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### Additional Comments:

We have the following comments/recommendations that are not approvability issues but should be addressed prior to or by the time of your NDA resubmission:

“We remind you that the current USP includes a monograph for Estradiol Vaginal Inserts. We understand that the current USP monograph may not be a suitable public standard for your new drug product. However, there is an expectation that your product will conform to the compendial monograph requirements. Alternatively, deviations from the monograph requirements should be identified on your product labels. We recommend that you petition the USP with proposed revisions to the monograph in order to accommodate your new drug product. Please see the following link for more information about that USP process: <http://www.usp.org/usp-nf/pending-monographs>.”

“Specifically, we note differences in assay test method and acceptance criteria, the dissolution test method and acceptance criteria, and in the procedure for determining related substances.”

“The proposed analysis of estradiol related compounds and degradation impurities by HPLC-MS may be acceptable for quality control purposes in the firm’s laboratory but is currently unacceptable for regulatory purposes because the method does not work with a similar mass spectrometer in two different locations. It is therefore incumbent upon you to propose methods that are suitable for regulatory purposes.”

“With regard to the dissolution test method, we recommend that you perform dissolution method validation in accordance with US<1092>, The Dissolution Procedure: Development and Validation, and adopt appropriate acceptance criteria.”

On September 19, 2017, the Agency held a Type B Post-Action Meeting (teleconference) with TherapeuticsMD to discuss the “Additional Comments, Chemistry, Manufacturing and Controls section of the Complete Response Letter (CRL) regarding the LC-MS method, TxMD-002R02, Analysis of Estradiol Related Compounds and Degradants / Impurities in Low Dose Estradiol Vaginal Inserts by HPLC-MS.”

See Section 3.2 of this review and the meeting minutes, dated October 16, 2017 for a discussion of CMC issues and concerns.

NDA 208564 resubmission includes:

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- The work initiated at (b) (4) to develop alternative method(s) based on HPLC with UV detection to determine unknown and known impurities that can be utilized as regulatory method(s). At the September 19, 2017 teleconference with the Agency, TherapeuticsMD committed to submit the results of this work to the NDA as a post-approval commitment.
- An updated method TxMD-002 R3.0: Analysis of Estradiol Related Compounds and Degradation Impurities in Low Dose Estradiol Vaginal Inserts by HPLC-MS providing additional detail from the commercial manufacturer's laboratory.
- A protocol designed to conduct a full revalidation of the dissolution method at the proposed commercial manufacturer's laboratory. The resubmission includes a revised method TxMD-003 R4.0: Dissolution of Estradiol in Estradiol Vaginal Inserts by HPLC, providing additional detail from the commercial manufacturer's laboratory. Per the applicant, the revalidation will be performed using this method. At the September 19, 2017 teleconference with the Agency, TherapeuticsMD committed to submit the validation protocol in the resubmission and to submit the results to the NDA as a post-approval commitment.
- An update of the previously submitted method for assay, identification, and uniformity of dosage. The specification for estradiol (b) (4) USP (b) (4) is updated to be consistent with the drug substance manufacturer, to include a footnote that, (b) (4) The manufacturers list for drug product was updated for recent dates of inspection at various facilities and to add to the test responsibilities at (b) (4) the ability to test product for release and stability. The Form FDA 356h was updated accordingly.

On January 12, 2018, TherapeuticsMD updated Section 3.2.P.8 Drug Product Stability of the NDA with available stability data for (b) (4) Catalent batches, including 30 months of stability data for (b) (4) registration batches and 18 months of stability data for Catalent registration batches. In addition, the submission includes up to 36-months stability data for the three phase 3 clinical batches with the pull date, test site, and analytical procedure version provided for these data.

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

Per the Quality Assessment Review, dated April 23, 2018, "Sufficient information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality, purity, potency and bioavailability of the drug product. The commercial drug substance and drug product manufacturing, packaging and testing facilities have acceptable CGMP status. The claimed categorical exclusion from the environmental assessment requirements is granted."

"Because there is a USP drug product monograph for Estradiol Vaginal Inserts, 10 mcg and 25 mcg per insert, there is an expectation that the TherapeuticsMD (TXMD) product

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will meet the compendial monograph requirements. However, because the TXMD product is a soft gelatin capsule formulation that is quite distinct from the tablet formulation (i.e., Vagifem) upon which the USP monograph is based, and because a new, lower strength (4 mcg) is proposed, the USP monograph is not a suitable public standard for TherapeuticsMD's new drug product. TherapeuticsMD, should therefore petition the USP with proposed revisions to the monograph in order to accommodate TXMD's new drug product."

In the CRL, dated May 5, 2017, and further discussed during the September 19, 2017 meeting with CMC, TherapeuticsMD proposed the following postmarketing commitments (PMCs) (per email correspondence dated January 23, 2018). Per the Office of Pharmaceutical Quality (OPQ) perspective, the following two (2) PMCs are acceptable if TherapeuticsMD complies as follows:

1. Develop, and if feasible, validate new regulatory methods for known and unknown estradiol impurities (related compounds) in the drug product.
2. Perform a revalidation of the dissolution method TxMD-003 in accordance with requirements of USP using one batch of each strength of the for-market formulations manufactured by the proposed commercial manufacturer.

On April 25, 2018, TherapeuticsMD agreed to the following PMC scheduled milestones:

### PMC #1

Description: Develop and validate a new regulatory method capable of detecting known and unknown estradiol-related impurities in the drug product.

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PMC Schedule Milestones:	Development Report Submission:	Within 30 days after Approval
	Study/Trial Completion:	Within 180 days after Approval
	Final Report Submission:	Within 180 days after Approval
	Other: <u>          N/A          </u>	<u>          N/A          </u>

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### PMC #2

Description: Perform a revalidation of the dissolution method TxMD-003 in accordance with requirements of USP using one batch of each strength of the for-market formulation manufactured by the proposed commercial manufacturer.

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PMC Schedule Milestones:	Draft Specification Submission:	30 days after the Approval
	Study/Trial Completion:	N/A
	Final Report Submission:	Submitted in first NDA Annual Report
	Other: N/A	N/A

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

See the original Quality Assessment Review, dated April 17, 2017 and the NDA resubmission Quality Assessment Review, dated April 23, 2018, for a discussion of CMC issues, concerns, comments and recommendations. See the archived PMR/PMC Development Template: Product Quality (CMC) documents for PMC #1 and PMC #2, dated May 14, 2018 and May 4, 2018, respectively.

### **4.3. Clinical Microbiology**

The original NDA 208564 Clinical Microbiology Review, dated January 30, 2017, determined that the non-sterile estradiol vaginal insert had a microbial release specification consistent with compendial recommendations and was tested regularly on stability for microbiological quality. No deficiencies were identified by the Clinical Microbiology Reviewer based upon the information provided for the estradiol vaginal insert in the original NDA application.

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

The Clinical Microbiology Reviewer recommended approval of NDA 208564 in the original NDA application. "No product quality microbiology deficiencies were identified based upon the information provided."

In the NDA resubmission, the drug substance specification was updated with a footnote stating that (b) (4) Per the Clinical Microbiology Review, "The applicant's proposed change to the drug substance

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specification is satisfactory since each lot of drug product is subjected to microbial enumeration testing at release.”

See the Clinical Microbiology Reviews, dated January 3, 2017 and February 16, 2018.

### 4.4. Nonclinical Pharmacology/Toxicology

TherapeuticsMD had not conducted any nonclinical safety pharmacology studies with the estradiol vaginal inserts in the original NDA application, relying instead, on the “well-established safety history of estradiol, and on published literature for the nonclinical toxicology, mutagenicity, and carcinogenicity sections of this NDA” to inform Section 8 (Use in Specific Populations) and Section 13 (Nonclinical Toxicology) of labeling.

The Pharmacology/Toxicology Reviewer determined that the literature submitted was adequate to support the nonclinical safety of estradiol without relying on previous findings of safety for an approved product. Pharmacology/Toxicology recommended approval of the original NDA 208564 application without additional nonclinical studies requested.

NDA 208564 resubmission continues to rely upon the well-established safety history of estradiol, and on published literature to inform Section 8 (Use in Specific Populations) and Section 13 (Nonclinical Toxicology) of labeling.

#### **Clinical Reviewer’s Comments:**

The Pharmacology/Toxicology Reviewer references the original NDA 208564 application, received July 7, 2016, for the literature the applicant submitted in support of the nonclinical safety of estradiol without relying on previous findings of safety for an approved product. Per the Pharmacology/Toxicology Review, dated April 17, 2018, “Nonclinical data support approval of TX-004HR for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.”

See the Pharmacology/Toxicology Reviews, dated March 29, 2017 and April 17, 2018.

### 4.5. Clinical Pharmacology

The NDA 208564 resubmission does not contain any new biopharmaceutics and pharmacokinetic information.

The pharmacology of the active pharmaceutical ingredient (API), (b) (4) estradiol (b) (4), is well-established.

The Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III (DCP III) recommended approval of estradiol vaginal inserts 4 mcg, 10 mcg, (b) (4) from a Clinical

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Pharmacology perspective in the original NDA application. See the Clinical Pharmacology Review, dated April 7, 2017.

Based upon the two phase 1 relative bioavailability studies (ESTR-1K-499-12 and ESTR-1K-500-12) reported in the original NDA, estradiol and estrone systemic exposures in postmenopausal women were lower with the 10 mcg and 25 mcg estradiol vaginal inserts compared to active comparators (Vagifem® 10 mcg and 25 mcg, respectively) and provided a more rapid systemic absorption profile with an earlier  $t_{max}$  at approximately 2 hours.

A pharmacokinetic (PK) sub-trial was conducted in the phase 3, 12-week clinical trial (Trial TXV14-01). Serum samples for PK measurements were analyzed for estradiol, free estrone, and total conjugated estrone (using estrone sulfate as the standard). At the lowest dose of 4 mcg estradiol vaginal insert, there was minimal systemic absorption of estradiol, estrone and estrone conjugate. The mean (SD) concentrations of estradiol, estrone and estrone conjugate were 3.92 (2.43), 15.33 (4.80) and 237.7, respectively, and were comparable to = the same analytes in the placebo groups, 4.94 (2.61), 19.37 (8.78) and 275.9 (153.67). Estradiol concentrations were comparable to baseline concentrations of 4-7 pg/mL in postmenopausal women at Day 1 and Day 14. The estradiol concentrations at Day 84 (4 days after last dose), for the 4 mcg estradiol vaginal insert, were also similar to Baseline. In addition, the 4 mcg estradiol vaginal insert did not lead to a significant increase in serum concentrations of estrone and estrone conjugates, which were both consistent with normal postmenopausal female concentrations.

For trial participants in the 10 mcg estradiol vaginal insert treatment group in the PK sub-trial, estradiol concentrations peaked at about 2 hours post-dose and dropped to the baseline range at ~6 hours post-dose. Baseline-adjusted  $C_{max}$ , but not  $AUC_{0-24}$ , was significantly higher compared to placebo on Day 1 and Day 14. Estradiol concentrations at Day 84 were similar to Baseline.

Highest estradiol exposures were seen with the 25 mcg estradiol vaginal insert. The baseline-adjusted  $AUC_{0-24}$  and  $C_{max}$  were both statistical significantly higher than placebo on Day 1 and at Day 14. Additionally, there was no evidence of accumulation at Day 84.

For 10 mcg and 25 mcg estradiol vaginal inserts, estrone exposures as measured by  $C_{max}$  and  $AUC_{0-24}$  were both similar to the placebo group with no statistical differences noted at either Day 1 or Day 14.

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

See the Clinical Pharmacology Review, dated April 7, 2017, for a discussion of the PK information related to the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal inserts reported in the original NDA application.

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At the Type C November 3, 2017 meeting with TherapeuticsMD, the Agency agreed that the absence of long-term general safety of the 4 mcg and 10 mcg estradiol vaginal inserts could be addressed through reliance on 1) published literature via the 505(b)(2) pathway, and 2) phase 4 required postmarketing observational study to assess long-term general and endometrial safety. Reliance on the published literature would require a “bridge” to the published literature. “Such a bridge could be a scientific-supported rationale that the literature is scientifically sound and relevant to the proposed product, thereby supporting that reliance on the literature is scientifically appropriate.”

In the NDA resubmission, the “bridge” between the published literature and the 4 mcg and 10 mcg estradiol vaginal inserts consists of the following elements:

1. Estradiol is estrogen therapy that has been studied and reported on in the relied upon published literature. The predominant biological effects of estradiol are mediated through ER $\alpha$  and ER $\beta$ . All estrogens are full ER $\alpha$  and ER $\beta$  agonists.
2. The FDA recognizes the scientific soundness of the published literature via its use as the basis of current estrogen class labeling (resubmission includes reference to the Agency’s draft 2005 Labeling Guidance for Industry). General safety of estradiol is well identified for doses ranging from 7.5 mcg to 2 mg, and different formulations (oral, transdermal/topical, and vaginal preparations).
3. Prior to the Women’s Health Initiative publications (regarding the CE-alone and CE plus MPA substudies), estrogen class labeling was supported by published data for estradiol and ethinyl estradiol.
4. Estradiol vaginal inserts, 4 mcg and 10 mcg, demonstrated lower systemic exposure than that of the approved products which form the basis of the relied-upon literature. “The steady state pharmacokinetic (PK) levels of TX-004HR (Table 1) are well below those of products that form the basis of the relied upon literature and are, in fact, similar to the estradiol and estrone concentrations of placebo treated subjects.” The Warnings and Precautions section in current estrogen class labeling are “based on literature of 17 $\beta$ -estradiol products of  $\geq$  1 mg and conjugated equine estrogens  $\geq$  0.625 mg.”

TherapeuticsMD provides the following information in the NDA resubmission to illustrate the “bridge”. See Table 2.

Table 2: Pharmacokinetic Profiles of Estrogen Products

	E2		E1		E1C	
	AUC <sub>0-24</sub> (pg.h/mL)	C <sub>avg(0-24)</sub> (pg/mL)	AUC <sub>0-24</sub> (pg.h/mL)	C <sub>avg(0-24)</sub> (pg/mL)	AUC <sub>0-24</sub> (pg.h/mL)	C <sub>avg(0-24)</sub> (pg/mL)
17 $\beta$ -estradiol 2 mg <sup>a</sup>	1620.55 <sup>b</sup>	59.38 <sup>c</sup>	8686.62 <sup>b</sup>	410.98 <sup>c</sup>	524,920 <sup>b</sup>	51,390 <sup>c</sup>

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	E2		E1		E1C	
17β-estradiol 1 mg <sup>d</sup>	---	35	---	190	---	---
17β-estradiol 1 mg <sup>e</sup>	823	34.0 <sup>c</sup>	2923	169 <sup>c</sup>	---	---
Conjugated equine estrogens 2 X 0.625 mg <sup>f</sup>	---	---	5016	139	134,000	7300
Estradiol vaginal insert 10 mcg <sup>g</sup>	138	5.76	463	19.3	5932	247
Estradiol vaginal insert 4 mcg <sup>g</sup>	92	3.92	290	13	5078	216
Placebo <sup>g</sup>	117	4.86	468	19.5	5638	245

Source: Adapted from NDA 208564 Resubmission, Module 1 Regional, Submodule 1.11 Information Amendment Information Not Covered Under Module 2 to 5, Submodule 1.11.14 Multiple Module Information Amendment, Table 1, page 8 of 33.

a Summary Basis of Approval, ANDA 40275, Bioequivalence Review, Tables 2, 5,8.

b AUC from 0 to 72 hours.

c C<sub>max</sub>

d Lobo and Cassidenti, 1992.

e Price, et al. 1997.

f Summary Basis of Approval, NDA 4782/S-115, S-130, page 16.

g Trial TXV14-01

Abbreviations: E2 = estradiol; E1 estrone; E1C = estrone conjugate; AUC<sub>0-24</sub>= area under curve for 0 to 24 hours;

C<sub>avg</sub> = average concentration for 0 to 24 hours.

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

Table 2 demonstrates that the AUC and C<sub>avg</sub> for oral estradiol 1 mg tablets identified in publications [Lobo RA and Cassidenti DL, 1992 (1 mg estradiol), and Price TM, et al. 1997 (1 mg estradiol)], are higher (up to 10 times) than the AUC and C<sub>avg</sub> for the 4 mcg and 10 mcg estradiol vaginal inserts as reported in phase 3, 12-week Trial TXV14-01.

These results are expected due to high systemic absorption of orally administered estrogens. We expect orally administered high dose estradiol tablets and orally administered high dose conjugated estrogens tablets to produce steady state estradiol and estrone PK levels that would exceed levels produced by low dose vaginally administered estradiol inserts (for example, 4 mcg and 10 mcg estradiol vaginal inserts). Therefore, this reviewer questions the appropriateness of selecting high dose oral estrogen products for inclusion in Table 2 to compare PK profiles. This reviewer opines that this was done to magnify the difference in PK profiles between orally and vaginally administered estrogen products, further supporting the lower dosage and lower systemic exposure of the 4 mcg and 10 mcg estradiol vaginal inserts as significantly lower than approved hormone therapy products with a VVA indication. A comparison to vaginally administered hormone therapy products is more appropriate. Nonetheless, Table 2 demonstrates the lower systemic exposure of the 4 mcg and 10 mcg vaginal

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inserts as compared with orally administered estrogens. The Clinical Pharmacology and Clinical Review Teams view the information submitted by TherapeuticsMD and provided in Table 2 from the SBA of ANDA 402075 for 2 mg oral estradiol tablets and from the SBA of NDA 04782 for oral conjugated estrogens tablets (total dose of 1.25 mg), as supportive but not required in their considerations of approvability of this resubmission.

The Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology-3 (DCP-3) concludes that:

- A review of the analytical methods for each trial was not possible and is therefore a limitation of a cross-trial review. The fold changes are suggestive of higher estrogen exposure from estradiol oral tablets and Premarin oral conjugated estrogens. However, a direct, quantitative comparison to the proposed estradiol vaginal inserts is not feasible due to the cross-trial nature of comparison.
- The Clinical Pharmacology Review, archived April 20, 2018, summarized a cross-study comparison showing that the systemic estradiol, estrone, and estrone conjugate exposure from Premarin, 2 x 0.3 mg oral tablets (data from approved labeling of NDA 04782) was generally higher compared to estradiol vaginal insert 10 mcg.
- In a cross-study comparison, this addendum shows that the systemic estradiol exposure is 6.0- and 3.1-fold higher in AUC<sub>0-24</sub> and C<sub>max</sub>, respectively, with estradiol oral tablet, 1 mg (data from Price TM, et al. 1997 publication), compared to estradiol vaginal insert, 10 mcg (data from sponsor's NDA).
- In a cross-study comparison, this addendum shows that the systemic unconjugated estrone exposure is 6.3- and 7.2-fold higher in AUC<sub>0-24</sub> and C<sub>max</sub>, respectively, with estradiol oral tablet, 1 mg (data from Price TM, et al. 1997 publication), compared to estradiol vaginal insert, 10 mcg (data from sponsor's NDA).
- Estradiol vaginal insert 4 mcg is known to have a lower systemic exposure than estradiol vaginal insert 10 mcg; therefore, systemic estrogen exposure from the 4 mcg dose is also lower than estradiol oral tablet, 1 mg.

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

DCP-3 recommends approval of 4 mcg and 10 mcg estradiol vaginal inserts from a Clinical Pharmacology perspective. See the Clinical Pharmacology Addendum Review, dated May 15, 2018.

## **4.6. Devices and Companion Diagnostic Issues**

There are no devices and companion diagnostic issues with the estradiol vaginal inserts.

## **4.7. Consumer Study Reviews**

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No label comprehension, patient self-selection, or other human factor studies were evaluated during the estradiol vaginal insert development program.

At a pre-NDA meeting held December 15, 2015, the Division of Medication Error Prevention and Analysis (DMEPA) recommended that TherapeuticsMD provide a comprehensive use-related risk analysis (URRA) and identify the use-related risks users might commit or the tasks they might fail to perform and the potential negative clinical consequences of such errors. Because the estradiol insert will not have an applicator (an applicator suggests that the product is not for oral administration), DMEPA was concerned that the “inserts” may lead to wrong route of administration errors (e.g., oral administration of the vaginal insert), and instructed TherapeuticsMD to include in their URRA the risk for wrong route errors and to propose how this risk can be mitigated.

The Applicant submitted a URRA in the original NDA application, indicating the following:

- The use-related risk analysis did not reveal a safety concern for oral or other incorrect routes of administration.
- The risk analysis included an evaluation of all the steps involved in using the vaginal product.
- The vaginal product is “non-toxic” and would not cause harm if a single or multiple doses were ingested. Per the applicant, the risk of oral ingestion of the vaginal insert can be mitigated in labeling by emphasizing the vaginal route of administration. “Vaginal” is included in the established name of the product, in the net quantity statement, and in the dosage administration statement.
- “For Vaginal Use Only” is proposed for the principle display panel of the carton labeling and on the blister label.

DMEPA, in consultation with the Division, considered the risk that the user would ingest the medication orally and determined that the 4 mcg and 10 mcg estradiol vaginal inserts posed no greater risk than other approved estrogen products if ingested in excess. DMEPA determined that the proposed labeling mitigation strategy appeared to be adequate in that it prominently emphasizes the route of administration in several locations in the labeling which increases the opportunity for the user to see this important information.

### **Clinical Reviewer’s Comments:**

Based on the information submitted by TherapeuticsMD in the first review cycle, DMEPA agreed that no Human Factor testing was necessary for the estradiol vaginal insert.

## **5. Sources of Clinical Data and Review Strategy**

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### 5.1. Table of Clinical Studies

The clinical development program for TX-004HR (estradiol vaginal insert) included the conduct and completion of five (5) clinical trials including:

- Three (3) phase 1 PK trials
- One (1) phase 2, 14-day efficacy and safety trial
- One (1) phase 3, 12-week efficacy and safety trial

See the Primary Clinical Review, dated April 28, 2017, Section 5 Source of Clinical Data, Subsection 5.1 Table of Studies/Clinical Trials, Table 12: Listing of Clinical Trials in in the TX-004HR (Estradiol Vaginal Insert) Development Program for detailed information on the clinical trials conducted during the estradiol vaginal inserts development program.

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

The absence of long-term endometrial safety data and chronic use drug exposure data was a safety concern in the original NDA 208564 application which received a CRL on May 5, 2017.

### 5.2. Review Strategy

See the Primary Clinical Review, dated April 28, 2017, Section 5 Source of Clinical Data, Subsection 5.2 Review Strategy for the review strategy employed during the original review of NDA 208564.

## 6. Review of Relevant Individual Trials Used to Support Efficacy

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### 6.1. TXV14-01

#### 6.1.1. Study Design

See the Primary Clinical Review, dated April 28, 2017, Section 5 Source of Clinical Data, Subsection 5.3 Discussion of Individual Studies/Clinical Trials, Heading 5.3.1 TXV14-01 for a full review of the study design of phase 3, 12-week, Trial TXV14-01.

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

DBRUP concurred with the trial design of Trial TXV14-01 including enrollment criteria (Inclusion and Exclusion criteria); co-primary efficacy endpoints: 1) percentage of vaginal superficial cells compared to placebo, 2) percentage of vaginal parabasal cells compared to placebo, 3) vaginal pH compared to placebo; 4) the severity of the MBS of dyspareunia associated with VVA compared to placebo; safety assessments; and

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statistical methodology including the primary efficacy analyses.

DBRUP did not concur, however, with the endometrial assessments presented in the original NDA 208564 application, specifically, the final reported histological findings of the three independent pathologists as a category rather than reporting the individual histologic characteristics of the endometrium reported by each of the three independent pathologists for each trial participant with a uterus who had an endometrial biopsy at end-of-treatment. On September 21, 2016, during the original NDA review cycle, DBRUP requested that the applicant provide a copy of each endometrial biopsy report generated by each of the three pathologists for each trial participant with a uterus. TherapeuticsMD provided the requested information on October 20, 2016.

The risk of endometrial hyperplasia/ cancer in non-hysterectomized postmenopausal women receiving estrogen-alone therapy is a major concern with the use of hormonal therapy for the treatment of VVA symptoms due to menopause.

See the Primary Clinical Review, dated April 28, 2017, Section 7 Review of Safety, Subsection 7.3 Major Safety Results, Subsection 7.3.5 Submission Specific Primary Safety Concerns, Subsection 7.3.5.1 Endometrial Safety for a full review of the endometrial assessment conducted in phase 3, 12-week Trial TXV14-01.

### **6.1.2. Study Results**

All three doses of the estradiol vaginal insert (4 mcg insert, 10 mcg insert, and 25 mcg insert) demonstrated statistically significant improvements compared with placebo in the four co-primary endpoints evaluated (change from Baseline versus placebo in severity of the most bothersome symptom of dyspareunia, vaginal pH, percentage of vaginal superficial cells and percentage of parabasal cells) in 12-week, phase 3 Trial TXV14-01. The Clinical and Statistical teams concurred with the applicant's finding of efficacy for estradiol vaginal inserts 4 mcg, 10 mcg, and 25 mcg based on successfully achieving the primary protocol-defined co-primary endpoints of 1) a statistically significant reduction versus placebo in moderate to severe dyspareunia, 2) a statistically significant increase in superficial epithelial cells and a corresponding statistically significant decrease in parabasal epithelial cells on a vaginal wall smear, and 3) a statistically significant reduction in vaginal pH in the single, primary, phase 3 clinical Trial TXV14-01 submitted in the original NDA application on July 7, 2016.

The Clinical team also concurred with the applicant's statements in the Clinical Information Amendment received October 11, 2016 that the proposed indication, treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause, is for a chronic use indication in postmenopausal women, and that the original NDA application did not provide exposure data at 6 months and 12 months for the 4 mcg, 10 mcg, and 25 mcg estradiol

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vaginal inserts. The available 12-week efficacy and safety data submitted in the original NDA 208564 application was insufficient to demonstrate long-term general and endometrial safety data and chronic use drug exposure data for the 4 mcg, 10 mcg, (b) (4) estradiol vaginal inserts.

The lack of long-term general and endometrial safety data in the application precluded a recommendation for approval of the estradiol vaginal inserts for the proposed indication during the original NDA review cycle.

## 7. Integrated Review of Effectiveness

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### 7.1. Assessment of Efficacy Across Trials

No assessment of efficacy across trials was completed during the original NDA 208564 review. Phase 3, 12-week, clinical Trial TXV14-01 was the single, phase 3 efficacy and safety trial conducted.

### 7.2. Additional Efficacy Considerations

#### 7.2.1. Considerations on Benefit in the Postmarket Setting

In the postmarketing setting, (b) (4)

Labeling must clearly define the dosing regimen which demonstrated efficacy of the 4 mcg and 10 mcg estradiol vaginal inserts in the single, 12-week, phase 3 clinical trial.

Subpopulation analyses in phase 3 Trial TXV14-01 by race and ethnicity did not show any consistent treatment effect of the estradiol vaginal inserts relative to placebo across age groups. However, Trial TXV14-01 was not powered to make any reasonable conclusions from these subgroup analyses.

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

See the Primary Clinical Review, dated April 28, 2017, and the Statistical Review, dated April 4, 2017 for more detailed information.

#### 7.2.2. Other Relevant Benefits

Estradiol vaginal inserts, 4 mcg and 10 mcg, are administered manually, via the index finger, into the vagina (approximately 2 inches) without the use of an applicator. This manual administration of the inserts may benefit postmenopausal women apprehensive about the use

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of an intravaginal applicator for application of the insert.

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

However, some postmenopausal may be uncomfortable with the manual insertion of the 4 mcg and 10 mcg estradiol vaginal inserts.

## **7.3. Integrated Assessment of Effectiveness**

In the first review cycle, this reviewer determined that TherapeuticsMD submitted substantial evidence of effectiveness for the 4 mcg and 10 mcg estradiol vaginal inserts in the single, 12-week Trial TXV14-01 conducted and submitted to support the indication of the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. A randomized, placebo-controlled, 12-week efficacy and safety clinical trial is appropriate and in compliance with the Agency's draft 2003 Clinical Evaluation Guidance for Industry for the proposed indication.

Efficacy results from Trial TXV14-01, submitted in the original application, successfully achieved the primary protocol-defined co-primary endpoints of 1) a statistically significant reduction versus placebo in moderate to severe dyspareunia, 2) a statistically significant increase in superficial epithelial cells and a corresponding statistically significant decrease in parabasal epithelial cells on a vaginal wall smear, and 3) a statistically significant reduction in vaginal pH in the single, primary, phase 3 clinical Trial TXV14-01 submitted in this NDA application. Therefore, clinical Trial TXV14-01 data supports effectiveness of the 4 mcg and 10 mcg estradiol vaginal inserts in the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

## **8. Review of Safety**

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### **8.1. Safety Review Approach**

The applicant's safety evaluation of the 4 mcg and 10 mcg estradiol vaginal inserts was considered to be inadequate in the original NDA 208564 application. No long-term general and endometrial safety data or chronic use drug exposure data was obtained during the estradiol vaginal inserts development program. The maximum time of exposure to estradiol vaginal inserts was 12-weeks in Trial TXV14-01. The 12-weeks safety data from Trial TXV14-01 was inadequate to assess long-term general and endometrial safety of the 4 mcg and 10 mcg estradiol vaginal inserts to support the proposed indication for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

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Treatment of symptoms of VVA, including moderate to severe dyspareunia, may involve long-term, chronic use hormone therapy. The risk of endometrial hyperplasia/cancer in non-hysterectomized postmenopausal women receiving estrogen-alone therapy is a major concern with the use of hormone therapy for the treatment of symptoms due to menopause. Endometrial histology evaluation, obtained at or greater than 12 months of use, is critical to the safety evaluation of unopposed estrogen.

See Section 3.2 Summary of Presubmission/Submission Regulatory Activity, in this review, for a summary of regulatory activity prior to the resubmission of NDA 208564 on November 29, 2017.

In the pre-NDA resubmission meeting on November 3, 2017, TherapeuticsMD commits to:

- Provide published literature via the 505(b)(2) regulatory pathway to support general safety and chronic use drug exposure information for estradiol vaginal inserts 4 mcg and 10 mcg.
- Provide a “bridge” to the published literature. Such a bridge can be a scientific-supported rationale that the literature is scientifically sound and relevant to the proposed product, thereby supporting that reliance on the literature is scientifically appropriate.
- Provide an appropriate patent certification or statement for each listed drug relied upon if the published literature describes a listed drug(s), that is considered reliance on FDA’s finding of safety for that listed drug(s).
- Accept non-contraceptive estrogen class labeling for general safety information if estradiol vaginal inserts 4 mcg and 10 mcg were to be approved based on reliance on the published literature to support general safety and chronic use drug exposure information.
- Conduct a postmarketing required (PMR) observational study to identify the incidence of endometrial cancer associated with long-term use of unopposed low dose vaginal estrogen products in postmenopausal women to address deficiency # 1 in the CRL.

## 8.2. Review of the Safety Database

NDA 208564 resubmission does not present any new clinical safety data for the 4 mcg and 10 mcg estradiol vaginal inserts to support the proposed indication, treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. For this chronic-use product, no new long-term safety data is presented for the 4 mcg and 10 mcg estradiol vaginal inserts to allow for an evaluation of adverse events (AEs) of the reproductive tract, endometrium and breast.

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Per TherapeuticsMD, (b) (4) estradiol (the active moiety on the 4 mcg and 10 mcg vaginal inserts) has been approved by the Agency in many estradiol hormone therapy products “based on extensive nonclinical pharmacology and toxicology data existing in the literature and previously reviewed by the Agency. The safety profile of 17β-estradiol has also been established with particular attention to the safety of the endometrium, breast, cardiovascular, cerebrovascular, and central nervous system.”

On September 14, 2017, TherapeuticsMD submitted a Clinical Information Amendment (Sequence-0031) presenting a systematic literature search conducted on the use of vaginal estrogens and the risk of endometrial hyperplasia or cancer.

On October 20, 2017, the Division of Epidemiology II (DEPI II) completed an assessment of the quality of evidence provided by TherapeuticsMD including an epidemiological assessment of the recently published Women’s Health Initiative (WHI) Observational Study (Crandall CJ, et al. 2017)<sup>5</sup>, and the Danish study (Mørch LS, et al, 2016)<sup>6</sup>.

### **Clinical Reviewer’s Comments:**

The DEPI II Review concludes:

“The WHI study and the Danish study both suggest a potential elevated risk for endometrial cancer with low dose vaginal estrogen use. Unfortunately, neither study reported the risk estimates by dose or duration of use, and neither was able to meet FDA’s regulatory need in determining a suitable cut-off dose for effective and safe “low-dose” vaginal estrogen use. We conclude that current evidence suggests a higher risk for endometrial cancer risk with vaginal estrogen use among postmenopausal women with VVA symptoms. However, given the limitations of the WHI study and the incomplete reporting of the Danish study results, a definite conclusion can’t be drawn on the association between VE use and risk of endometrial cancer.”

See the DEPI II review archived October 20, 2017 for a discussion of the DEPI II assessment of the WHI Observational Study and the Danish study.

On November 15, 2017, the Clinical Team completed an assessment of the quality of evidence provided by TherapeuticsMD in the September 14, 2017 systematic literature search conducted on the use of vaginal estrogens and the risk of endometrial hyperplasia or cancer. Thirty-seven (37) articles/ abstracts were identified that included information regarding vaginal estrogen use

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<sup>5</sup> Crandall CJ, Hovey KM, Andrews CA, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women’s Health Initiative observational study. *Menopause*; 25(1) (published ahead of print).

<sup>6</sup> Mørch LS, Kjaer SK, Keiding N, et al. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. *Int J Cancer*. 2016;138(6):1506-1515.

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and endometrial histology. Of the 37 articles/ abstracts identified, 20 were randomized, controlled clinical trials with drug exposure duration ranging from 2-weeks up to 52-weeks. In addition, the Clinical Information Amendment included prospective interventional, prospective observational, and retrospective observational/ registry studies. Non-US approved estriol vaginal products and non-estrogen prasterone vaginal inserts are not included in the publications reviewed.

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

Overall, the breadth of the literature review conducted by TherapeuticsMD appeared complete in its scope for reports of endometrial histology, including endometrial hyperplasia or endometrial cancer, and the use of vaginal estrogens in postmenopausal women. This reviewer did not identify additional major publications of randomized, controlled clinical trials utilizing US approved vaginally administered estrogen-alone drug products (for example, conjugated estrogens or estradiol).

The Clinical Team did not agree with TherapeuticsMD's assessment of the published literature that, "The evidence we assessed as part of the systematic literature review conducted does not support a risk of endometrial hyperplasia or endometrial cancer with vaginal estrogens." Only 6 articles of 48- to 52-weeks duration provide relevant endometrial safety data applicable to estradiol vaginal inserts 4 mcg and 10 mcg [Bachman et al, 2008 (Vagifem 10 mcg and 25 mcg estradiol vaginal inserts versus placebo vaginal inserts), Simon et al, 2008 (Vagifem 10 mcg estradiol vaginal inserts versus placebo vaginal inserts), Simon et al, 2010 (Vagifem 10 mcg estradiol vaginal inserts versus placebo vaginal inserts), Mettler and Olsen, 1991 (Vagifem 25 mcg estradiol vaginal inserts), Weisberg et al, 2005 (Estring 7.5 mcg per day estradiol vaginal ring versus Vagifem 25 mcg estradiol vaginal inserts), and Ulrich et al, 2010 (Vagifem 10 mcg estradiol vaginal inserts)]. Approximately 1188 postmenopausal women in these 6 clinical trials had evaluable endometrial biopsies at end-of-trial or early termination. Reported endometrial histological assessments include 1 simple hyperplasia without atypia [Bachman et al, 2008 (25 mcg Vagifem)], 1 endometrial adenocarcinoma [Simon et al, 2008 (10 mcg Vagifem)], 1 complex hyperplasia without atypia [Simon et al, 2010 (10 mcg Vagifem)], and 1 hyperplasia in a polyp [Ulrich et al, 2010 (10 mcg Vagifem)]. The Clinical Team concluded that safety data from published literature in the September 14, 2017 Clinical Information Amendment is not adequate to determine the general and endometrial safety and chronic use drug exposure safety risk of low-dose vaginal estrogens. "Therefore, this available published literature does not support definitive conclusions regarding the endometrial safety of vaginally administered unopposed low-dose vaginal estrogen products in postmenopausal women with moderate to severe vulvar and vaginal atrophy."

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See the Clinical Memorandum to the File, dated November 15, 2017 for a discussion of the literature search conducted by TherapeuticsMD on the use of vaginal estrogens and the risk of endometrial hyperplasia or cancer.

In the November 29, 2017 NDA 208564 resubmission, TherapeuticsMD:

- Seeks approval of the 4 mcg and 10 mcg estradiol vaginal inserts for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.
- Commits to conduct a PMR observational study to identify the incidence of endometrial cancer associated with long-term use of unopposed low dose vaginal estrogen products in postmenopausal women. A proposed study synopsis is provided in the NDA resubmission for consideration by the Agency.
- Submits published literature via the 505(b)(2) regulatory pathway to support general safety and chronic use drug exposure for the 4 mcg and 10 mcg estradiol vaginal inserts with a “bridge” to the published literature that consists of a scientific rationale for utilizing data in the literature to support the long-term general safety and chronic use of 4 mcg and 10 mcg estradiol vaginal inserts.
- Submits a Request for Proprietary Name Review: Imvexxy™.

Per the applicant, the published literature being relied upon to establish the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts includes studies of Prempro (NDAs 020527 and 020303), Premarin (NDAs 020216, 010402, 004782 and 020303), Norinyl-2 and Norinyl-1 (NDA 013625) Ovulen (NDA 016029), Norlestrin (NDA 016853), and Demulen (NDAs 018168, 016927, 018160 and 016936). A mapping table is provided which identifies the sections of the proposed estradiol vaginal inserts labeling that are supported by each referenced publication. The mapping table also cites, by labeling section, information the applicant considered supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts that is available in current estrogen class labeling (text and references), and references found in the 1977 and 2002 Premarin Prescribing Information labeling. See Table 3.

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Table 3: NDA 208564 Resubmission 505(b)(2) Mapping Table

Information Provided	Source of Information
5 WARNING AND PRECAUTIONS	
5.1 Risks for Systemic Absorption	Resubmission cites information available in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts.
5.2 Cardiovascular Disorders Stroke	<p>Resubmission cites two references in current estrogen class labeling as supportive of the general safety of the 4 mcg 10 mcg estradiol vaginal inserts:</p> <ul style="list-style-type: none"> <li>• Hendrix SL, et al. Effects of Conjugated Equine Estrogens on Stroke in the Woman’s Health Initiative. <i>Circulation</i>. 2006; 113:2425-2434.</li> <li>• Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. <i>JAMA</i>, 2007; 297:1465-1477.</li> </ul> <p>Resubmission cites two references located in the 1977 Premarin Prescribing Information labeling:</p> <ul style="list-style-type: none"> <li>• Collaborative Group for the Study of Stroke in Young Women. Oral Contraception and increased risk of cerebral ischemia or thrombosis. <i>N Engl J Med</i>. 1973; 288:871-878.</li> <li>• Pfeiffer RI, Van Den Noort S. Estrogen use and stroke risk in postmenopausal women. <i>Am J Epidemiol</i>. 1976; 103(5):445-456.</li> </ul>
5.2 Cardiovascular Disorders Coronary Heart Disease	<p>Resubmission cites two references in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts:</p> <ul style="list-style-type: none"> <li>• Hsia J, et al. Conjugated equine estrogens and coronary heart disease. <i>Arch intern Med</i>. 2006; 166:357-365.</li> <li>• Rossouw JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. <i>JAMA</i>, 2007; 297:1465-1477.</li> </ul> <p>Resubmission cites information/data in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts:</p> <ul style="list-style-type: none"> <li>• Hulley S, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. <i>JAMA</i>. 1998; 280:605-613.</li> <li>• Grady D, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II) <i>JAMA</i>, 2002; 288:49-57.</li> </ul> <p>Resubmission cites two references located in the 1977 Premarin Prescribing Information labeling:</p> <ul style="list-style-type: none"> <li>• Rosenberg L, et al. Myocardial infarction and estrogen therapy in postmenopausal women. <i>N Engl J Med</i>. 1976; 294:1256-1259.</li> <li>• Mann JJ, Inman WHW. Oral contraceptive and death from myocardial infarction. <i>Br Med J</i>, 1975; 2 (5965):245-248.</li> </ul>

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Table 3: NDA 208564 Resubmission 505(b)(2) Mapping Table - continued

Information Provided	Source of Information
<p>5.2 Cardiovascular Disorders Venous Thromboembolism (VTE)</p>	<p>Resubmission cites two references in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts:</p> <ul style="list-style-type: none"> <li>• Curb JD, et al. Venous thrombosis and conjugated equine estrogen in women without a uterus. Arch Intern Med, 2006; 166:772-780</li> <li>• Cushman M, et al. Estrogen plus progestin and risk of venous thrombosis. JAMA, 2004; 292:1573-1580.</li> </ul> <p>Resubmission cites two references located in 1977 Premarin Prescribing Information labeling:</p> <ul style="list-style-type: none"> <li>• Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. BR Med J, 1969; 2 (5658):651-657</li> <li>• Bailar JC 3rd. Thromboembolism and oestrogen therapy. Lancet, 1967; 2 (7515):560.</li> </ul>
<p>5.3 Malignant Neoplasms Endometrial Cancer</p>	<p>Resubmission cites four references located in 1977 Premarin Prescribing Information labeling:</p> <ul style="list-style-type: none"> <li>• Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med, 1975; 293(23):1167-1170.</li> <li>• Smith DC, et al. Association of exogenous estrogen and endometrial carcinoma. N Engl J Med, 1975; 293(23):1164-1167.</li> <li>• Mack TM, et al. Estrogens and endometrial cancer in a retirement community. N Engl. J Med, 1976; 294 (23): 1262-1267.</li> <li>• Weiss NS, et al. Increasing incidence of endometrial cancer in the United States. N Engl J Med, 1976; 294 (23): 1259-1262.</li> </ul>
<p>5.3 Malignant Neoplasms Breast Cancer</p>	<p>Resubmission cites two references in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts:</p> <ul style="list-style-type: none"> <li>• Stefanick ML, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA, 2006; 295:1647-1657.</li> <li>• Chlebowski RT, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. JAMA, 2003; 289:3243-3253.</li> </ul> <p>Resubmission cites two references located in the 1977 Premarin Prescribing Information labeling:</p> <ul style="list-style-type: none"> <li>• Surgically confirmed gallbladder disease, venous thromboembolism, and breast tumors in relation to postmenopausal estrogen therapy. A report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. N Engl J Med, 1974; 290(1):15-19.</li> <li>• Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet, 1997; 350 (9084):1047-1059.</li> </ul>

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Table 3: NDA 208564 Resubmission 505(b)(2) Mapping Table - continued

Information Provided	Source of Information
5.3 Malignant Neoplasms Ovarian Cancer	Resubmission cites one reference in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts: <ul style="list-style-type: none"> <li>• Anderson GL, et al. Effects of estrogen plus progestin on gynecologic cancers and associated diagnostic procedures. The Women’s Health Initiative Randomized Trial. JAMA, 2003; 290:1739-1748.</li> </ul> Resubmission cites information/data in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts: <ul style="list-style-type: none"> <li>• Beral V, et al. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet, 2015; 385(9980):1835-1842.</li> </ul>
5.4 Probable Dementia	Resubmission cites one reference in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts: <ul style="list-style-type: none"> <li>• Shumaker SA, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women. JAMA, 2004; 291:2947-2958.</li> </ul>
5.5 Gallbladder Disease	Resubmission cites one reference located in the 1977 Premarin Prescribing Information labeling: <ul style="list-style-type: none"> <li>• Bennion LJ, et al. Effects of oral contraceptives on gall bladder bile of normal women. N Engl J Med, 1976; 294(4):189-192.</li> </ul>
5.6 Hypercalcemia	Resubmission cites information available in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts.
5.7 Visual Abnormalities	Resubmission cites two references located in the 1977 Premarin Prescribing Information labeling: <ul style="list-style-type: none"> <li>• Inman WHW, et al. Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. Br Med J, 1970; 2(5703):203-309.</li> <li>• Stolley PD, et al. Thrombosis with low-estrogen oral contraceptives. Am J Epidemiol, 1975; 102 (3):197-208.</li> </ul>
5.8 to 5 (b)(4)	Resubmission cites information available in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts.
6 Adverse Reactions	See Sections 5.2 and 5.3 above <ul style="list-style-type: none"> <li>• Integrated Summary of Safety (ISS)</li> </ul>
13 Nonclinical Toxicology 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Resubmission cites information available in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts, supported by literature as agreed with FDA as part of the pre-NDA meeting. See nonclinical Module 2, Sections 2.4 and 2.6.

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Table 3: NDA 208564 Resubmission 505(b)(2) Mapping Table - continued

Information Provided	Source of Information
14 Clinical Studies 14.2 Women's Health Initiative Studies 14.3 Women's Health Initiative Memory Study	Resubmission cites information available in current estrogen class labeling as supportive of the general safety of the 4 mcg and 10 mcg estradiol vaginal inserts. See Section 5 Warning and Precautions above

Source: Adapted from NDA 208564 Resubmission, Module 1 Regional, Submodule 1.11 Information Amendment Information Not Covered Under Module 2 to 5, Submodule 1.11.14 Multiple Module Information Amendment, Appendix B: Literature Citation and 505(b)(2) Mapping Table, Table 3.

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

TherapeuticsMD submits a total of 27 individual publication to support the general and endometrial safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts as shown in Table 3. The published literature includes studies of the following FDA approved and active drug products:

- Premarin (conjugated estrogens) Tablets (NDA 004782), Premarin (conjugated estrogens) Vaginal Cream (NDA 020216), Premarin Intravenous (conjugated estrogens) for Injection (NDA 010402)
- Prempro (conjugated estrogens/medroxyprogesterone acetate tablets) Premphase (conjugated estrogens plus medroxyprogesterone acetate tablets) (NDA 020527).

The remaining publication include studies of FDA approved but discontinued products:

- Premarin (conjugated estrogens) 2.5 mg tablets (NDA 004782)
- Prempro (Premarin; Cycrin) and Premphase (Premarin; Cycrin 14/14) both under NDA 020303
- Norinyl-2 and Norinyl-1 (mestranol; norethindrone tablets) (NDA 013625)
- Ovulen (ethynodiol diacetate; mestranol tablets) (NDA 016029)
- Norlestrin 21 (ethinyl estradiol; norethindrone acetate tablets) (NDA 016852)
- Demulen (ethinyl estradiol; ethynodiol diacetate tablets) (NDAs 018168, 018160, 016927, and 016936).

TherapeuticsMD confirms “no patents are listed in the Orange Book for any of these listed drugs.”

Per the Agency's 505(b)(2) Assessment Committee, reliance upon discontinued products is acceptable if these products were not discontinued for reasons of safety/ effectiveness as confirmed via a Federal Register (FR) Notice. No FR notices are available for the 6 listed discontinued products identified above.

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

The clinical team does not agree that the discontinued oral contraceptive products identified by the applicant (Norinyl-2, Norinyl-1, Ovulen, Norlestrin, and Demulen) are

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relevant to the support of the general safety and chronic use drug exposure information for the 4 mcg and 10 mcg estradiol vaginal inserts. These discontinued oral contraceptive products contained different active pharmaceutical ingredients (ethinyl estradiol or mestranol) than the 4 mcg and 10 mcg estradiol vaginal inserts. Ethinyl estradiol and mestranol are 1) approximately 10-fold more potent than the natural estrogen estradiol, 2) are provided in substantially higher dosage strengths than used in symptomatic hormone therapy, and 3) have a different mechanism of action than estradiol used for hormone therapy in postmenopausal women. Therefore, the clinical review did not consider Norinyl-2, Norinyl-1, Ovulen, Norlestrin, and Demulen in its review of safety considerations and its recommendation regarding approvability of the 4 mcg and 10 mcg estradiol vaginal inserts

The clinical team believes that the published literature for Premarin (0.625 mg conjugated estrogens) utilized in the Women's Health Initiative (WHI) estrogen-alone subtrial, and for Prempro (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate) utilized in the WHI estrogen plus progestin subtrial are appropriate and adequate to inform Sections 4 and 5 of the proposed labeling for the 4 mcg and 10 mcg estradiol vaginal inserts.

Supplement-136 for 2.5 mg Premarin (conjugated estrogens) Tablets (NDA 004782) was received on December 5, 2003 containing numerous requested changes including the following requested change for the indication for the treatment of advanced androgen-dependent carcinoma of the prostate, for palliation only in the Dosage and Administration Section. Wyeth Pharmaceuticals had decided to discontinue manufacturing the Premarin 2.5 mg dosage strength. To retain the approved dose range for this indication of 1.25 mg to 2.5 mg three times daily, Wyeth Pharmaceuticals proposed the following modification: 1.25 mg to 2 x 1.25 mg three times daily, which was acceptable to the Agency. Supplement-136 was approved on April 20, 2004. Discontinued Premarin 2.5 mg tablets are not relevant to the support of the general safety and chronic use drug exposure information for the 4 mcg and 10 mcg estradiol vaginal inserts for an indication for the treatment of moderate to severe dyspareunia due to menopause.

On April 21, 2006, Wyeth Pharmaceuticals requested withdrawal of NDA 020303 [Prempro/Premphase (conjugated estrogens/ medroxyprogesterone acetate tablets)], approved December 30, 1994, because the product was not marketed under this NDA, but rather under NDA 020527 approved November 17, 1995. Discontinued Prempro/Premphase under NDA 020303 is not relevant to the support of the general safety and chronic use drug exposure information for the 4 mcg and 10 mcg estradiol vaginal inserts for an indication for the treatment of moderate to severe dyspareunia due to menopause.

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Nine (9) of the 27 publications in Table 3 report results of the WHI estrogen-alone and estrogen plus progestin subtrials. These WHI publications (Anderson GL, et al 2003; Chlebowski RT, et al. 2003; Curb JD, et al. 2006, Cushman M, et al. 2004; Hendrix SL, et al. 2006; Hsia J, et al. 2006; Rossouw JE, et al. 2007; Shumaker SA, et al. 2004; and Stefanick ML, et al. 2006), among other WHI publication, serve as the basis for the Agency's current estrogen class labeling as recommended in the Agency's draft 2005 Hormone Therapy Labeling Guidance for Industry.

Data from three (3) additional publications included in the NDA resubmission, are also incorporated in current estrogen class labeling in Section 5 Warnings and Precautions, Subsection 5.2 Cardiovascular Disorders, *Coronary Heart Disease* (Hulley S, et al. 1998<sup>7</sup> and Grady D, et al. 2002<sup>8</sup>), and Subsection 5.3 Malignant Neoplasms, *Ovarian Cancer* (Beral V, et al. 2015<sup>9</sup>). The results of these total twelve (12) publications can be viewed in approved hormone therapy product labeling in the Warning and Precautions section and the subsections they support per Table 3. Current estrogen class labeling is relevant to the 4 mcg and 10 mcg estradiol vaginal inserts. These 12 publication will not be reviewed here.

The remaining fifteen (15) publications are summarized in the following Table 4 by the section of labeling they support, per the NDA resubmission. Table 4 also includes references to current estrogen class labeling in support of the general safety and chronic use drug exposure of the 4 mcg and 10 mcg estradiol vaginal inserts.

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<sup>7</sup> Hulley S, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA*, 1998; 280:605-613.

<sup>8</sup> Grady D, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II). *JAMA*, 2002; 288: 49-57.

<sup>9</sup> Beral V, et al. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *Lancet*, 2015; 385(9980):1835-1842.

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Table 4: Review of the Published Literature in NDA 208564 Resubmission

Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
5 Warnings and Precautions		
5.2 Cardiovascular Disorders		
<b>Stroke<sup>10</sup></b>		
<ul style="list-style-type: none"> <li>Collaborative Group for the Study of Stroke in Young Women. Oral contraception and increased risk of cerebral ischemia or thrombosis. N Engl J Med. 1973; 289:3243-3253.</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective case control study conducted between 1969 and 1971</li> <li>598 nonpregnant women 15 to 44 years of age hospitalized in 12 university hospital (and their affiliate hospitals) with a discharged diagnosis of the first episode of any type of nontraumatic cerebrovascular disease</li> <li>For each case, two control women selected: a hospital control and a neighbor control matched for age and race</li> <li>Detailed contraceptive history obtained from 70% of women</li> </ul> <p>Reported Results</p> <ul style="list-style-type: none"> <li>Current use of oral contraceptive among women with thrombotic stroke was more than 3 times that of hospital controls (42.1 vs. 11.7) and 4 times that of neighbor control (42.1 vs. 10.1)</li> <li>Relative risk for cerebral ischemia or thrombosis estimated to be about nine times greater for women who used oral contraceptive than for those who do not</li> </ul>	<p><b>Not Relevant:</b></p> <p>Oral contraceptive data is not an appropriate class of products upon which to rely on the published literature to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts because:</p> <ul style="list-style-type: none"> <li>Oral contraceptive products contain different active ingredients, ethinyl estradiol or mestranol</li> <li>Synthetic contraceptive estrogens are approximately 10-fold more potent than the natural estrogen estradiol</li> <li>Oral contraceptive products have substantially higher dosage strengths of estrogen than used in symptomatic hormone therapy</li> <li>Synthetic contraceptive estrogens have a different mechanism of action than estradiol used for hormone therapy</li> </ul>

<sup>10</sup> See Table 3 in this review for additional publications supporting Subsection 5.2 Cardiovascular Disorders, Headings Stroke, Coronary Heart Disease, and Venous Thromboembolism (VTE).

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Table 4: Review of the Published Literature in NDA 208564 Resubmission - continued

Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
5 Warnings and Precautions		
5.2 Cardiovascular Disorders		
<b>Stroke<sup>10</sup></b>		
<ul style="list-style-type: none"> <li>• Pfeiffer, RL, Van Den Noort S. Estrogen use and stroke risk in postmenopausal women Am J Epidemiol. 1976; 103 (5):445-456.</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective case control study in a stable retirement community conducted between 1964 and 1973</li> <li>• Potential cases of first stroke identified from 4 hospital discharge rosters and medical center death records</li> <li>• 569 hospital charts for female residents and 46 death records were ascertained; all white females</li> <li>• 1065 controls drawn from all women in residence during study period matched for age and concomitant residence</li> <li>• Only first strokes while in community residence were accepted; stratified for hypertension and diabetes</li> <li>• Oral estrogen use obtained from prescription file of medical center pharmacy; type and dose of oral estrogen used not provided</li> <li>• Duration of oral estrogen use in study period provided as: current, use within 3 months, and most recent continuous use &gt; 12 months</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>• Study failed to detect overall association between estrogen use and stroke (relative risk 1.12)</li> <li>• Hypertension and diabetes were highly associated with stroke (relative risk 2.93 and 3.15, respectively)</li> </ul>	<p><b>Relevant (Limited):</b> This retrospective case control publication provides only limited information to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts because:</p> <ul style="list-style-type: none"> <li>• Oral estrogens are systemically absorbed</li> <li>• Dose of oral estrogen used is not provided</li> <li>• Duration of oral estrogen use is limited to study period</li> </ul>

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Table 4: Review of the Published Literature in NDA 208564 Resubmission - continued

Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
Warnings and Precautions		
5.2 Cardiovascular Disorders		
<b>Coronary Heart Disease<sup>10</sup></b>		
<ul style="list-style-type: none"> <li>Rosenberg L, et al. Myocardial infarction and estrogen therapy in post-menopausal women. N Eng J Med. 1976; 294:1256-1259</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective case control study of hospitalized women enrolled in the Boston Collaborative Drug Surveillance Program</li> <li>Multipurpose surveys of hospitalized patient conducted by specially trained nurse</li> <li>336 postmenopausal women, 40 to 75 years of age hospitalized with nonfatal myocardial infarction were included; 8 (2.4%) were regular estrogen users (more than one year) prior to admission</li> <li>6,730 reference patients (without history of neoplasms, gallbladder disease, diabetes, obesity and vascular disease); 330 with regular estrogen use more than one year (4.9%)</li> <li>Oral Premarin commonest estrogen used; no dosage strength information available</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>No evidence of a statistically significant association between current regular estrogen use and nonfatal acute myocardial infarction</li> </ul>	<p><b>Relevant (Limited):</b></p> <p>This retrospective case control publication provides only limited information to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts because:</p> <ul style="list-style-type: none"> <li>Oral Premarin is systemically absorbed</li> <li>Dose of oral Premarin used is not provided</li> <li>Duration of oral Premarin use is selective</li> <li>Descriptive data for each patient are incomplete</li> <li>Difficult to identify risk on basis of recall data</li> </ul>
<ul style="list-style-type: none"> <li>Mann JI, Inman WHW. Oral contraceptives and death from myocardial infarction. Br Med J. 1975; 2(5965): 245-248</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective review of death certificates in women under 50 years of age coded myocardial infarction in 1973</li> <li>153 deaths included, 104 necropsy confirmed cases</li> <li>Two living controls matched for age group and marital status were selected for patients under 40 years of age, and one for those over 40</li> <li>Interview conducted with healthcare provider</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>Frequency of oral contraceptive use significantly greater during month before death than during the corresponding month in control group</li> <li>Risk of fatal myocardial infarction greater in women using oral contraceptives, particularly in older age groups</li> <li>Proportion of women being treated for hypertension and diabetes greater in group who died than in controls</li> </ul>	<p><b>Not Relevant:</b></p> <p>Oral contraceptive data is not an appropriate class of products upon which to rely on the published literature to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts because:</p> <ul style="list-style-type: none"> <li>Oral contraceptive products contain different active ingredients, ethinyl estradiol or mestranol</li> <li>Synthetic contraceptive estrogens are approximately 10-fold more potent than the natural estrogen estradiol</li> <li>Oral contraceptive products have substantially higher dosage strengths of estrogen than used in symptomatic hormone therapy</li> <li>Synthetic contraceptive estrogens have a different mechanism of action than estradiol used for hormone therapy</li> </ul>

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Table 4: Review of the Published Literature in NDA 208564 Resubmission - continued

Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
5 Warnings and Precautions		
5.2 Cardiovascular Disorders		
<b>Venous Thromboembolism (VTE)<sup>10</sup></b>		
<ul style="list-style-type: none"> <li>Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J. 1969; 2(5658):651-657.</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective review of hospitalized women discharged with diagnosis of thromboembolic disease in 1967</li> <li>Update to 1968 publication covering years 1964 to 1966; 29 new patients were identified; 58 others were selected as controls</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>42 patients (50%) of a total 84 patients with DVT or PE had used oral contraceptives during the month preceding onset of DVT or PE compared with 23 (14%) of the total 158 controls</li> <li>11 patients (58%) of a total 19 patients with cerebral thrombosis had been using oral contraceptives compared with an expected figure of 3.5 of the controls</li> <li>2 patients (12%) of a total 17 patients with coronary thrombosis had been using oral contraceptives compared with an expected figure of 2.1</li> <li>No difference in risk were found for the type of preparation used or for the duration of use</li> <li>Oral contraceptives are a cause of VTE and cerebral thrombosis but not coronary thrombosis</li> </ul>	<p><b>Not Relevant:</b> Oral contraceptive data is not an appropriate class of products upon which to rely on the published literature to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts because:</p> <ul style="list-style-type: none"> <li>Oral contraceptive products contain different active ingredients, ethinyl estradiol or mestranol</li> <li>Synthetic contraceptive estrogens are approximately 10-fold more potent than the natural estrogen estradiol</li> <li>Oral contraceptive products have substantially higher dosage strengths of estrogen than used in symptomatic hormone therapy</li> <li>Synthetic contraceptive estrogens have a different mechanism of action than estradiol used for hormone therapy</li> </ul>
<p>Bailar JC 3<sup>rd</sup>. Thromboembolism and oestrogen therapy. Lancet. 1967; 2(7515):560</p>	<ul style="list-style-type: none"> <li>Letter to the Editor</li> <li>5 mg diethylstilbestrol used for long periods in the palliative treatment of cancer of the prostate</li> <li>Patients at substantially increased risks of death from myocardial infarction, congestive heart failure, and CVA</li> </ul>	<p><b>Not Relevant:</b></p> <ul style="list-style-type: none"> <li>This publication regarding the palliative treatment of prostate cancer is not appropriate information upon which to rely upon to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts</li> </ul>

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

Resubmission NDA 208564

Imvexxy™ (estradiol vaginal inserts) 4 mcg and 10 mcg

Table 4: Review of the Published Literature in NDA 208564 Resubmission - continued

Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
5 Warnings and Precautions		
5.3 Malignant Neoplasm		
<b>Endometrial Cancer<sup>11</sup></b>		
<ul style="list-style-type: none"> <li>Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. <i>N Engl J Med</i>. 1975; 293(23):1167-1170</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective case control study conducted between 1970 and 1974 using tumor registry of the Kaiser Permanente Medical center</li> <li>Control subjects selected from same Kaiser Foundation Health Plan matched for age, duration of plan membership, and area of residence</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>57% (n=54) of 94 cases of endometrial adenocarcinoma or adenoacanthoma recorded conjugated estrogens (CE) use; risk ratio (RR) 7.6 with a one-sided 95 % confidence interval (CI) of 4.7 versus 15% (n=29) of controls (n=188)</li> <li>RR estimate increased with duration of exposure from 5.6 for 1 to 4.9 years of exposure to 13.9 for 7 or more years of exposure</li> <li>Data suggest that CE has an etiologic role in endometrial cancer</li> </ul>	<p><b>Relevant (Limited):</b></p> <ul style="list-style-type: none"> <li>This 1975 retrospective case control study was important to the general understanding of the effects of unopposed estrogen use in a postmenopausal woman with a uterus</li> <li>An increase in the risk of endometrial cancer associated with the use of unopposed estrogens in a woman with a uterus became evident in the early 1970'S</li> <li>In 1975, the FDA Obstetrics and Gynecology Advisory Committee recommended that estrogen labeling include a specific warning for an increased risk of endometrial cancer in non-hysterectomized women and unopposed estrogen use</li> <li>Dosage strengths of conjugated estrogens used in 1970's greatly exceeded the 4 mcg and 10 mcg estradiol vaginal inserts</li> </ul>
<ul style="list-style-type: none"> <li>Smith DC, et al. Association of exogenous estrogen and endometrial carcinoma. <i>N Engl J Med</i>. 1975; 293 (23):1164-1170.</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective case control study of hospital records of women, 48 years of age or older, with endometrial cancer diagnosis made between 1960 and 1972</li> <li>Matched controls selected at same hospitals from women with other gynecologic neoplasms</li> <li>Study did not address estrogen dosage, specific estrogen used or duration of estrogen use</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>48% (n=152) of 317 women with endometrial cancer used estrogen compared with 17% (54) of 317 controls</li> <li>Risk of endometrial cancer was 4.5 times greater in women exposed to estrogens</li> <li>Relative risk was less apparent in women with obesity and hypertension</li> </ul>	<p><b>Relevant (Limited):</b></p> <ul style="list-style-type: none"> <li>This 1975 retrospective case control study was important to the general understanding of the effects of unopposed estrogen use in a postmenopausal woman with a uterus</li> <li>An increase in the risk of endometrial cancer associated with the use of unopposed estrogens in a woman with a uterus became evident in the early 1970'S</li> <li>In 1975, the FDA Obstetrics and Gynecology Advisory Committee recommended that estrogen labeling include a specific warning for an increased risk of endometrial cancer in non-hysterectomized women and unopposed estrogen use</li> <li>Study did not address estrogen dosage, specific estrogen used, or duration of estrogen use</li> </ul>

<sup>11</sup> See Table 3 in this review for additional publications supporting Subsection 5.3 Malignant Neoplasms, Headings Endometrial Cancer, Breast Cancer, and Ovarian Cancer.

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Table 4: Review of the Published Literature in NDA 208564 Resubmission - continued

Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
5 Warnings and Precautions		
5.3 Malignant Neoplasm		
<b>Endometrial Cancer<sup>11</sup></b>		
<ul style="list-style-type: none"> <li>Mack TM, et al. Estrogens and endometrial cancer in a retirement community. N Engl J Med. 1976; 294 (23):1262-1267</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective case control study in a residential retirement community in Los Angeles, CA between 1971 and 1975; nearly all white, affluent women; records from single medical care facility and pharmacy; interviews conducted</li> <li>Controls chosen from a roster of all women in the community</li> <li>Very few women had taken progesterone</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>RR for any estrogen use estimated to be 8.0 (95% CI, 3.5-18.1); RR for conjugated estrogen use (&lt; 0.625 mg, &gt; 0.625 mg) 5.6 (95% CI, 2.8-11.1)</li> <li>Increased risk was shown for invasive and noninvasive cancer and dose-response effect was demonstrated</li> <li>Risk for endometrial cancer exceeds the baseline risk from any other single cancer</li> </ul>	<p><b>Relevant (Limited):</b></p> <ul style="list-style-type: none"> <li>This 1976 retrospective case control study was important to the general understanding of the effects of unopposed estrogen use in a postmenopausal woman with a uterus</li> <li>An increase in the risk of endometrial cancer associated with the use of unopposed estrogens in a woman with a uterus became evident in the early 1970's</li> <li>In 1975, the FDA Obstetrics and Gynecology Advisory Committee recommended that estrogen labeling include a specific warning for an increased risk of endometrial cancer in non-hysterectomized women and unopposed estrogen use</li> <li>Conjugated estrogens dosage strengths used in 1970's greatly exceeded 4 mcg and 10 mcg estradiol vaginal inserts</li> </ul>

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Table 4: Review of the Published Literature in NDA 208564 Resubmission - continued

Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
5 Warnings and Precautions		
5.3 Malignant Neoplasm		
<b>Endometrial Cancer<sup>11</sup></b>		
<ul style="list-style-type: none"> <li>• Weiss NS, et al. Increasing incidence of endometrial cancer in the United States. N Engl J Med. 1976; 294(23):1259-1262</li> </ul>	<ul style="list-style-type: none"> <li>• Summary report of published data of population-based cancer reporting system serving eight areas of the country between 1969 and 1973</li> <li>• Population data presented were generated from specimens examined by pathologists without uniform histologic criteria</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>• Annual incidence of corpus cancer in Connecticut rose from 18.0 to 23.0 per 100,000 from 1969 to 1972</li> <li>• California reported an increase in corpus cancer or 15.4 per 100,000 during the same interval</li> <li>• Estimate that 51% of menopausal women in Seattle-Tacoma area used “replacement” estrogens for at least 3 months, and that the median duration of use was 10 years</li> <li>• Histologic criteria for the diagnosis of endometrial cancer have remained relatively constant between 1969 and 1973</li> <li>• Incidence rates of endometrial cancer have risen sharply in the 1070’s</li> </ul>	<p><b>Relevant (Limited):</b></p> <ul style="list-style-type: none"> <li>• This 1976 report on the incidence of endometrial cancer in the US was important to the general understanding of the effects of unopposed estrogen use in a postmenopausal woman with a uterus</li> <li>• An increase in the risk of endometrial cancer associated with the use of unopposed estrogens in a woman with a uterus became evident in the early 1970’s</li> <li>• In 1975, the FDA Obstetrics and Gynecology Advisory committee recommended that estrogen labeling include a specific warning for an increased risk of endometrial cancer in non-hysterectomized women and unopposed estrogen use</li> <li>• Publication does not address specific estrogen used, estrogen dosage strengths used, or duration of estrogen use</li> </ul>

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Table 4: Review of the Published Literature in NDA 208564 Resubmission - continued

5 Warnings and Precautions		
5.3 Malignant Neoplasm		
Breast Cancer <sup>11</sup>		
<ul style="list-style-type: none"> <li>Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 1997; 350(9084):1047-1029.</li> </ul>	<ul style="list-style-type: none"> <li>Reanalysis of worldwide epidemiological evidence on relationship between risk of breast cancer and hormone therapy use</li> <li>Individual data on 52,705 women with breast cancer and 108,411 women without breast cancer from 51 studies in 21 countries</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>Relative risk of breast cancer increased by factor of 1.02 (95% CI, 1.01-1.04) for each year of use</li> <li>Relative risk of breast cancer was 1.35 (95% CI, 1.21-1.49) for women who used hormone therapy for 5 years or longer</li> <li>Risk of having breast cancer is increased in women using hormone therapy and increases with increasing duration of use</li> <li>Effect is reduced after cessation of use, and largely disappears after about 5 years</li> </ul>	<p><b>Relevant (Limited):</b></p> <ul style="list-style-type: none"> <li>This 1997 epidemiologic study was important to the general understanding of breast cancer and the duration of estrogen use</li> <li>This publication provides only limited information to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts because: <ul style="list-style-type: none"> <li>Less specific information is available for type of estrogen used, either alone or in combination with a progestogen, and dosage strengths</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>Surgically confirmed gallbladder disease, venous thromboembolism, and breast tumors in relation to postmenopausal estrogen therapy. A report from the Boston Collaborative Drug Surveillance Program, Boston University Medical Center. N Engl J Med. 1974; 290(1): 12-19</li> </ul>	<ul style="list-style-type: none"> <li>Hospital survey in postmenopausal women 45 to 69 years of age with discharge diagnosis of biopsy proven breast tumor for the first time were selected for analysis (N=103); 51 newly diagnosed cases of breast cancer and 52 cases of benign breast tumors</li> <li>744 controls selected from collaborating hospitals (admitted for acute illness, elective surgery or orthopedic treatment) matched for age</li> <li>Medical history obtained following admission; drug use and frequency of use recorded; information on exact dose was not obtained</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>98 women (cases and controls) used estrogen-containing products; 85 used oral conjugated estrogens, 5 used stilbesterol, 2 used ethinyl estradiol, and 6 were unspecified</li> <li>No significant association between estrogens and newly diagnosed breast cancer or benign breast tumors was present</li> </ul>	<p><b>Relevant (Limited):</b></p> <p>This publication provides only limited information to support the general safety and chronic use drug exposure data of 4 mcg and 10 mcg estradiol vaginal inserts because:</p> <ul style="list-style-type: none"> <li>Dose of estrogen used not provided</li> <li>Duration of estrogen use not provided</li> </ul>

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Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
5 Warnings and Precautions		
5.3 Malignant Neoplasm		
<b>Ovarian Cancer<sup>11</sup></b>		
<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> </ul>	<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> </ul>	<p><b>Relevant:</b> Current estrogen class labeling for ovarian cancer is relevant to all estrogen formulations, dosage strengths, and routes of administration</p>
5 Warnings and Precautions		
5.4 Probable Dementia		
<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> </ul>	Current estrogen class labeling	<p><b>Relevant:</b> Current estrogen class labeling for probable dementia is relevant to all estrogen formulations, estrogen dosage strengths, and routes of administration</p>
5.5 Gallbladder Disease <sup>12</sup>		
<ul style="list-style-type: none"> <li>Bennion LJ, et al. Effects of oral contraceptives on the gallbladder bile of normal women. N Engl J Med. 1976; 294 (4):189-192.</li> </ul>	<ul style="list-style-type: none"> <li>Research study in 22 healthy women; routine use of oral contraceptive during normal menstrual cycle versus no medication</li> <li>Reports effects of contraceptive steroids on the lipid composition of gallbladder bile</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>Gallbladder bile more highly saturated with cholesterol during oral contraceptive use than during normal menstrual cycling with no medication (125% versus 92%)</li> <li>Exogenous sex steroids induce alterations in the composition of human gallbladder bile</li> <li>Finding suggest a biochemical basis for the increase in gallbladder disease observed with oral contraceptive use</li> </ul>	<p><b>Not Relevant:</b> Oral contraceptive data is not an appropriate class of products upon which to rely on the published literature to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts because:</p> <ul style="list-style-type: none"> <li>Oral contraceptive products contain different active ingredients, ethinyl estradiol or mestranol</li> <li>Synthetic contraceptive estrogens are approximately 10-fold more potent than the natural estrogen estradiol</li> <li>Oral contraceptive products have substantially higher dosage strengths of estrogen than used in symptomatic hormone therapy</li> <li>Synthetic contraceptive estrogens have a different mechanism of action than estradiol used for hormone therapy</li> </ul>

<sup>12</sup> General knowledge included in estrogen class labeling.

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Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
5 Warnings and Precautions		
5.6 Hypercalcemia <sup>13</sup>		
<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> </ul>	<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> </ul>	<p><b>Relevant:</b> Current estrogen class labeling for hypercalcemia is relevant to all estrogen formulations, estrogen dosage strengths, and routes of administration</p>
5.7 Visual Abnormalities <sup>14</sup>		
<ul style="list-style-type: none"> <li>Inman WHW, et al. Thromboembolic disease and steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. Br Med J. 1970; 2(5703):203-209.</li> </ul>	<ul style="list-style-type: none"> <li>Detailed analysis of reports received by UK Committee on Safety of Drugs, Swedish Adverse Drug Reaction Committee, and Danish National Health Service's Board on Adverse Reactions to Drugs between 1965 and 1969</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>1024 reports including 316 cases of PE with and without venous thrombosis, 249 cases of DVT in lower limbs, 266 cases in lower limbs of superficial or unspecified thrombosis; 83 cases of cerebral thrombosis, 63 cases of coronary thrombosis; 37 cases of venous thrombosis affecting parts of body other than legs including 7 reports of retinal artery thrombosis</li> <li>Excess of reports associated with oral contraceptives containing higher doses of mestranol (50 to 100 mcg) or ethinyl oestradiol (100 mcg)</li> </ul>	<p><b>Not Relevant:</b> Oral contraceptive data is not an appropriate class of products upon which to rely on the published literature to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts because:</p> <ul style="list-style-type: none"> <li>Oral contraceptive products contain different active ingredients, ethinyl estradiol or mestranol</li> <li>Synthetic contraceptive estrogens are approximately 10-fold more potent than the natural estrogen estradiol</li> <li>Oral contraceptive products have substantially higher dosage strengths of estrogen than used in symptomatic hormone therapy</li> <li>Synthetic contraceptive estrogens have a different mechanism of action than estradiol used for hormone therapy</li> </ul>

<sup>13</sup> General knowledge included in estrogen class labeling.

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Section of Labeling Reference	Publication Description Reported Results	Relevance to the General Safety of the 4 mcg and 10 mcg Estradiol Vaginal Inserts
5 Warnings and Precautions		
5.7 Visual Abnormalities <sup>14</sup>		
<ul style="list-style-type: none"> <li>Stolley PD, et al. Thrombosis with low-estrogen oral contraceptives. Am J Epidemiol. 1975; 102(3):197-208.</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective case control investigation of women, 15 to 49 years of age, with thromboembolic disease admitted to 37 hospitals during 1970 to 1973</li> </ul> <p>Reported Results:</p> <ul style="list-style-type: none"> <li>104 idiopathic cases (no previous thrombosis, predisposing disease, or recent surgery or trauma), 357 other thrombotic cases, and 1302 matched controls (race, age, marital status)</li> <li>Breakdown in only two estrogen dosage strengths: less than 100 mcg and 100 mcg or more</li> <li>Risk for women using 100 mcg or more of estrogen is estimated to be 7.2 times than for non-users</li> </ul>	<p><b>Not Relevant:</b></p> <p>Oral contraceptive data is not an appropriate “scientific bridge” to support the general safety and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts because:</p> <ul style="list-style-type: none"> <li>Oral contraceptive products contain different active ingredients, ethinyl estradiol or mestranol</li> <li>Synthetic contraceptive estrogens are approximately 10-fold more potent than the natural estrogen estradiol</li> <li>Oral contraceptive products have substantially higher dosage strengths of estrogen than used in symptomatic hormone therapy</li> <li>Synthetic contraceptive estrogens have a different mechanism of action than estradiol used for hormone therapy</li> </ul>
6 Adverse Reactions		
<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> </ul>	<ul style="list-style-type: none"> <li>See Subsection 5.2, 5.3, 5.4, 5.5, and 5.7 in this table</li> </ul>	See comments above in this table
13 Nonclinical Toxicology		
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility		
<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> </ul>	<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> <li>Supported by literature as agreed by FDA. See module 2 Sections 2.4 and 2.6</li> </ul>	<p><b>Relevant:</b></p> <ul style="list-style-type: none"> <li>Current estrogen class labeling for Section 13 Nonclinical Toxicology, Subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility is relevant to all estrogen formulations, estrogen dosage strengths, and all routes of administration</li> </ul>
14 Clinical Studies		
14.2 Women’s Health Initiative Studies		
14.3 Women’s Health Initiative Memory Study		
<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> </ul>	<ul style="list-style-type: none"> <li>Current estrogen class labeling</li> </ul>	<p><b>Relevant:</b></p> <ul style="list-style-type: none"> <li>Current estrogen class labeling for Section 14 Clinical Studies, Subsection 14.2 Women’s Health Initiative Studies, and Subsection 14.3 Women’s Health Initiative Memory Study is relevant to all estrogen formulations, estrogen dosage strengths, and all routes of administration</li> </ul>

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Source: Adapted from NDA 208564 Resubmission, Module 1 Regional, Submodule 1.11 Information Amendment Information Not Covered Under Module 2 to 5, Submodule 1.11.14 Multiple Module Information Amendment, Appendix B: Literature Citation and 505(b)(2) Mapping Table, Table 3.

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

As previous noted, 12 of the 27 publications included in the NDA resubmission form the basis for the Agency's current estrogen class labeling as recommended in the Agency's draft 2005 Labeling Guidance for Industry. The reported findings in these 12 publications are relevant to all estrogen hormone therapy dosage strengths and all routes of administration (oral, transdermal, vaginal), including the 4 mcg and 10 mcg estradiol vaginal insert and inform the Boxed Warnings and Warning and Precautions sections of estrogen class labeling.

Eight (8) of the 15 remaining publications are important to our current understanding of the risk of unopposed estrogen use in a postmenopausal woman with a uterus (Ziel HK, et al 1975; Smith DC, et al. 1975; Mack TM, et al. 1976; and Weiss NS, et al. 1974), estrogen effect on the breast (Collaborative Group on Hormone Factors in Breast Cancer, 1997; Boston University Medical Center, 1974), estrogen effect on stroke in postmenopausal women (Pfeiffer RI, et al. 1976), and estrogen effect on coronary heart disease in postmenopausal women (Rosenberg L, et al 1976). As shown in Table 4, this reviewer considers these 8 publications relevant, with stated limitations, to support the general safety and chronic use drug exposure of the 4 mcg and 10 mcg estradiol vaginal inserts.

The remaining 6 observational case control publications regarding oral contraceptive use, and the 1 letter to the editor (diethylstilbestrol use in prostate cancer), primarily identified in the 1977 Premarin (conjugated estrogens, USP) labeling, are not relevant to the 4 mcg and 10 mcg estradiol vaginal inserts for the reasons cited in Table 4.

Long-term clinical trials of sufficient duration are needed with lower-dose vaginally administered estrogen products to determine the true risk of these products with attention to endometrium, breast, cardiovascular, cerebrovascular, and central nervous system outcomes.

Overall, additional safety data is needed to establish the general and endometrial safety and chronic use drug exposure data for the 4 mcg and 10 mcg estradiol vaginal inserts. TherapeuticsMD has committed to conduct a PMR observational study to identify the incidence of endometrial cancer associated with long-term use of unopposed low dose vaginal estrogen products in postmenopausal women. A proposed study synopsis is provided in the NDA resubmission for consideration by the Agency.

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### **8.2.1. Overall Exposure**

No new information on overall exposure is included in the resubmission for the 4 mcg and 10 mcg estradiol vaginal inserts. See the Primary Clinical Review, dated April 28, 2017, Section 7 Review of Safety, Subsection 7.2 Adequacy of Safety Assessments, Subsection 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations for overall exposure in the 12-week, phase 3 Trial TXV14-01.

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

A mean duration of exposure of 78.8 days (SD 16.97) in single, 12-week Trial TXV14-01 is insufficient to advise on the long-term safety of the 4 mcg and 10 mcg estradiol vaginal inserts.

### **8.2.2 Relevant characteristics of the safety population:**

See the Primary Clinical Review, dated April 28, 2017, Section 5 Sources of Clinical Data, Subsection 5.3 Discussion of Individual Studies/Clinical Trials, Subsection 5.3.1 Trial TXV14-01 for a full discussion of demographic characteristics and other characteristics of the safety population.

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

Demographic data were similar across treatment groups in 12-week, phase 3 Trial TXV14-01. The Black or African American trial participants, while significantly less than White trial participants, represent 11.6% of the trial population. This signified an acceptable percentage in a US trial population for the stated VVA indication.

### **8.2.3 Adequacy of the safety database:**

As previously noted, the 12-week safety data, submitted in the original NDA application, from Trial TXV14-01 was inadequate to assess long-term general and endometrial safety data and chronic use drug exposure data of the 4 mcg and 10 mcg estradiol vaginal inserts to support an indication for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. A major concern with the use of estrogen-alone hormonal therapy for the treatment of symptoms due to menopause in a woman with a uterus is the risk of endometrial hyperplasia/ cancer. Importantly, 12-weeks of drug exposure is not adequate to advise this safety concern of unopposed estrogen use in a non-hysterectomized woman.

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

Overall, general and endometrial safety of estradiol is well identified for a wide range of estradiol doses and formulations approved the treatment of moderate to severe VMS and/or VVA symptoms (for example from 7.5 mcg per day to 2 mg per day). However, most of this long-term general and endometrial safety risk/benefit data was obtained for higher dosed estrogen products (for example, oral 0.625 mg CE used in the WHI and

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oral 1 mg to 2 mg estradiol). The Agency determined that 12-weeks duration of use of the 4 mcg and 10 mcg estradiol vaginal inserts was inadequate to identify the true risk of endometrial cancer and other long-term safety effects of this low-dose virginally administered estradiol product.

To identify the incidence of endometrial cancer associated use of unopposed low dose vaginal estrogen products in non-hysterectomized postmenopausal women, TherapeuticsMD has committed to conduct a PMR long-term observational study, of 3 to 5 years of use/follow up information, to identify the incidence of endometrial cancer associated use of unopposed low dose vaginal estrogen products in non-hysterectomized postmenopausal women.

### 8.3. Adequacy of Applicant's Clinical Safety Assessments

No new safety data for the 4 mcg and 10 mcg estradiol vaginal inserts is provided in the NDA resubmission.

On May 5, 2017, a CR determination was made for NDA 208564 for estradiol vaginal inserts 4 mcg, 10 mcg, (b) (4) for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The CRL indicating that the NDA could not be approved because:

- The application does not provide long-term endometrial safety data for the 4, 10, (b) (4) (b) (4) estradiol vaginal inserts.
- Sufficient assessment of endometrial histology to support chronic use is critical to the safety evaluation of unopposed estrogen and to ensure adequate labeling for the safe use of your product.

See the Primary Clinical Review, dated April 28, 2017, for complete information regarding the NDA 208564 original application.

### 8.4. Safety Results

No new safety data for the 4 mcg and 10 mcg estradiol vaginal inserts is provided in the NDA resubmission.

See the Primary Clinical Review, dated April 28, 2017, Section 7 Review of Safety for a detailed assessment of the adverse events and other safety results reported during the estradiol vaginal inserts development program, and particularly, during the conduct of 12-week, phase 3 Trial TXV14-01.

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

Overall, the long-term safety profiles of the 4 mcg and 10 mcg estradiol vaginal inserts

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was not supported in the original NDA application. No long-term general and endometrial safety data, of at least 12-months duration, is available for these two estradiol vaginal insert products.

TherapeuticsMD has committed to conduct a PMR observational study to identify the incidence of endometrial cancer associated with long-term use of unopposed low dose vaginal estrogen products in postmenopausal women.

## 8.5. Analysis of Submission-Specific Safety Issues

### 8.5.1. General and Endometrial Safety

The NDA resubmission contains a draft PMR protocol synopsis (Version 1.0) entitled (b) (4)

This draft PMR protocol proposes (b) (4)

The proposed primary objective:

(b) (4)

The proposed secondary objectives:

(b) (4)

Proposed Inclusion Criteria:

(b) (4)

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[Redacted] (b) (4)

**Clinical Reviewer's Comments:**

[Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

**Clinical Reviewer's Comments:**

On March 23, 2018, the Division of Epidemiology II (DEPI II) reviewed the PMR protocol synopsis. DEPI II identified the following issues in the synopsis to be addressed:

[Redacted] (b) (4)

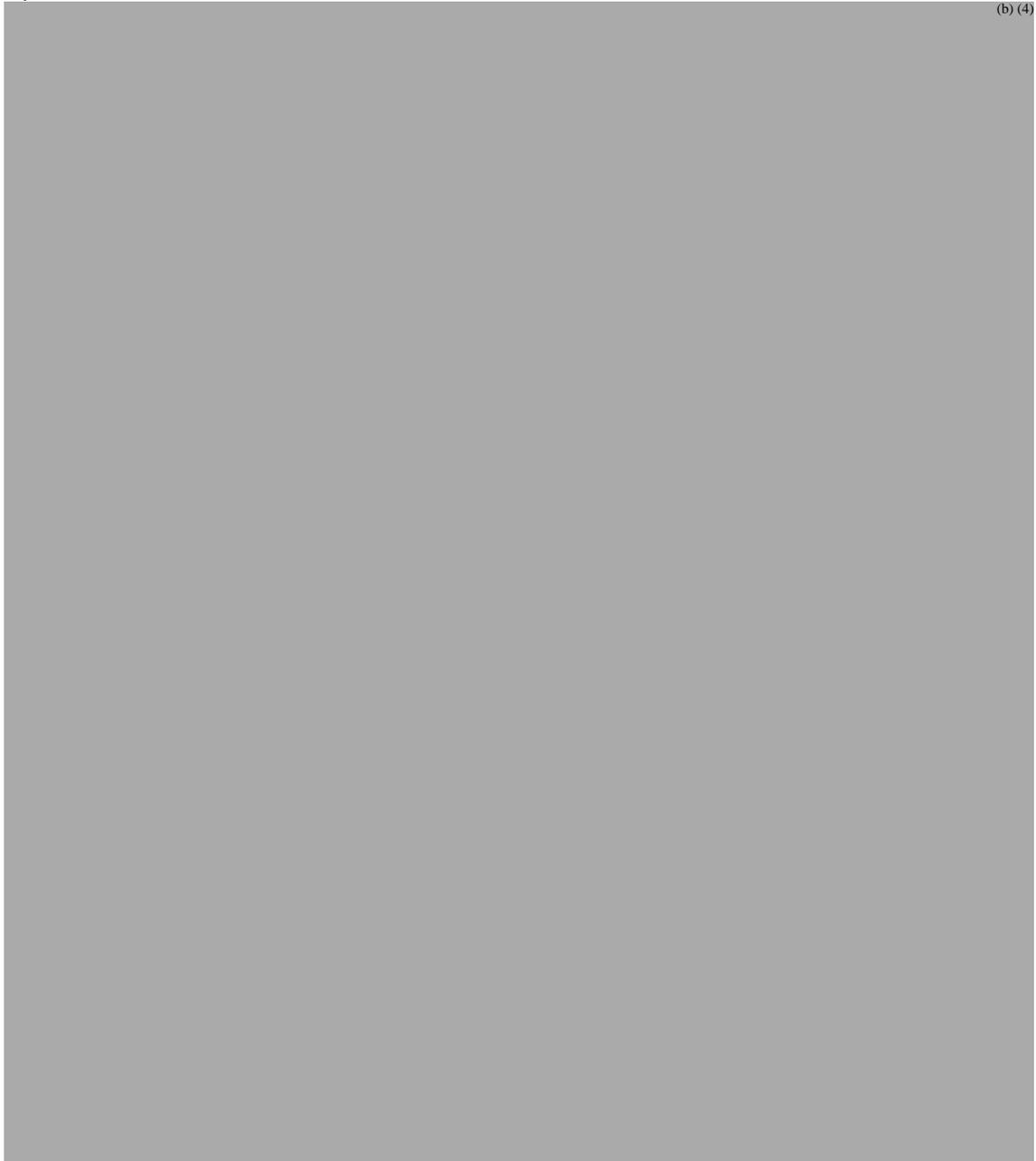
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Theresa H. van der Vlugt, M.D., M.P.H.

Resubmission NDA 208564

Imvexxy™ (estradiol vaginal inserts) 4 mcg and 10 mcg

DEPI requested that TherapeuticsMD address the following issues in the PMR protocol synopsis:



**Medical Officer's Comments:**

On April 5, 2018, TherapeuticsMD was advised of the above recommendations regarding the PMR protocol synopsis included in the NDA resubmission. TherapeuticsMD responded on April 19, 2018.

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### **8.6. Safety Analyses by Demographic Subgroups**

No studies of drug-demographics were conducted during the estradiol vaginal inserts development program.

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

See the Primary Clinical Review of NDA 208564, dated April 28, 2017, Section 5 Source of Clinical Data, Subsection 5.3 Discussion of Individual Studies/Clinical Trials for the analysis of general and endometrial safety information presented in the original NDA application for phase 3, 12-weeks clinical Trial TXV14-01.

### **8.7. Specific Safety Studies/Clinical Trials**

Phase 3 Trial TXV14-01 was the only clinical trial submitted in the original NDA application. This 12-week clinical trial was inadequate to advise on the long-term general and endometrial safety and chronic use drug exposure data for the 4 mcg and 10 mcg estradiol vaginal inserts. No clinical trial of at least 12- months duration was submitted in the original NDA application to evaluate safety of the endometrium in a woman with a uterus.

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

Three cases of proliferative endometrium, including one reported case of disordered proliferative endometrium, were reported in 12-week clinical Trial TXV14-01 in non-hysterectomized women. These endometrial findings are potentially concerning in this trial of 12-weeks of drug exposure, because use of unopposed estrogen is known to increase the risk of endometrial hyperplasia and cancer. Disordered proliferative endometrium is thought to be the precursor for endometrial hyperplasia. All said, a 12-week trial is of insufficient duration to assess endometrial safety.

To explore the association between the use of low-dose vaginal estrogen and endometrial cancer TherapeuticsMD commits to conduct a PMR observational study to identify the incidence of endometrial cancer associated with long-term use of unopposed low dose vaginal estrogen products in postmenopausal women.

### **8.8. Additional Safety Explorations**

No drug-drug interaction (DDI) studies were submitted in the original NDA application. The potential for local (vaginal) DDI with other administered vaginal products (for example, vaginal antifungals) was of concern. TherapeuticsMD addresses the Agency's concerns in proposed labeling. The potential metabolic interaction between estradiol and CYP3A4 inhibitors (ketoconazole and itraconazole) is labeled.

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

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Per the Clinical Pharmacology Review, dated April 7, 2017, from a safety perspective, the 4 mcg and 10 mcg estradiol vaginal inserts are immediate release products that demonstrated low systemic exposure and clearance within 24 hours. “Estradiol is metabolized by CYP3A4; therefore, inhibitors and inducers of CYP3A4 enzymes may affect estradiol metabolism. No drug interaction studies were conducted with TX-004HR. Class labeling would apply to this product.”

See the Clinical Pharmacology Review, dated April 7, 2017, for a full discussion.

### **8.9. Safety in the Postmarket Setting**

No postmarketing safety data is available for the 4 mcg and 10 mcg estradiol vaginal inserts.

### **8.10. Integrated Assessment of Safety**

The NDA resubmission includes an Integrated Summary of Safety (ISS). The NDA resubmission ISS includes the clinical safety data submitted and reviewed in phase 2 Trial TXV13-01 and phase 3 Trial TXV14-01 in the original NDA application. No new safety data is presented in the NDA resubmission ISS for the 4 mcg and 10 mcg estradiol vaginal inserts. See the Primary Clinical Review of NDA 208564, dated April 28, 2017, Section 7 Safety for a full discussion of the Integrated Summary of Safety (ISS) in the original NDA application.

As previously noted in this review, this 505(b)(2) application, relies, in part, on specific publication that support the well-established long-term risk/benefit profile of estrogen-alone and estrogen plus progestin hormone therapy. It is, in large part, the same publications identified in current estrogen class labeling for approved hormone therapy products. See Table 3 in this review. The proposed labeling in the NDA resubmission adopts estrogen class labeling for the 4 mcg and 10 mcg estradiol vaginal inserts.

Published literature suggests that the risks associated with low-dose vaginal estrogens (like 4 mcg and 10 mcg estradiol vaginal inserts) are lower than the risks associated with the higher, more systemically available doses that form the basis of FDA’s estrogen class labeling.

For completeness, select examples of recently published literature included in the NDA resubmission is summarized below:

- Working Group on Women’s Health and Well Being in Menopause, Why the product labeling for low-dose vaginal estrogen should be changed. *Menopause*. 2014; 21(9):911-016 - This publication is a commentary that summarized the activities of several clinicians and researchers to encourage modifications to the labeling of low-dose vaginal estrogen. The authors propose labeling modifications they feel “would enhance women’s safety and improve their health and well-being” and that “women would be better served by a modified label that more closely reflects the safety profile of low-

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dose vaginal estrogen and could ultimately enhance safety by emphasizing the key information that women and clinicians need to know about the products.”

- Crandall CJ, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women’s Health Initiative Observational Study. *Menopause*. [Epub ahead of print August 14, 2017a] - This publication is a prospective observational cohort study that collected data from participants of the WHI-Observational Study regarding incident coronary heart disease (CHD), invasive breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, death, and self-reported use of vaginal estrogen (cream, tablet) from 2005 to 2010, reflecting 7.2 years of median follow-up. The authors conclude that the risk of cardiovascular disease and cancer (endometrial and breast) were not increased in postmenopausal women using vaginal estrogen.
- Crandall CJ, et al. Comparison of clinical outcomes among users of oral and transdermal estrogen therapy in the Woman’s Health Initiative Observational Study. *Menopause*. [Epub ahead of print July 10, 2017b] - This publication examines the association of estrogen preparations with an index of health risks versus benefits using data from 45,112 participants of the WHI-Observational Study regarding the associations of estrogen type and oral CE dose with time to first global index event, defined as CHD, breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer or death. The authors conclude that 1) the summary index of risks versus benefits was similar for oral CE versus other oral or transdermal estradiol-containing regimens, 2) CE plus MPA regimens containing less than 0.625 mg per day of CE for less than 5 years appeared safer, and 3) no notable differences in overall risk versus benefit in users of oral estradiol or transdermal estradiol-containing regimens compared with users of oral CE-containing regimens.
- Mørch LS, et al. The influence of hormone therapies on type I and II endometrial cancer: A nationwide cohort study. *Int J Cancer*. 2016; 138:1506-1515 - All Danish women aged 50 -79 without previous cancer or hysterectomy (n=914,595) were followed during 1995-2009. Incident endometrial cancer (n=6,202) were identified from the National Cancer Registry. The rate ratio (RR) of endometrial cancer was increased with vaginal estrogen: 1.96 (1.77-2.17) but not with continuous combined therapy: 1.02 (0.87-1.20). The risk of Type II tumors appeared decreased with continuous combined therapy: 0.45 (0.20-1.01), and estrogen therapy implied a non-significantly altered risk of 1.43 (0.85-2.41). The authors conclude that continuous combined hormone therapy is free for Type I endometrial cancer, while other hormone therapy increases risk, with further risk among long-term users. Type II endometrial cancer was less convincingly associated with hormone use and continuous combined therapy appeared to decrease risk. Increased risk was suggested for vaginal and transdermal routes of administration, which needs to be further assessed.
- Manson JE et al. Menopausal hormone therapy and long-term all-cause and cause-specific mortality: The Woman’s Health Initiative Randomized Trials. *JAMA*, 2017;

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318(10):927-938 - This publication reports the observational follow-up of postmenopausal women enrolled in the two WHI randomized clinical trials between 1993 and 1998 and followed up through December 31, 2014. The authors conclude that CE plus MPA for a median of 5.6 years or with CE-alone for a median of 7.2 years was not associated with risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years.

- Lethaby A, et al. Local estrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst rev.* 2016 Aug 31; (8): CD001500. Doi: 10.1002/14651858.CD001500.pub3. Review - The authors conclude 1) there is no conclusive evidence of a difference in efficacy between various intravaginal estrogenic preparations when compared with each other, 2) there is no conclusive evidence of a difference in the overall body of evidence in adverse events between the various estrogenic preparations compared with each other or with placebo, 3) women using intravaginal estrogenic preparations who have postmenopausal bleeding should have endometrial investigation.
- Bergendal A, et al. Risk of venous thromboembolism associated with local and systemic use of hormone therapy in peri- and postmenopausal women and in relation to type and route of administration. *Menopause.* 2016; 23(6): 593-599 - This publication is a case control study, conducted in Sweden between 2003 and 2009, that includes 838 cases of venous thromboembolism (VTE) and 891 controls with a mean age of 55 years. The authors conclude that 1) the VTE risk was higher in users of systemic combined estrogen plus progestogen treatment than estrogen-alone, 2) risk of VTE was lower for women who used local estrogen treatment, and 3) transdermal estrogen-alone treatment seem not to be related to an increased risk for VTE.

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

See Subsection 8.2 Review of the Safety Database, in this review, for a summary of the DEPI II review of the Crandall CL, et al. 2017 and Mørch LS, et al. 2016 publications. DEPI II concludes, "However, given the limitations of the WHI study and the incomplete reporting of the Danish study results, a definite conclusion can't be drawn on the association between VE use and risk of endometrial cancer." See the DEPI II review achieved October 20, 2017 for a discussion of the DEPI II assessment of the WHI Observational Study and the Danish study.

The recently published literature discussed above demonstrate the inconsistency in reporting the effects of estrogens, particularly low-dose vaginally administered estrogens. None of the recently published literature included in the NDA resubmission, report the finding from appropriately sized, randomized, placebo-controlled, prospective clinical trials with lower-dose vaginally administered estrogens.

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## 9. Advisory Committee Meeting and Other External Consultations

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This NDA Class 2 Resubmission does not require advice of the Reproductive Health Advisory Committee or other external consultation.

## 10. Labeling Recommendations

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### 10.1. Prescription Drug Labeling

The following changes were made to the proposed labeling for the 4 mcg and 10 mcg vaginal inserts:

- HIGHLIGHTS:
  - Initial U.S. Approval date changed from (b) (4) to 1975
  - Indications and Usage changed to “IMVEXXY is an estrogen indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.”
  - Dosage and Administration changed to “IMVEXXY should be administered 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 changed to “IMVEXXY vaginal inserts contain 4 mcg and 10 mcg estradiol. (3)
  - Contraindications, last bullet (b) (4) removed.
  - Adverse Reactions changed to “In a single, prospective, randomized, placebo-controlled, double-blind study, the most common adverse reaction with IMVEXXY (incidence ≥ 3 percent) and greater than placebo was headache. (6.1)
  - (b) (4) and accompanying text was deleted under Use in Specific Populations.
- FULL PRESCRIBING INFORMATION: CONTENTS\*:
  - 1.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause was added under 1 INDICATIONS AND USAGE
  - The following were deleted under 5 WARNINGS AND PRECAUTIONS:
    - (b) (4)
  - 17 PATIENT COUNSELING INFORMATION was modified; (b) (4) were removed
- FULL PRESCRIBING INFORMATION:

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- 1.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, due to Menopause was added under 1 INDICATIONS AND USAGE
- Text under 2.1 changed to “IMVEXXY should be administered intravaginally; insert with the smaller end up for a depth of about two inches into the vaginal canal. Insert 1 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). Generally, women should be started at the 4 mcg dosage strength. Dosage adjustment should be guided by clinical response.
- Section 3 DOSAGE FORMS AND STRENGTHS changed to “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.”
- Section 4 CONTRAINDICATIONS, bullet two changed to “Known, suspected, or history of breast cancer.”
- Section 4 CONTRAINDICATIONS, bullet four changed to “Active DVT, PE, or history of these conditions.
- Section 4 CONTRAINDICATIONS, last bullet (b) (4) removed.
- Subsection (b) (4) second sentence changed to “Systemic absorption may occur with the use of IMVEXXY [see Pharmacokinetics (12.3)].”
- Subsection 6.1 Clinical Trials Experience; second paragraph changed to “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).”
- Subsection 6.1 Clinical Trials Experience; third paragraph changed to “Adverse reactions with an incidence of  $\geq 3$  percent in any IMVEXXY group and numerically greater than those reported in the placebo group, are listed in Table 1.”
- Subsection 8.1 Pregnancy changed to “IMVEXXY is not indicated for use in pregnancy. There are no data with the use if IMVEXXY in pregnant women; however, epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to combined hormonal contraceptives before conception or during early pregnancy.”
- Subsection 8.2 Lactation changed to “IMVEXXY is not indicated for use in females of reproductive potential. 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.”
- Section 11 DESCRIPTION, first sentence changed to “IMVEXXY (estradiol vaginal inserts) are small, light pink, tear-shaped inserts for manual placement into the

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vagina.”; second sentence changed to “Inserts contain 4 mcg or 10 mcg of estradiol.”; last sentence changed to “When the insert comes in contact with the vaginal mucosa, estradiol is released into the vagina.”

- Subsection 14.1 Effects on Moderate to Severe Dyspareunia was changed as follows:  
“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 (b) (4) 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 had  $\leq 5$  percent 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. 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 ( $p < 0.0001$ ).”

- Subsection 16.1 How Supplied, first paragraph, was changed to “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.”
- Other minor and/or format changes were made to FULL PRESCRIBING INFORMATION labeling.
- Patient Information:
  - “What is the most important information I should know about IMVEXXY (an estrogen hormone)”, bullet 4 “Using estrogen-alone may increase your chances of getting strokes or blood clots” was added.
  - “What is IMVEXXY?” was changed to “IMVEXXY is a prescription medicine that contains an estrogen hormone in a vaginal insert.

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- “What is IMVEXXY used for?” was changed to “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:”, bullet 1 “Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb)” added; bullet 3 relocated to bullet 4 position; bullet 8 “IMVEXXY is not for pregnant women” added.
- “How should I use INVEXXY?” was changed as follows:
  - Added “For detailed instructions, see the step-by-help instructions for using IMVEXXY at the end of this Patient Information.”
  - IMVEXXY is a vaginal insert that you place in your vagina.
  - Steps for use was relocated to Instructions for Use.
  - “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.”
  - Added “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?” was changed as follows:
  - Removed (b) (4)
  - “Serious, but less common side effects could include:” modified to include side effects listed in estrogen class labeling.
  - “Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:” modified to include warning signs listed in estrogen class labeling.
  - Removed (b) (4)
  - Other minor and/or format changes were made to Patient Information labeling.
- Instructions for use was changed as follows:
  - Added “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?” changed to:
    - IMVEXXY is an insert only for use in the vagina. Do not take by mouth.

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- Put 1 IMVEXXY insert into your vagina, 1 time a day at about the same time for the first two weeks, then insert 1 IMVEXXY 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: changed to “Push 1 IMVEXXY insert through the foil of the blister package.”
- Step 2: changed to “Hold the IMVEXXY insert with the large end between your fingers.”
- Step 3: changed to “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.”  
Removed (b) (4)
- “How should I store IMVEXXY” and accompanying text added.

## 11. Risk Evaluation and Mitigation Strategies (REMS)

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A REMS is not indicated for the 4 mcg and 10 mcg estradiol vaginal inserts.

## 12. Postmarketing Requirements and Commitments

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See Subsection 8.5.1 General and Endometrial Safety for a discussion of TherapeuticsMD’s PMR protocol synopsis. See also the Epidemiology Review dated March 23, 2018

## 13. Appendices

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### 13.1. References

See the references reviewed and discussed throughout this primary clinical review.

### 13.2. Financial Disclosure

See the Primary Clinical Review, dated April 28, 2017, Section 3 Ethics and Good Clinical Practices, Subsection 3.3 Financial Disclosures. The Primary Reviewer concluded that

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TherapeuticsMD had adequately disclosed financial agreements for participating investigators/sub-investigators in the primary clinical trial conducted to support the NDA application (phase 3 Trial TXV14-01).

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/s/  
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THERESA H VAN DER VLUGT  
05/29/2018

SHELLEY R SLAUGHTER  
05/29/2018

I concur with the conclusions and recommendation of Dr. van der Vlugt that NDA 208564 should receive approval.

Memorandum to the File

TO: NDA 208564  
Estradiol Vaginal Inserts: 4 and 10 mcg

THROUGH: Shelley R. Slaughter, M.D., Ph.D.  
Medical Team Leader  
Division of Bone, Reproductive, and Urologic Products

FROM: Theresa H. van der Vlugt, M.D., M.P.H.  
Medical Officer  
Division of Bone, Reproductive, and Urologic Products

SUBJECT: Office of Surveillance and Epidemiology, Division of Epidemiology II  
Request Regarding Safety Concerns for NDA 208564 for Inclusion in the  
ARIA Sufficiency/ Insufficiency Memorandum

DATE: April 4, 2018

**Background:**

On March 7, 2018, the Office of Surveillance and Epidemiology (OSE), Division of Epidemiology II (DEPI II) requested the assistance of the Division of Bone, Reproductive, and Urologic Products (DBRUP) regarding a response to Question 1.2. Describe the Safety Concern in the ARIA Sufficiency/ Insufficiency memorandum for NDA 208564. The Agency is requesting a Postmarketing Required (PMR) trial for NDA 208564.

On March 12, 2018. DEPI II provided the following in an email communication with a request to complete Question 1.2 Describe the Safety Concern:

**1. BACKGROUND INFORMATION**

**1.1. Medical Product**

- Describe what the drug is, its (proposed) indications, and mechanism of action.
- Include any relevant pharmacologic properties that might be related to the safety concern.

**1.2. Describe the Safety Concern**

- The overall goal of this section is to characterize the strength of the evidence driving the concern and provide enough clinical detail to understand whether the ARIA is sufficient to assess the safety concern.
- Describe all the lines of evidence that led to the development of this safety concern. This can include therapeutic mechanism of action, pre-clinical studies, clinical studies, postmarket surveillance from the US or other countries, etc.
- Describe the case or patient characteristics from the data above. Do the data suggest any

*clinical patterns in temporal distribution of the time-to-onset, patient population, or associated factors?*

*- Is this a known risk or potential risk?*

*- Describe how the safety concern is labeled and any other relevant risk management strategies (e.g., REMS, postmarket studies in other countries).*

*- Describe any other relevant regulatory background, (e.g., prior PMR/PMR, product class considerations)*

### **DBRUP Response to Question 1.2 Describe the Safety Concern:**

Scientific and clinical evidence has existed since the early 1970's that use of unopposed estrogens in a woman with a uterus is associated with an increase in the risk of endometrial cancer.<sup>1,2</sup> In 1975, the FDA Obstetrics and Gynecology Advisory Committee recommended that estrogen labeling be revised to include a specific warning for an increased risk of endometrial cancer in a postmenopausal woman with a uterus and unopposed estrogen use.<sup>3</sup> In 1976, FDA regulated a Boxed Warning that endometrial cancer is associated with long-term unopposed estrogen use.<sup>4</sup> The risk of endometrial cancer increases substantially with long duration of unopposed estrogen use, and the increased risk persists for several years after discontinuation of estrogen. The addition of a progestin to unopposed estrogen therapy was demonstrated to reduce the risk in a duration dependent fashion.<sup>5,6,7</sup>

The exact risk of unopposed estrogen use was not evaluated in the Women's Health Initiative (WHI), estrogen-alone substudy, as women assigned to this substudy of the WHI were hysterectomized at enrollment. However, risk of endometrial cancer in women treated with a combination estrogen plus progestin product was evaluated in the WHI estrogen plus progestin substudy. After 5.6 years' median intervention and 13 years' median cumulative follow-up in the estrogen plus progestin substudy, there were fewer endometrial cancers in the combined

Estrogen plus progestin therapy group compared with the placebo group [66 vs 95 case patients, yearly incidence, 0.06% versus 0.10%; hazard ratio (HR) = 0.65, 95% confidence interval [CI] = 0.48 to 0.89, p = 0.007]. While there were somewhat fewer endometrial cancers during intervention (25 vs 30, respectively; HR = 0.77, 95% CI = 0.45 to 1.31), the difference became statistically significant post-intervention (41 vs 65,

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<sup>1</sup> Antunes CM. Endometrial cancer and estrogen use. Report of a large case-control study. 1979;300(1):9-13.

<sup>2</sup> Garden J. et al. Oestrogen and endometrial carcinoma, an independent pathology review supporting original size estimate. 1977;297:570.

<sup>3</sup> 1975 FDA Obstetrics and Gynecology Advisory Committee – Transcripts.

<sup>4</sup> Federal Register. Wednesday September 29, 1976;41(190):43117.

<sup>5</sup> Whitehead MI, et al. Effects of various types and dosages of progestogens on the postmenopausal endometrium. J Repro Med. 1982;27:539-548.

<sup>6</sup> Gelfand MM and Ferenczy A. A prospective 1-year study of estrogen and progestin in postmenopausal women: Effects on the endometrium. 1989;74:398-402.

<sup>7</sup> Grady D. Hormone replacement therapy and endometrial cancer risk: A meta-analysis. Obstet Gynecol. 1995;85:304-313.

respectively; HR = 0.59, 95% CI = 0.40 to 0.88, p = .008), but hazard ratios did not differ between phases (p difference = .46). There was a statistically non-significant reduction in deaths from endometrial cancer in the estrogen plus progestin group (5 vs 11 deaths, HR = 0.42, 95% CI = 0.15 to 1.22).<sup>8</sup>

The signs and individual symptoms of vulvar and vaginal atrophy result from the absence of estrogen stimulation to the respective tissues as a result of menopause. In the absence of treatment, signs and symptoms return. Therefore, treatment, once begun, is expected to be life-long (or in the case of dyspareunia, as long as the woman engages in vaginal intercourse). The data to support the known risk of unopposed estrogen on the endometrium as well as the data from the Women's Health Initiative and previous smaller clinical trials and observational trials were obtained from higher dosed products.

There is minimal information available on the long-term endometrial safety of lower-dosed vaginally-administered estrogen alone products. Two 12-month, placebo-controlled endometrial safety trials were conducted with Vagifem 10 mcg estradiol vaginal inserts, a lower-dosed approved vaginally administered product. Results indicate one case of endometrial adenocarcinoma grade 2 and two cases of complex endometrial hyperplasia without atypia. Endometrial polyps (atrophic and adenomyomatous type), adenomyosis, and atypical endometrial proliferation were also reported for Vagifem 10 mcg. No data is available specific to endometrial safety of Estring 7.5 mcg estradiol per 24 hour vaginal ring following exposures of greater than 12-weeks in placebo-controlled clinical trials.

The clinical development program for a low dose product currently under consideration from TherapeuticsMD, did not include any long-term, 12-months or more, endometrial safety data. However, 12-week exposures to this product resulted in the finding of proliferative endometrium and disordered proliferative endometrium, confirming that long-term safety trials are needed.

Information on endometrial safety based on lower systemic pharmacokinetic (PK) exposures is not sufficient as PK data does not take into consideration a direct local effect of vaginally administered products on the endometrium.

The only way to know if lower-dosed and lower serum-exposure products are associated with risks for endometrial cancers is to conduct long-term clinical trials of sufficient duration to allow a true determination of the risk for endometrial cancer. It cannot appropriately be concluded that vaginal administration of lower-dosed estrogen eliminates the risk of endometrial cancer.

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<sup>8</sup> Chlebowski RT, et al. Continuous combined estrogen plus progestin and endometrial cancer: The Women's Health Initiative randomized trial. *J Natl Cancer Inst.* 2016;108(3):1-10.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THERESA H VAN DER VLUGT  
04/04/2018

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I concur.

## CLINICAL REVIEW

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Drug Evaluation III (ODE III)

Reviewer Name(s) Theresa H. van der Vlugt, M.D.  
Review Completion Date April 27, 2017

Established Name Estradiol Vaginal Insert  
(Proposed) Trade Name (b) (4)  
Therapeutic Class Estrogen  
Applicant TherapeuticsMD

Formulation(s) Estradiol  
Dosing Regimen (b) (4)  
Indication(s) Treatment of Moderate to  
Severe Dyspareunia, a  
Symptom of Vulvar and  
Vaginal Atrophy, due to  
Menopause

Intended Population(s) Postmenopausal Women

Template Version: March 6, 2009

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

This clinical reviewer recommends that (b) (4)™ (estradiol vaginal insert) 4 mcg, 10 mcg, (b) (4) not be approved for the applicant's proposed indication of the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. This recommendation of non-approval is based on the absence of long-term safety and drug exposure data in the NDA application. Refer to Subsections 7.2.1, 7.2.6, and 7.3.5.1 for complete discussions.

This clinical reviewer concurs with the applicant's finding of efficacy for (b) (4)™ (estradiol vaginal insert) 4 mcg, 10 mcg, (b) (4) based on successfully achieving the primary protocol-defined co-primary endpoints of 1) a statistically significant reduction versus placebo in moderate to severe dyspareunia, 2) a statistically significant increase in superficial epithelial cells and a corresponding statistically significant decrease in parabasal epithelial cells on a vaginal wall smear, and 3) a statistically significant reduction in vaginal pH in the single, primary, phase 3 clinical Trial TXV14-01 submitted in this NDA application.

This clinical reviewer concurs with the applicant's statements in the Clinical Information Amendment received October 11, 2016 that the proposed indication is for a chronic use indication in postmenopausal women, and that the NDA application does not provide exposure data at 6 months and 12 months for the 4 mcg, 10 mcg, (b) (4) estradiol vaginal inserts. Refer to Subsection 7.2.1. The available 12-week efficacy and safety data submitted is insufficient to demonstrate long-term general and endometrial safety data and chronic use drug exposure data for (b) (4)™ (estradiol vaginal insert) 4 mcg, 10 mcg, (b) (4).

The lack of long-term general and endometrial safety data in the application precludes this reviewer from recommending approval of (b) (4)™ (estradiol vaginal insert) for the proposed indication at this time.

### 1.2 Risk Benefit Assessment

Menopause is a natural biological process and marks the end of fertility as a result of permanent ovarian failure. Symptoms of menopause, such as vasomotor symptoms (VMS; hot flashes/hot flushes) and vulvar and vaginal atrophy symptoms [VVA; vaginal dryness, vaginal irritation/itching, and pain with sexual activity (dyspareunia)] can be

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debilitating with respect to a woman's ability to accomplish her normal activities including sleep. However, menopause is not a life-threatening condition. In 2000, there were an estimated 45.6 million postmenopausal women in the United States. About 40 million of them were older than age 51, the average age of natural menopause in the Western world. By the year 2020, the number of US women older than age 51 is expected to be more than 50 million.<sup>1</sup>

Current treatment options for an indication for the treatment of moderate to severe dyspareunia (self-identified as most bothersome by the woman) include: Premarin® (conjugated estrogens) Vaginal Cream (intravaginally applied estrogen cream); Intrarosa® (prasterone) Vaginal Insert (intravaginally applied steroid insert); Enjuvia® (synthetic conjugated estrogens, B) Tablets (oral estrogen tablet); and Ospemifene® (ospemifene) Tablets (oral estrogen agonist/antagonist tablet).

Current treatment options for the general indication for the treatment of moderate to severe symptoms of VVA, involve multiple estrogen products, used alone in a woman without a uterus, or in combination with a progestogen in a woman with a uterus. Most of these products were approved under estrogen class labeling, and were not supported by clinical trial data demonstrating relief of one or more individual moderate to severe symptoms of vulvar and vaginal atrophy. These approved products offer a range of dosage strengths and different routes of administration including oral tablets, transdermal systems, topical gels, vaginal creams, and vaginal inserts. Estradiol is the active moiety in the majority of the Agency's approved estrogen-alone and estrogen plus progestin products with a general indication for the treatment of moderate to severe VVA symptoms due to menopause.

All three dosage strengths of the estradiol vaginal insert (4 mcg, 10 mcg, and 25 mcg) administered intravaginally once daily for two weeks, then twice weekly for an additional 10 weeks demonstrated statistically significant improvement over placebo, in the relief of self-identified moderate to severe dyspareunia, in the single, primary, phase 3 Trial TXV14-01 included in the NDA application.

Three cases of proliferative endometrium, including one reported case of disordered proliferative endometrium, were reported in 12-week clinical Trial TXV14-01 in non-hysterectomized women. These endometrial findings are concerning in this trial of 12-weeks of drug exposure, because use of unopposed estrogen is known to increase the risk of endometrial hyperplasia and cancer. Disordered proliferative endometrium is thought to be the precursor for endometrial hyperplasia.

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

No long-term endometrial safety data is included in the [REDACTED]® application. In general, long-term safety trials are recommended to support general and endometrial safety (evaluate the prevalence of endometrial hyperplasia and endometrial cancer), as well as to provide sufficient drug exposure for chronically administered estrogen and/or estrogen plus progestogen products. The finding of proliferative endometrium and disordered proliferative endometrium at 12-weeks of drug exposure confirm that long-term safety trials should be obtained premarket to support the long-term endometrial and general safety and chronic use exposure of the 4 mcg, 10 mcg, [REDACTED] estradiol vaginal insert for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

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

As the recommendation is that the product not be approved until long-term safety data is obtained and reviewed, no postmarketing risk evaluation and mitigation strategies (REMS) are recommended.

### 1.4 Recommendations for Postmarket Requirements and Commitments

As the recommendation is that the product not be approved until long-term safety data is obtained and reviewed, no postmarketing requirements and commitments are recommended.

## 2 Introduction and Regulatory Background

### 2.1 Product Information

TherapeuticsMD has developed a new “muco-adhesive [REDACTED] vaginal formulation containing [REDACTED] estradiol [REDACTED] equivalent to 4 mcg, 10 mcg, [REDACTED] of [REDACTED] estradiol, code name of TX-004HR used in development and throughout the new drug application (NDA), for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

In the NDA application, TherapeuticsMD indicates that “the established name for this product should be estradiol vaginal [REDACTED] as it precisely describes the product and route of administration.” TherapeuticsMD proposes that a USP monograph for this new product be instituted upon NDA approval. On February 13, 2017,

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TherapeuticsMD received an email correspondence request to amend the Request for Proprietary Name Review to include the established name as “estradiol vaginal inserts” as required for conformance to the United States Pharmacopeia (USP).

TherapeuticsMD complied on February 16, 2017, Sequence 0013. Henceforth, this reviewer uses “estradiol vaginal insert” in this review.

Estradiol, first isolated in 1935, is an estrane (C18) steroid, an estrogen, and the primary female sex steroid. Estradiol is essential for the development and maintenance of female reproductive tissues such as breasts, uterus, and vagina during puberty, adulthood, and pregnancy. It also has important effects on other tissues including bone, fat, skin, liver, and the brain. Estradiol is also known as 17 $\beta$ -estradiol or as estra-1,3,5(10)-triene-3, 17 $\beta$ -diol. It has two hydroxyl groups, one at the C3 position and the other at the 17 $\beta$  position, as well as three double bonds in the A ring. Due to its two hydroxyl groups, estradiol is often abbreviated as E2. Estradiol (b) (4) is the 17-beta-isomer of estradiol.

During the reproductive years, most estradiol in women is produced by the granulosa cells of the ovaries by the aromatization of  $\Delta^4$ -androstenedione (produced in the theca folliculi cells) to estrone, followed by conversion of estrone to estradiol by 17 $\beta$ -hydroxysteroid dehydrogenase. Smaller amounts of estradiol are also produced by the adrenal cortex in women. In postmenopausal women, fat cells produce active precursors to estradiol. Estradiol is conjugated in the liver to form estrogen conjugates (estradiol sulfate, estradiol glucuronide) and, as such, is excreted via the kidneys. Some of the water-soluble conjugates are excreted via the bile duct, and partly reabsorbed after hydrolysis from the intestinal tract. This enterohepatic circulation contributes to maintaining estradiol levels.

Estradiol vaginal inserts, 4 mcg, 10 mcg, (b) (4) are light pink, tear-shaped, inserts with a cloudy fill appearance and printed with the strength identifiers “04,” “10,” (b) (4) respectively, in white ink on one side of the capsule. Each capsule is formulated as a (b) (4) fill and then encapsulated. Each individual dosage strength of the estradiol vaginal insert will be packaged for commercial distribution into blister strips with an 18-count starter pack carton and an 8-count maintenance pack carton. A 2-count blister pack physician sample will also be available for each individual dosage strength of the insert.

Per the applicant, this new estradiol vaginal insert is designed for “easy insertion, with no need for an applicator, and formulated to dissolve completely and quickly, without requiring vaginal secretions to activate the formulation, minimizing vaginal discharge following administration.” The stated NDA goal of TX-004HR is to (b) (4)

“Since estrogen drug products are well absorbed through the skin and mucous membranes, the vaginal delivery of estrogens circumvents first-pass metabolism.” “The new dosage form may also mitigate the common limitations found

with other vaginal forms of estradiol (i.e., messiness from vaginal creams, pain from applicator insertion, etc).”

## 2.2 Tables of Currently Available Treatments for Proposed Indications

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

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

<b>Vaginal Cream Product</b>	<b>Available Dosage Strength/Dosing Regimens</b>
Premarin® (conjugated estrogens) Vaginal Cream	Cyclic Administration: 0.5 g intravaginally daily for 21 days then off for 7 days  Twice Weekly Administration: 0.5 g intravaginally twice weekly (for example, Monday and Thursday)
<b>Vaginal Insert Product</b>	<b>Available Dosage Strength/Dosing Regimens</b>
Intrarosa® (prasterone) Vaginal Insert	6.5 mg insert administered intravaginally once daily at bedtime
<b>Oral Estrogen-alone Product</b>	<b>Available Dosage Strength/Dosing Regimens</b>
Enjuvia® (synthetic conjugated estrogens, B) Tablets*	0.3 mg taken orally once daily
<b>Oral Estrogen Agonist/Antagonist Product</b>	<b>Available Dosage Strength/Dosing Regimens</b>
Osphena® (ospemifene) Tablet	60 mg tablet taken orally once daily with food

\* Teva Women’s Health, Inc. no longer manufactures or distributes Enjuvia® (synthetic conjugated estrogens, B) tablets under NDA 21443. NDA 21443 for Enjuvia® remains active. The last approved Enjuvia® (synthetic conjugated estrogens, B) tablets labeling is dated (b) (4)

Several estrogen-alone and estrogen plus progestin products are approved with a general indication for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy (VVA) due to menopause. See the “Table of Currently Available Treatments for a Non-Specific VVA Symptom Indication”, in Subsection 9.4 of this review, for information on currently approved estrogen-alone and estrogen plus progestin products with a general indication for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy, due to menopause. Most of these products approved for a general indication for the treatment of moderate to severe symptoms of VVA, were approved under estrogen class labeling, and were not supported by clinical trial data demonstrating relief of individual moderate to severe symptoms of vulvar and vaginal atrophy. Subsequent to the approval under class labeling of products for the general indication of treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, the Division of Reproductive and Urologic Drug Products [(DRUDP), now known as the Division of Bone, Reproductive, and Urologic Products (DBRUP)] discussed the approach of approval under class labeling with its Fertility &

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Maternal Health Drugs Advisory Committee (AC). Taking the advice of the AC into consideration, we determined that sponsors seeking an indication for any symptom of vulvar and vaginal atrophy should conduct clinical trials in support of the indication.

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

Estradiol, the active moiety of TX-004HR, has been used in women and men for several decades for various indications with numerous routes of administration and dosage strengths. Estradiol is approved for use in postmenopausal women for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause, and for the treatment of vulvar and vaginal atrophy (VVA) due to menopause. Estradiol-alone products approved for VVA include:

- Oral products: Menest<sup>®</sup> (esterified estrogens) tablets, various generic (estradiol) tablets
- Transdermal products: Alora<sup>®</sup> (estradiol matrix transdermal system), Climara<sup>®</sup> (estradiol matrix transdermal system), Estraderm<sup>®</sup> (estradiol reservoir transdermal system), VivelleDot<sup>®</sup> (estradiol matrix transdermal system), and various generic estradiol matrix transdermal systems
- Topical products: EstroGel<sup>®</sup> 0.06% (estradiol gel) for topical use
- Vaginal cream products: Estrace<sup>®</sup> Cream (estradiol vaginal cream)
- Vaginal ring products: Estring<sup>®</sup> (estradiol vaginal ring), Femring<sup>®</sup> (estradiol acetate vaginal ring)
- Vaginal insert products: Vagifem<sup>®</sup> (estradiol vaginal insert)

Estradiol plus progestin products approved for VVA include:

- Oral products: Angeliq<sup>®</sup> (drospirenone plus estradiol) tablets, for oral use; Prefest<sup>®</sup> (estradiol/norgestimate) tablets
- Transdermal products: CombiPatch<sup>®</sup> (estradiol/norethindrone acetate transdermal system)

### 2.4 Important Safety Issues With Consideration to Related Drugs

After an average follow-up of 7.1 years, the Women's Health Initiative (WHI) estrogen-alone substudy was stopped early (year 2004) because the use of conjugated estrogens (CE) 0.625 mg-alone increased the risk of all strokes (relative risk [RR] 1.33, 95% confidence interval [CI], 1.05-1.68 for CE-alone versus placebo) and deep vein thrombosis (DVT), and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen-alone in predetermined primary endpoints. Centrally adjudicated results for ischemic stroke in the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, also reported an increased risk for ischemic stroke (RR 1.55, 95% CI, 1.19-2.01). No effect on coronary heart disease (CHD), after an average follow-up of 7.1 years, was reported (RR 0.95, 95% CI, 0.78-1.16). Other findings in the CE-alone substudy included a decreased risk of hip fracture (RR 0.65,

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95% CI, 0.45-0.94), a decreased risk of invasive breast cancer (RR 0.80, 95% CI, 0.62-1.04 for women 50 to 79 years of age), and an increased risk for probable dementia (RR 1.49, 95% CI, 0.83-2.66).

In addition, the WHI estrogen-alone substudy, stratified by age, showed in women 50 to 59 years of age a non-significant trend toward reduced risk for CHD (hazard ratio [HR] 0.63, 95% CI, 0.36-1.09) and overall mortality (HR 0.71, 95% CI, 0.46-1.11).

The risk and benefit information available in the WHI estrogen-alone substudy in year 2004 prompted changes in labeling for estrogen-class drug products including, but not limited to, the expansion of the Boxed Warning to include the reported increased risk of stroke in the WHI estrogen-alone substudy. In years 2006 and 2007, additional changes were made in labeling for estrogen-class drug products based on centrally adjudicated results for the WHI estrogen-alone substudy. In addition, Boxed Warning information states that “In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens”, and that “Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual women.”

After an average follow-up of 5.6 years, the CE (0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) substudy of WHI was stopped early (year 2002) because the increased risk of invasive breast cancer and cardiovascular events exceeded the pre-specified limits in the “Global Index”. Centrally adjudicated data, after an average follow-up of 5.6 years, reported an increased risk of invasive breast cancer (RR 1.24, 95% CI, 1.01-1.54), increased risk of all strokes (RR 1.31, 95% CI, 1.03-1.68) and ischemic stroke (RR 1.44, 95% CI, 1.09-1.90), increased risk of coronary heart disease (RR 1.23, 95% CI, 0.99-1.53), increased risk of DVT (RR 1.95, 95% CI, 1.43-2.67), increased risk of pulmonary embolism (RR 2.13, 95% CI, 1.45-3.11), increased risk of probable dementia (RR 2.05, 95 percent CI, 1.21-3.48), and a decreased risk of hip fracture (RR 0.67, 95 % CI, 0.47-0.96).

The risk and benefit information available in the WHI estrogen plus progestin substudy in year 2002 prompted changes in labeling for estrogen-class drug products including, but not limited to, the addition of a Boxed Warning to all estrogen plus progestin product labels and the expansion of the existing Boxed Warning to include the increased risk of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis reported in the estrogen plus progestin WHI substudy. In addition, Boxed Warning information states that “In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestin”, and that “Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual women.”

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Risk information available in the WHI Memory Study (WHIMS) in years 2003 and 2004 prompted additional changes in labeling for estrogen-class drug products to include the reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older. WHIMS findings for both the estrogen-alone ancillary study and the estrogen plus progestin ancillary study were added to the Boxed Warning, and the Clinical Studies and Warnings and Precautions sections of estrogen-class labeling.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 118439 for TX-004HR ((b) (4) estradiol) was initially submitted by TherapeuticsMD on April 26, 2013, received May 10, 2013. The initial submission presented two phase 1 protocols designed to investigate the pharmacokinetics and bioavailability of estradiol vaginal insert (10 mcg and 25 mcg) compared to 10 mcg and 25 mcg Vagifem® (estradiol vaginal insert), respectively. Phase 1 Trials ESTR-1K-499-12 and ESTR-1K-500-12 received comments and recommendations from DBRUP on July 8, 2013 in an Advice/Information Request (A/IR) letter with reference to the Agency's 2003 draft Guidance for Industry entitled, "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms – Recommendations for Clinical Evaluation."

On May 8, 2014, TherapeuticsMD requested a Type C meeting to discuss development plans for TX-004HR including a draft phase 3 protocol. Written Responses only (WRO) were provided on July 18, 2014. Clinical questions and FDA responses are presented below:

#### Clinical:

Question Number 2: "Does the Agency concur that the design of the proposed Phase 3 study is acceptable and sufficient for the Phase 3 evaluation of TX-004HR for the stated indication?"

#### **FDA Response:**

"No, we do not concur. We have the following general comments:

- We do not agree with your proposal, as stated in subsection 10.9.4 of your draft protocol, to allow "as needed" use of a vaginal lubricant during the conduct of Study TXV14-01.
- Per the Agency's 2003 draft clinical evaluation Guidance for Industry, we recommend that the endometrial tissue obtained by endometrial biopsy at screening, during the conduct of the study, and at the end-of-study be processed in the same manner by a central laboratory. For the evaluation of protection of the endometrium, we recommend concurrent readings by three independent expert pathologists from institutions with independent fiduciary and organizational reporting. Each pathologist should be blinded to the treatment group and to the readings of the other pathologists. We also recommend that standardized

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criteria be used for the diagnosis of endometrial hyperplasia, and that endometrial polyps be fully characterized as to glandular proliferation and atypia. The concurrence of two of the three pathologists is accepted as the final diagnosis. If there is no agreement among the three pathologists, the most severe pathologic diagnosis would be used as the final diagnosis. The standardized criteria for histologic evaluation, and the Agency's 2003 draft clinical evaluation guidance can be viewed at

<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133343.pdf>

- We do not agree with your draft protocol proposal to have assessment of “treatment unscheduled biopsy” or End-of-Treatment (or early withdrawal if after week 10 of drug administration) endometrial biopsies by two primary pathologists with involvement of a third pathologist only in cases of disagreement by the two initial readers regarding the presence of endometrial hyperplasia, endometrial polyp, or endometrial cancer. Refer to our previous bulleted comment regarding evaluation of endometrial pathology.
- Your draft protocol does not address the administration of a progestogen following collection of the end-of-study endometrial biopsy (or early withdrawal endometrial biopsy after week 10).
- Data collected for secondary endpoints will not be used to determine effectiveness of your drug product. (b) (4)
- You propose to study multiple doses of TX-004HR (4 mcg, 10 mcg and 25 mcg) compared to placebo.
  - Clarify whether you intend to submit your new drug application for multiple dose strengths and if so, how those different dose strengths will be given to patients.
  - Provide your rationale of dose selection and the dosage and administration instructions at the time of your new drug application submission. These should be well supported by the Phase 3 data.
- Should you decide to conduct a single study to support the indication, the evidence of efficacy needs to be at an alpha level of at least 0.01. In addition, in the statistical analysis plan, we recommend the mixed model for repeated measures (MMRM) instead of last observation carried forward (LOCF) for handling missing values. The latter could be used for sensitivity analysis.
- You should submit a final protocol for our review and comment. Provide the following with your protocol:
  - Complete information regarding the use of “non-hormonal medications” that the Medical Monitor can approve if the study participant experiences hot flashes.
  - A copy of the Pathology Committee Charter which includes “Instructions and other additional information regarding performing the endometrial biopsies, submission of samples and reporting” designed “to ensure uniformity and interpretation”.

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- Specify the following regarding PK characterization:
  - blood sampling time points
  - a proposal on how the baseline will be characterized
  - number of subjects

Question Number 3: “Does the Agency agree with the sample size calculation for the Phase 3 study as described in Section 9.4.2?”

### **FDA Response:**

No, we do not agree. In order to have a subject’s data included in the efficacy analysis for proposed Study TXV14-01, the subject should have identified at baseline, moderate to severe pain with sexual activity (dyspareunia) as most bothersome to her and have a baseline percentage of superficial cells that does not exceed 5% and have a vaginal pH greater than 5.0.

For powering the study with respect to the co-primary endpoint of severity of dyspareunia, you assumed effect size in terms of percent change (41.2%), while the required efficacy is the mean change from baseline. Justify that the sample size of 120 is adequate for the mean change.

Phase 3 Trial TXV14-01 was submitted for review on August 6, 2014. The following comments and recommendations were conveyed to TherapeuticsMD on October 27, 2014:

1. Inclusion criterion number 9, based on “an acceptable result from an evaluable screening endometrial biopsy”, needs to take into consideration the age of the woman, the number of years since menopause and any recent use of a hormone therapy product. For example, a screening endometrial biopsy in a postmenopausal woman who has not recently used hormone therapy and is 60 to 75 years of age or 10 or more years post-menopause, should not commonly demonstrate a finding of proliferative endometrium, weakly proliferative endometrium, or disordered proliferative endometrium. Such a woman should ideally not be randomized into Study TXV14-01 for the treatment of the symptoms of vulvar and vaginal atrophy. We recommend that you propose entrance criteria for an “acceptable result from an evaluable screening endometrial biopsy” that factors in the age of the woman and/or the number of years since menopause and recent hormone therapy use.
2. Inclusion criterion number 10 needs to be revised to read, “Subjects who have a Body Mass Index (BMI) less than or equal to 38 kg/m<sup>2</sup>.”
3. We have concerns regarding the proposed permitted non-hormonal medications in Study TXV14-01 (at the discretions of the investigator) for use by postmenopausal women in this study who are experiencing hot flashes. Your protocol includes non-hormonal products that are not approved for the treatment of moderate to severe vasomotor symptoms (VMS). The only nonhormonal approved product is Brisdelle™ (paroxetine) capsule, 7.5 mg daily. We

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recommend that only Brisdelle™, 7.5 mg daily, be administered to a study participant experiencing 7-8 moderate to severe hot flashes per day.

4. We do not recommend therapy for any postmenopausal woman who is experiencing mild hot flashes.
5. We do not agree with your proposal to have endometrial biopsies read by two primary pathologists with involvement of a third pathologist only in cases of disagreement by the two initial readers regarding the presence of endometrial hyperplasia, endometrial polyp, or endometrial cancer. Three independent expert pathologists should concurrently evaluate End-of-Treatment [or early withdrawal (when treated  $\geq 10$  weeks)] endometrial biopsies. Each of these three pathologists should be blinded to the study treatment group and to the readings of the other pathologists. The Agency's 2003 draft clinical evaluation guidance can be viewed at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133343.pdf>
6. Your proposed protocol should provide details as to how a study participant with a diagnosis of endometrial hyperplasia or cancer "will be given appropriate treatment." The protocol should be more specific as to additional follow-up that should occur if two attempts at end-of-study endometrial biopsy results in insufficient tissue for diagnosis.
7. Clarify whether progestin treatment is planned after 12-weeks of treatment with your estrogen only product in postmenopausal women with intact uteri.

Trial TXV14-01 was amended on November 26, 2014. The following comments and recommendation were conveyed to TherapeuticsMD on February 9, 2015:

1. We do not concur with the proposed procedure regarding "appropriate treatment" when a study participant is diagnosed with endometrial hyperplasia, either during the study conduct or at the end-of-study. It is the your responsibility to assure that appropriate treatment for a diagnosis of endometrial hyperplasia is provided, either by the study Investigator or by the woman's primary care physician, and to follow these women who have developed on-study or end-of study endometrial hyperplasia until this adverse event is resolved.
2. Clarify whether progestin treatment is planned after 12-weeks of treatment with your estrogen-only product in postmenopausal women with intact uteri.

On October 12, 2015, TherapeuticsMD requested a Type B pre-NDA meeting via teleconference granted for December 15, 2015. One question pertained to narratives for integrated summaries submitted in the NDA application as follows:

Question 6: "Does the Division agree that sections 1.7.3 and 2.7.4 may serve as the narrative portion of the ISE and ISS as described in the FDA guidance, with any appendices of tables, figures, and datasets located in sections 5.3.5.3, as needed?"

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### **FDA Response:**

We agree that your proposed NDA application would meet the exception situation set forth in the Agency's 2009 Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, in which the narrative portion of section 2.7.3, Summary of Clinical Efficacy, under Module 2 Common Technical Document Summaries, 2.7 Clinical Summary, could be sufficiently detailed to serve as the narrative portion of the Integrated Summary of Efficacy (ISE).

In addition to the Summary of Clinical Safety in section 2.7.4, we recommend that your proposed NDA application include an Integrated Summary of Safety (ISS) in section 5.3.5.3 under Module 5 Clinical Study Reports.

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

In the pre-NDA meeting package, information was provided for the completed clinical development program, which per the applicant consisted of five studies: "three single-dose PK studies, one 14-day phase 2 safety and efficacy study, one pivotal, 12-week, phase 3, safety and efficacy study." DBRUP failed to proactively remind the applicant that a 12-month long-term safety and drug exposure clinical trial would be needed to support their drug product.

As part of the pre-NDA meeting package, TherapeuticsMD provided illustrations and step-wise instructions for self-administration of the estradiol vaginal insert, and requested agreement from the Agency that a label comprehension study would not be required.

Question 9: "Does the Agency agree no label comprehension study is needed?"

### **FDA Response:**

We recommend a comprehensive use-related risk analysis of your product to inform whether a labeling comprehension study would be needed. Your proposed product and package design does raise concerns for FDA regarding the potential for wrong route of administration errors (e.g., oral administration of the insert). The absence of an applicator for use with your product may suggest to patients that the 'inserts' can be given by routes other than vaginal. Therefore, we recommend you perform a use-related risk analysis to identify the use-related risks associated with your proposed product. Your risk analysis should include an evaluation of all the steps involved in using your product, the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors. Your use-related risk analysis should also discuss the risk-mitigation strategies you employed (e.g., labeling interventions). In your risk analysis, you should evaluate the risk for wrong route of administration errors and consider how this risk can be mitigated. The use-related risk analysis will inform whether a labeling comprehension study is needed to

validate your risk mitigation strategies. Your risk analysis, along with any data you may have to support the design of your user interface, should be included in your original NDA submission.

**Clinical Reviewer's Comments:**

Per the application, TherapeuticsMD engaged the services of (b) (4) to lead them through development of a comprehensive use-related risk assessment in order to address the FDA recommendation to develop a comprehensive user Failure Modes and Effects Analysis (uFMEA). A risk assessment matrix was used to determine if additional design mitigations might be necessary based on the severity and probability ratings of the risk. See the User Risk Assessment in Section 5.3.5.4 in the application.

Per the User Risk Assessment, all of the potential harms were rated at the "Acceptable Risk" level except one item. Only the potential for contamination of the capsule and inducing an infection fell into the "yellow" category, with the "potential harm being minor and the probability remote." In addition, the User Risk Assessment included an evaluation of all the steps involved in using the product, the use errors or task errors that might occur (including known problems for similar products), and the potential negative clinical consequences of use errors. Pre the applicant, the risk analysis did not raise a safety concern for oral or other incorrect routes of administration of the estradiol vaginal insert.

The Agency's review of the submitted use-related risk assessment is pending as of the date of this review.

On April 9, 2015, TherapeuticsMD submitted a proprietary name/request for review for the proposed name (b) (4). On September 9, 2015, a Proprietary Name Request Unacceptable letter was sent to the applicant indicating this name is unacceptable:

"Your proposed proprietary name, (b) (4) may be confused with the currently marketed product, (b) (4) due to orthographic similarity between this name pair and overlapping product characteristics. (b) (4)

(b) (4) Additionally, we have postmarketing evidence showing that even if the modifier is included, errors still occur between orthographically similar names with numerical overlapping strengths. Specifically, there is a report from 2013 in the Institute of Safe Medication Practices Community/Ambulatory Care newsletter about an order written as Effexor XR 75 mg being misinterpreted by a pharmacist as Enablex 7.5 mg".

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“Therefore, based on the totality of information considered above, we conclude there is a risk for name confusion between (b) (4) and (b) (4) that can result in wrong drug errors.”

On October 20, 2015, Yuvvexy™ (hereafter referred to as Yuvvexy) was submitted for review under IND 118439. On February 3, 2016, a Proprietary Name Request Conditionally Acceptable letter was sent to the applicant with instruction that a request for proprietary name review should be submitted with the NDA. A proprietary name request for Yuvvexy is included in the NDA application.

On February 2, 2017, Therapeutics withdrew the proposed proprietary Yuvvexy and submitted the proposed proprietary name (b) (4) (hereafter referred to as (b) (4)). However, on February 17, 2017 TherapeuticsMD received a Proprietary Name Request Unacceptable letter from the Agency stating: “The proposed proprietary name, (b) (4), is vulnerable to medication errors due to confusion with another product that is also under review. Therefore, the ultimate acceptability of your proposed name, (b) (4) is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed name of (b) (4) you will be requested to submit another name.”

### **Clinical Reviewer’s Comments:**

On February 24, 2017, TherapeuticsMD submitted a Request for Alternative Proprietary Name Review for the name (b) (4). This submission includes a Drug Safety Institute, Inc. (DSI) Failure Mode and Effect Analysis (FEMA) report in support of the proposed alternative proprietary name. TherapeuticsMD indicates that the previously proposed proprietary name (b) (4) remains their first choice.

On March 22, 2017, TherapeuticsMD received a Proprietary Name Request Unacceptable letter from the Agency stating: (b) (4) as proposed is overly fanciful. The tradename as proposed misleadingly imply that the drug will (b) (4) and thus is suggestive of positive outcomes far beyond the indication for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.” No additional alternative proprietary name was submitted by the applicant.

On March 27, 2017, TherapeuticsMD submitted a request for a re-review of the proposed name (b) (4) following an email communication from the Agency, dated March 24, 2017, which stated “that there is no longer an issue with (b) (4) similarity to another name...”

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A full pediatric waiver is requested in the application. Per the application, “The disease identified in the proposed indication does not exist in the pediatric population.” On March 4, 2015, the Agency agreed with the initial Pediatric Study plan (iPSP) submitted under IND 118439. The iPSP states that no extrapolation of data from the adult population to the pediatric population is proposed. Moreover, no nonclinical or clinical studies are planned to support pediatric use of TX-004HR.

**Clinical Reviewer’s Comments:**

On March 23, 2015 and March 29, 2017, the Division of Pediatric and Maternal Health, Pediatric Review Committee (PeRC) concurred with the iPSP for a full waiver. We concur that a full pediatric waiver be granted from the study requirements of the Pediatric Research Equity Act for (b) (4) (estradiol vaginal insert).

2.6 Other Relevant Background Information

Per the applicant, estradiol vaginal insert “does not adequately describe the dosage form of (b) (4) TherapeuticsMD (TXMD) proposes that the established name “estradiol vaginal (b) (4) is more descriptive and less confusing to healthcare providers, pharmacies, and patients.” “Vaginal inserts conveys nothing to a prescriber or patient about the nature of the dosage form itself.” “TXMD has developed appropriate patient information and labeling to prevent misadministration of the product. Based on user Failure Modes and Effects Analysis, TXMD concluded that the potential harm associated with any use errors are not severe, and the likelihood of use errors for oral administration are low.” “TXMD believes that the appropriate established name for TXV004-HR, in conformance with USP’s general rule for nomenclature and the FDA Standards Manual for dosage forms, is “estradiol vaginal (b) (4)” and proposes that a USP monograph for the new product be established upon NDA approval.”

A Clinical Information Amendment is included in the NDA application to address proposed labeling for (b) (4). This information amendment summarizes the areas in the proposed (b) (4) prescribing information that differs from estrogen class labeling recommended in the Agency’s draft 2005 Guidance for Industry. Highlights of proposed (b) (4) labeling include:

(b) (4)

Rationale:

(b) (4)

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(b) (4)

(b) (4) "Generally, when estrogen is prescribed for a postmenopausal women with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer"

(b) (4)

Rationale:

(b) (4)

(b) (4) "Known, suspected, or history of breast cancer" (b) (4)

Rationale:

(b) (4)

**Clinical Reviewer's Comments:**

The applicant includes references in support of the proposed changes in the (b) (4) labeling. This reviewer is familiar with the references included in this Clinical Information Amendment and does not agree that these references provide substantial evidence to warrant (b) (4) and the other proposed (b) (4) labeling changes.

The Agency's 2005 draft labeling guidance recommends consistency in labeling across all approved estrogen-alone and estrogen plus progestin products irrespective of dose or route of administration.

On October 10, 2016 (received October 11, 2016), the applicant submitted product labeling revised in accordance with estrogen class labeling per the Agency's draft 2005 Guidance for Industry.

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On (b) (4) an eight-item Form FDA 483(09/08) was issued to (b) (4) following an inspection of this facility between (b) (4). (b) (4) is the drug manufacturer of the estradiol vaginal insert used in the clinical trials conducted in support of this NDA application. (b) (4)

On (b) (4), (b) (4) responded to the Form FDA 483. Per the IQA – Facilities Final Review, (b) (4)

“Based on the review of the firm’s responses, which notes ongoing corrections and plans in progress, there are open concerns, but none that arise to the level to support a withhold based on data generated at this site for the NDA.”

**Clinical Reviewer’s Comments:**

Per the Quality Assessment Review, dated April 17, 2017, “... (b) (4)

Furthermore, there is no evidence that the overall quality and suitability for clinical study use of the (b) (4) product was adversely impacted.” “Although numerous deficiencies were noted during a recent inspection of the manufacturer (b) (4) of the phase 3 clinical trial materials, the totality of information indicates that those materials were of suitable quality for investigational use.”

See the Quality Assessment Review, dated April 17, 2017 for a full discussion of CMC issues under NDA 208564.

This reviewer remains concerned regarding the deficiencies cited in the Form FDA 483 sent to (b) (4). (b) (4) manufactured and supplied all investigational products used in the estradiol vaginal insert development program.

### **3 Ethics and Good Clinical Practices**

#### **3.1 Submission Quality and Integrity**

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TherapeuticsMD conducted numerous internal audits at participating centers during its development program to ensure compliance with procedures that incorporate the ethical principles of Good Clinical Practices (GCP), and to assess the adequacy of quality control procedures. Per the applicant, these internal audits focused on trial documentation, investigator sites, and clinical trial reports.

Investigator site audits were performed by external auditors under the supervision of TherapeuticsMD's Quality Assurance and independently of the site monitors. The dates and locations of these audits were as follows:

- Site 431: Visions Clinical Research, Tucson, AZ; Cynthia Goldberg, MD  
Date of Audit: June 22-23, 2015
- Site 484 – Ideal Clinical Research, North Miami Beach, FL; Christ-Ann Magloire, MD  
Date of Audit: August 11-12, 2015
- Site 478 – Clinical Research Center, Eastern Virginia Medical School, Norfolk, VA; David F. Archer, MD  
Date of Audit: March 31, 2015 – April 1, 2015
- Site 434 – Wake Research Associates, LLC, Raleigh, NC; Poursu Bhiwandi, MD  
Date of Audit: May 28-29, 2015
- Site 498 – Diex Research Montreal Inc., Montreal, Quebec Canada; Manon Gelin, MD  
Date of Audit: July 23-14, 2015
- Site 435 – Seattle Women's: Health, Research, and Gynecology, Seattle, WA; Robin Kroll, MD  
Date of Audit: April 9-10, 2015
- Site 433 – Affiliated Clinical Research, Inc., Las Vegas, NV; Garn Mabey, MD  
Date of Audit: June 25-26, 2015
- Site 436 – Radiant Research, Chicago, IL; Phyllis Marx, MD  
Date of Audit: March 17-18, 2015
- Site 400 – Women's Health Research a Subsidiary of Aventiv Research, Columbus, OH; David F. Portman, MD  
Date of Audit: May 18-19, 2015
- Site 401 – Downtown Women's Health Care, Denver, CO; Arthur Waldbaum, MD  
Date of Audit: May 12-13, 2015
- Site 454 – Medical Center for Clinical Research, San Diego, CA; William Koltun, MD  
Date of Audit: March 23-24, 2015

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

No corrective action appears to have resulted from these internal audits. Per the applicant, this audit program helps to provide reassurance that valid procedures for data management and analysis were adhered to, and that the

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TherapeuticsMD's clinical trial program was carried out in accordance with GCP guidelines.

The mandatory Biomedical Research (BIMO) information requested by the Office of Scientific Investigations (OSI) is included in the application for 12-week, primary efficacy clinical Trial TXV14-01.

On September 21, 2016, DBRUP requested clinical site inspection by OSI, Division of Clinical Compliance Evaluation (DCCE) for the following clinical sites in the U.S.:

- Priority 1: Site 454; William Koltun, MD, Medical Center for Clinical Research, 9040 Friars Road, Suite 540, San Diego, CA 92108. Site 454 enrolled 33 postmenopausal women. Two (2) of the 8 women in the 10 mcg estradiol vaginal insert treatment group had major protocol deviations. Participating woman Number (b) (6) used Boron (trace mineral) for the entire trial duration. Boron is reported to help arthritis and osteoporosis, and help to reduce postmenopausal symptoms. Participating woman Number (b) (6) used Prempro® on Days 36 to 45 of trial duration. Prempro® is used to treat moderate to severe vulvar and vaginal atrophy symptoms due to menopause. The effects of use of these prohibited medications, on the efficacy of the 10 mcg estradiol vaginal insert, are not known.
- Priority 2: Site 435; Robin Kroll, MD, Seattle Women's: Health, Research, Gynecology, 3216 NE 45<sup>th</sup> Place, Suite 100, Seattle, WA 98105. Site 435 enrolled 18 postmenopausal women.
- Priority 3: Site 484; Christ-Ann Magloire, MD, Ideal Clinical Research, 1880 NE 163<sup>rd</sup> Street, Suite 102, North Miami Beach, FL 33162. Site 484 enrolled 41 postmenopausal women. Four (4) major protocol deviations are reported for Site 484. These four protocol deviations involved not collecting Pap smears, per protocol procedure, at Week 12 on the following postmenopausal women: 1) number (b) (6) in the 4 mcg estradiol vaginal insert treatment group, 2) Number (b) (6) in the 25 mcg estradiol vaginal insert treatment group, 3) Number (b) (6) in the placebo vaginal insert treatment group, and 4) Number (b) (6) in the placebo vaginal insert treatment group. These four protocol deviations demonstrate inconsistency in following established end-of-trial procedures.
- Priority 4: Site 400; David Portman, MD, Women's Health Research, a Subsidiary of Aventiv Research, 99 North Brice Road, Suite 120, Columbus, OH 43213. Site 400 enrolled 27 postmenopausal women. The Statistical reviewer determined that Site 400 was critical to the efficacy evaluation of the 4 mcg estradiol vaginal insert due to significant variability.

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

On February 15, 2017, OSI/DCCE provided an evaluation of the clinical inspection for Site 400; David Portman, MD, conducted between October 24, 2016 and October 28, 2016. Dr. Portman received a letter indicating "...we

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conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protection of human subjects.” A form FDA 483 was not issued at the conclusion of the inspection. Site 400 received a No Action Indicated (NAI) classification.

On February 15, 2017, OSI/DCCE provided an evaluation of the clinical inspection for Site 435; Robin Kroll, MD, conducted between November 29, 2016 and December 6, 2016. Dr. Kroll received a letter indicating “...we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protection of human subjects.” A form FDA 483 was not issued at the conclusion of the inspection. Site 435 received a NAI classification.

On March 20, 2017, OSI/DCCE provided an evaluation of the clinical inspection for Site 454; William Koltun, MD, conducted between January 25, 2017 and January 30, 2017. Dr. Koltun received a letter indicating “...we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protection of human subjects.” A form FDA 483 was not issued at the conclusion of the inspection. Site 454 received a NAI classification.

On March 20, 2017, OSI/DCCE provided an evaluation of the clinical inspection for Site 484; Christ-Ann Magloire, MD, conducted between January 19, 2017 and January 26, 2017. Dr. Magloire received a letter indicating “...we conclude you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and protection of human subjects.” A form FDA 483 was not issued at the conclusion of the inspection. Site 484 received a NAI classification.

### 3.2 Compliance with Good Clinical Practices

Twelve-week clinical Trial TXV14-01 appears to have been conducted in accordance with the ethical principles originating from the Declaration of Helsinki and undertaken in accordance with the ethical principles of Good Clinical Practice (GCP) as required by the International Conference on Harmonisation Guidelines for GCP (ICH-E6).

Postmenopausal women, 40 to 75 years of age (inclusive), who qualified according to the inclusion and exclusion entry criteria, were enrolled in this trial after they provided written informed consent as described in 21 CFR 50. The informed consent form contained the required Health Insurance Portability and Protection Act (HIPAA) information.

The Debarment Certification, dated May 2, 2016 states: “TherapeuticsMD, Inc. hereby certifies that it did not and will not use in any capacity the services of any person

debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.”

### 3.3 Financial Disclosures

Form FDA 3454 (3/16) dated May 3, 2016 states: “As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study where by the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payment of other sorts (as defined in 21 CFR 54.2(f)).”

A Form FDA 3454 in the application provides a tabular listing of investigators/sub-investigators who participated in clinical Trial TXV14-01 certifying no disclosable interests.

(b) (6) a sub-investigator at (b) (6) reported a significant equity interest that met the criteria for disclosure. (b) (6) has stock options that would potentially exceed \$50,000 US in aggregate. He disclosed ownership of a total of 216,000 options in TherapeuticsMD stock. Of these, the first 108,000 options are at \$0.10 per option and the second 108,000 options are at \$0.25 per option. Per the applicant, the circumstances which prevent potential bias are:

- (b) (6) was a subinvestigator at (b) (6) and not directly responsible for conduct of the trial at the site.
- Trial TXV14-01 was a multicenter, randomized, placebo-controlled trial. A total of 100 sites consented participating women during screening, with 89 sites randomizing 764 women to the trial. (b) (6) screened (b) (6) and randomized (b) (6) women. These (b) (6) women represent less than (b) (6) of the randomized patient population. A Form FDA 3455 for (b) (6) is available in the application.

#### **Clinical Reviewer’s Comments:**

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

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



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(b) (4) (estradiol vaginal insert)

manufactured at (b) (4) are included in Section 3.2.P.8.3 of the application.

Stability data for registration stability batches (3 for each product strength) through 6 months are also included in the application. Catalent Pharma Solutions LLC, St. Petersburg, FL (Catalent STP), has been qualified as the proposed commercial manufacturer instead of (b) (4)

See the Quality Assessments Review, dated April 17, 2017, for a full discussion of issues.

Question 6: "Does the Agency agree with this proposal?" Per the information provided, registration batches were packaged by Catalent in the for-market configuration and placed on long-term stability. (b) (4)

**FDA Response:**

No. (b) (4)

At the EOP2 CMC meeting, TherapeuticsMD made a Request for a Categorical Exclusion from preparation of an Environmental Assessment for the NDA, since the estimated concentration of the drug substance, estradiol, at the point of entry into the aquatic environment is projected to be less than 1 part per billion. The Agency agreed that a claim for categorical exclusion per 21 CFR 25.31(b) and a statement of no extraordinary circumstances is appropriate for this drug application, and requested that the environmental assessment document and calculations be submitted in the NDA application.

**Clinical Reviewer's Comments:**

In support of the request for a categorical exclusion from environmental assessment, the applicant calculated an expected introduction concentration EIC-Aquatic of  $2.82 \times 10^{-5}$  ppb. This is well below the 1 ppb threshold. The environmental assessment team has advised that the categorical assessment can be granted.

The Quality Assessment Review, dated April 17, 2017, recommends "In its present form, TherapeuticsMD's 505(b)(2) New Drug Application #208564, for

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(b) (4) (estradiol vaginal insert)

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Estradiol Vaginal Inserts, 4 mcg, 10 mcg, (b) (4) per vaginal insert, is not ready for approval. Labeling (package insert, container/carton) negotiations have not been completed, and in its present form, the labeling does not comply with the requirements under 21 CFR 201. For labeling deficiencies, see Attachment II. *Note: Labeling deficiencies and comments will not be conveyed to the applicant during the current review cycle.*

The following comments are recommended to be included in the Complete Response action letter, per the Quality Assessment Review:

“We remind you that the current USP includes a monograph for Estradiol Vaginal Inserts. We understand that the current USP monograph may not be a suitable public standard for your new drug product. However, there is an expectation that your product will conform to the compendial monograph requirements. Alternatively, deviations from the monograph requirements should be identified on your product labels. We recommend that you petition the USP with proposed revisions to the monograph in order to accommodate your new drug product. Please see the following link for more information about that USP process: <http://www.usp.org/usp-nf/pending-monographs>.”

“Specifically, we note differences in assay test method and acceptance criteria, the dissolution test method and acceptance criteria, and in the procedure for determining related substances.”

“The proposed analysis of estradiol related compounds and degradation impurities by HPLC-MS may be acceptable for quality control purposes in the firm’s laboratory but is currently unacceptable for regulatory purposes because the method does not work with a similar mass spectrometer in two different locations. It is therefore incumbent upon you to propose methods that are suitable for regulatory purposes.”

“With regard to the dissolution test method, we recommend that perform dissolution method validation in accordance with US<1092>, The Dissolution Procedure: Development and Validation, and adopt appropriate acceptance criteria.”

See the Quality Assessment Review, dated April 17, 2017, for a full discussion of CMC issues under NDA 208564.

## 4.2 Clinical Microbiology

The drug product is a non-sterile formulation. However, the product specification includes microbial limits testing both at release and on stability.

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(b) (4) (estradiol vaginal insert)

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

Per the Microbiology Review, dated January 30, 2017, "The drug product is a non-sterile (b) (4) capsule for vaginal administration. The drug product has a microbial release specification consistent with compendial recommendations and is tested regularly on stability for microbiological quality. No deficiencies were identified based upon the information provided. Non-sterile drug product recommended for approval."

See the Microbiology Review, dated January 30, 2017, for a full discussion from a microbiology perspective.

### 4.3 Preclinical Pharmacology/Toxicology

TherapeuticsMD has not conducted any nonclinical safety pharmacology studies with TX-004HR. The applicant is relying on the well-established safety history of estradiol, and on published literature for the nonclinical toxicology, mutagenicity, and carcinogenicity sections of this NDA. At the pre-NDA meeting held on December 15, 2015, the applicant was advised that, under the 505(b)(2) pathway, they would need to "Submit published literature for information necessary to inform Section 8 (Use in Specific Populations) and Section 13 (Nonclinical Toxicology) of labeling. If relevant clinical data in the literature are more informative than animal data, this could be used as an alternative, provided it does not reference a specific product."

In response to the Agency's A/IR dated July 8, 2013, TherapeuticsMD conducted a 28-day, repeat-dose, vaginal irritation study in rabbits (Study (b) (4)/1013/G/T077) entitled "28 Day Repeated Dose Toxicity Study of (b) (4) in New Zealand White Female Rabbits by Vaginal Route" of the capsule fill material. This study evaluated the local tolerance of the inactive ingredient (b) (4). The final study report was received May 13, 2015. Overall, the TX-004HR fill material containing (b) (4) was well tolerated and was not irritating to the vaginal mucosa at doses up to 1.2 mL/animal/day (b) (4) dose of ~376 mg/kg/day). "There were no deaths or other test article-related effects on clinical examinations, body weights, or gross pathology. The formulation was non-irritating based on daily vaginal cage-side observations and microscopic examinations of the vagina at scheduled necropsy, with an irritation index of < 0.5 and ≤ 0.0, respectively."

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

Per the Pharmacology/Toxicology Review, dated March 29, 2017, "The literature that the sponsor has submitted is adequate to support the nonclinical safety of estradiol without relying on previous findings of safety for an approved product."

Pharmacology/Toxicology recommends "approval of TX-004HR for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause." "No additional nonclinical studies are recommended."

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### 4.4 Clinical Pharmacology

#### 4.4.1 Mechanism of Action

The pharmacology of the active pharmaceutical ingredient (API), (b) (4) estradiol (b) (4) is well-established. Estrogens, including estradiol, act primarily as an agonist (binds to and activates) the estrogen receptors ER $\alpha$  and ER $\beta$ . The result of ER activation is a modulation and expression in ER-expressing cells, which is the predominant mechanism by which estradiol mediates its biological effects in the body.<sup>2</sup> Additional signaling mechanisms for estrogens include cell membrane receptors coupled with G-proteins which can activate intracellular signal cascades.<sup>3</sup> Estradiol is highly efficacious and selective, with a relative binding affinity (RBA) of 100 for both ER $\alpha$  and ER $\beta$ .<sup>2</sup>

#### 4.4.2 Pharmacodynamics

Per the application, no primary or secondary pharmacodynamic studies have been conducted with TX-004HR. It is known, however, that estradiol affects many tissues in the human body due to the presence of ERs in reproductive tissue and a variety of non-reproductive tissues, including the heart, CNS, bone, liver, gastrointestinal tract, immune system, and vascular endothelium.

Estradiol is extensively bound to plasma proteins in blood plasma, including sex steroid-binding globulin (SSBG) and serum albumin. Estradiol readily distributes past the vascular space and into tissues due to its size and lipophilic nature. In general, estradiol undergoes rapid biotransformation with a half-life of only minutes. Estradiol is metabolized by 17 $\beta$ -hydroxysteroid dehydrogenase to estrone, which is in turn converted by 16 $\alpha$  hydroxylation and 17-keto reduction to estriol, which is the major urinary metabolite along with a variety of sulfate and glucuronide conjugates. Estrogens also undergo enterohepatic recirculation by the formation of sulfate and glucuronide conjugates in the liver followed by biliary secretion into the intestine, hydrolysis and then reabsorption by the intestine.

In this application, prospective, randomized, double-blind, placebo-controlled, phase 2 Trial TXV13-01 evaluated the 10 mcg estradiol vaginal insert for the treatment of VVA. Fifty (50) postmenopausal were randomly assigned (1:1 allocation) to self-administer 10 mcg estradiol vaginal insert or placebo vaginal insert once daily for 14 days.

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2 Goodman L, Hardman J, et al. Estrogens and Progestins. In: Hardman JG, Limburt LE, Gilman AG, editors. Goodman Gilman's Pharmacol Basis Ther. 10<sup>th</sup> ed. New York: McGraw-Hill; 2001:1597-1634.

3 Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric. 2005;8(sup 1):3-63.

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This phase 2 clinical trial reported statistically significant improvements with 10 mcg estradiol vaginal insert compared to placebo vaginal insert in the vaginal maturation index (increase in superficial epithelial cells and decrease in parabasal epithelial cells), and a reduction in vaginal pH. Based on the results of this phase 2 trial, the 10 mcg and 25 mcg estradiol vaginal insert doses were selected for inclusion in the phase 3 clinical trial. Per the applicant, "In order to preserve dose proportionality with the 25 mcg and 10 mcg doses, a 4 mcg dose was also selected for inclusion in the phase 3 trial, with each dose being 2.5 times greater than the lower dose."

### 4.4.3 Pharmacokinetics

Two separate, single dose pharmacokinetic (PK) phase 1 trials (Trials ESTR-1K-499-12 and ESTR-1K-500-12) were conducted during the TX-004HR development program. In addition, the applicant conducted phase 1 Trial ESTR-2036-14 to assess the effect of body position on the PK of the estradiol vaginal insert.

#### Trial ESTR-1K-499-12

This was an open-label, randomized, two-treatment, two period, two-sequence, single-dose, 2-way crossover trial to assess the relative bioavailability of a 10 mcg dose estradiol vaginal insert (Test) and a 10 mcg dose of Vagifem® (Reference), comparing plasma concentrations of estradiol, estrone and estrone sulfate in 36 healthy postmenopausal women (18 women randomized to Test and 18 women randomized to Reference in each period).

Trial participants were housed in the clinical facility for two consecutive nights for each of two dosing periods, from at least 11 hours before dosing (at least 10 hours fasting) until after the 24 hours post dose blood draw in each period. All trial participants received 10 mcg of both the Test (10 mcg estradiol vaginal insert, manufactured by (b) (4) Lot No. PN0089-02) and Reference (Vagifem® 10 mcg estradiol vaginal insert, manufactured by Novo Nordisk A/S, Lot No. CE70136) products, inserted intravaginally, during the trial (one product per dosing period), with a 14-day washout period between dosing periods. Each woman was required to remain in a supine position for 4 hours after dosing and to refrain from strenuous activity until they were checked out of the clinical facility. Trial participants were fasted for an additional four hours after dosing, then provided a standard diet. Trial participants were continuously monitored throughout the trial (including adverse events, physical examination, vitals, and laboratory test at the post-trial assessment).

A total of 13 blood samples were taken at prescribed time points per the trial protocol: - 1.00, -0.50, 0.00, 1.00, 2.00, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00, 18.00 and 24.00 hours with reference to the time of insertion of the Test and Reference inserts into the vagina.

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(b) (4) (estradiol vaginal insert)

After completion of Period I of the trial, trial participants entered a 14-day washout period prior to crossing over to Period II. All procedures in Period II were identical to those described for Period I with subjects receiving the alternative treatment.

Plasma samples were analyzed for estradiol and estrone simultaneously using a LC-MS/MS method, and a separate LC-MS/MS method was used for the determination of estrone sulfate in plasma. Analysis was performed at Esoterix Endocrinology, Calabasas, California. The lower limits of quantification for estradiol, estrone, and estrone sulfate were 1.0 pg/mL, 2.5 pg/mL, and 10.0 pg/mL, respectively, during analysis. Pharmacokinetic parameters for baseline-adjusted and baseline-unadjusted estradiol, estrone, and estrone sulfate were determined by performing a non-compartmental analysis. Estimates of the PK parameters area under the concentration-time curve to 24 hours ( $AUC_{0-24}$ ), peak concentration ( $C_{max}$ ), and time to reach peak concentration ( $t_{max}$ ) were reported.

One woman did not complete the study for reasons unrelated to the trial drug and was excluded from the PK analysis. One woman's baseline adjusted values for estradiol were below zero and her data was excluded from the PK analysis. A summary of the PK parameters of Test product and Reference product for estradiol baseline-adjusted is provided in Table 2. A summary of the PK parameters of Test product and Reference product for estradiol baseline-unadjusted is provided in Table 3.

Table 2: Summary of Pharmacokinetic Parameters for Estradiol Baseline-Adjusted for Test Product (10 mcg TX-004HR) and Reference Product (10 mcg Vagifem®) (N=34)

Pharmacokinetic Parameter	Arithmetic Mean $\pm$ SD	Coefficient of Variation
<b>Test Product (Tx-004HR)</b>		
- $C_{max}$ (pg/mL)	15.72 $\pm$ 7.92	50.38
- $AUC_{0-24}$ (pg.hr/mL)	53.01 $\pm$ 19.56	36.90
- $t_{max}$ (hr)	1.98 $\pm$ 1.29	65.34
<b>Reference Product (Vagifem®)</b>		
- $C_{max}$ (pg/mL)	24.19 $\pm$ 11.93	49.29
- $AUC_{0-24}$ (pg.hr/mL)	163.86 $\pm$ 72.09	44.00
- $t_{max}$ (hr)	10.53 $\pm$ 5.58	52.94

Source: Adapted from NDA 208564, Clinical Trial Report for ESTR-1K-499-12, Table 11 and Table 12, page 47 of 87.

Abbreviations: SD = standard deviation;  $AUC_{0-24}$  – area under the concentration-time curve 24 hours;  $C_{max}$  = peak concentration;  $t_{max}$  = time to reach peak concentration

Table 3: Summary of Pharmacokinetic Parameters for Estradiol Baseline-Unadjusted for Test Product (TX-004HR) and Reference Product (Vagifem®) (N=35)

Pharmacokinetic Parameter	Arithmetic Mean $\pm$ SD	Coefficient of Variation
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(b) (4) (estradiol vaginal insert)

<b>Test Product (Tx-004HR)</b>		
- C <sub>max</sub> (pg/mL)	21.22 ± 10.89	51.31
- AUC <sub>0-24</sub> (pg.hr/mL)	178.19 ± 150.07	84.22
- t <sub>max</sub> (hr)	1.98 ± 1.27	64.35
<b>Reference Product (Vagifem®)</b>		
- C <sub>max</sub> (pg/mL)	32.51 ± 22/25	68.43
- AUC <sub>0-24</sub> (pg.hr/mL)	355.24 ± 452.79	127.46
- t <sub>max</sub> (hr)	10.52 ± 5.49	52.23

Source: Adapted from NDA 208564, Clinical Trial Report for ESTR-1K-499-12, Table 14 and Table 15, page 50 of 87.

Abbreviations: SD = standard deviation; AUC<sub>0-24</sub> – area under the concentration-time curve 24 hours; C<sub>max</sub> = peak concentration; t<sub>max</sub> = time to reach peak concentration

Per the application, the statistical analyses to compare treatments were conducted using the general linear model (GLM). PK parameters AUC<sub>0-24</sub> and C<sub>max</sub> were evaluated after natural logarithmic transformation. Summary statistics, descriptive statistics, analysis of variance (ANOVA), and 90% confidence intervals (CI) were calculated for baseline-adjusted and baseline-unadjusted estradiol, estrone and estrone sulfate for all PK parameters for both Test and Reference products. Table 4 shows the reported comparative bioavailability results for estradiol baseline-adjusted in Trial ESTR-1K-499-12. Table 5 shows the reported comparative bioavailability results for estradiol baseline-unadjusted in Trial ESTR-1K-499-12. Reported results for estrone and estrone sulfate can be viewed in the Clinical Trial Report for Trial ESTR-1K-499-12 in the application.

Table 4: Statistical Results of 10 mcg TX-004HR Versus 10 mcg Vagifem® for Estradiol Baseline-Adjusted (n = 34)

Pharmacokinetic Parameter	Geometric Least Square Mean		Intra Subject CV%	T/R Ratio (%)	90% Confidence Interval	P-Value*
	TX-004HR (Test)	Vagifem (Reference)				
<b>C<sub>max</sub> (pg/mL)</b>	14.45	20.20	60.68	71.54**	56.82 - 90.08	0.0194
<b>AUC<sub>0-24</sub> (pg.h/mL)</b>	49.73	131.04	70.64	37.95**	29.21 - 49.31	< 0.0001

Source: Adapted from NDA 208465, Clinical Trial Report for ESTR-1K-499-12, Table 29, page 62 of 87.

\*Results of the statistical evaluation by ANOVA (α = 0.05) for the hypothesis of equal treatment effects.

\*\*Comparison was detected as statistically significant (P < 0.05).

Abbreviations: AUC<sub>0-24</sub> – area under the concentration-time curve 24 hours; C<sub>max</sub> = peak concentration; CV = coefficient of variation

Table 5: Statistical Results of 10 mcg TX-004HR Versus 10 mcg Vagifem® for Estradiol Baseline- Unadjusted (n = 35)

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(b) (4) (estradiol vaginal insert)

Pharmacokinetic Parameter	Geometric Least Square Mean		Intra Subject CV%	T/R Ratio (%)	90% Confidence Interval	P-Value*
	TX-004HR (Test)	Vagifem (Reference)				
C <sub>max</sub> (pg/mL)	19.21	28.70	36.18	66.93**	58.07 – 77.13	< 0.0001
AUC <sub>0-24</sub> (pg.h/mL)	147.9	288.08	30.87	51.36**	45.46 – 58.03	< 0.0001

Source: Adapted from NDA 208564, Clinical Trial Report for ESTR-1K-499-12, Table 30, page 63 of 87

\*Results of the statistical evaluation by ANOVA ( $\alpha = 0.05$ ) for the hypothesis of equal treatment effects.

\*\*Comparison was detected as statistically significant ( $P < 0.05$ ).

Abbreviations: AUC<sub>0-24</sub> – area under the concentration-time curve 24 hours; C<sub>max</sub> = peak concentration; CV = coefficient of variation.

No adverse events or serious adverse events were reported in this phase 1 PK clinical trial. All post-trial laboratory parameters (clinical chemistry and hematology) were reported to be within clinically acceptable ranges.

The applicant concludes that the extent of systemic exposure of 10 mcg estradiol vaginal insert was statistically significantly lower than that of Vagifem® 10 mcg in healthy postmenopausal females. “Estradiol concentrations are only modestly higher than baseline, endogenous concentrations.”

### **Clinical Reviewer’s Comments:**

In this phase 1 trial, intrasubject CV% for estradiol was reported to range from 36% to 84%. Therefore, the individual observed estradiol plasma concentrations time profiles were highly variable. Although variable, estradiol peak concentration (C<sub>max</sub>) and area under the concentration time curve (AUC) for TX-004HR were approximately two-thirds of the C<sub>max</sub> and two-fifths of the AUC exposures of Vagifem® at the same dose (baseline-adjusted estradiol Test/Reference ratios [90% CIs) for C<sub>max</sub> and AUC were 72% (57% to 90%) and 38% (29% to 49%), respectively]. Baseline-unadjusted estradiol plasma concentrations T/R ratios showed similarly lower plasma levels for TX-004HR compared to Vagifem® for C<sub>max</sub> (67%) and for AUC (51%).

This reviewer agrees that the results reported in Trial ESTR-1K-499-12 show that the systemic exposure of 10 mcg TX-004HR is significantly lower than that of 10 mcg Vagifem® in the healthy postmenopausal women participating in this clinical trial.

### **Trial ESTR-1K-500-12**

This was an open-label, randomized, two-treatment, two period, two-sequence, single-dose, 2-way crossover trial to assess the relative bioavailability of a 25 mcg dose estradiol vaginal insert (Test) and a 25 mcg dose of Vagifem® (Reference), comparing plasma concentrations of estradiol, estrone and estrone sulfate in 36 healthy

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(b) (4) (estradiol vaginal insert)

postmenopausal women (18 women randomized to Test and 18 women randomized to Reference in each period).

The study design in Trial ESTR-1K-500-12 was the same as previously described for phase 1 Trial ESTR-1K-499-12 in all aspects except for the location of the facility conducting the trial plasma samples analysis. For Trial ESTR-1K-500-12, trial plasma samples were analyzed at Micro Therapy Research Labs Private Limited, Chennai, India. Per the application, trial samples were analyzed for estradiol and estrone using a validated LC-MS/MS method over a concentration range of 1.9960 to 703.1640 pg/mL and 9.9080 to 3490.5920 pg/mL, respectively. Estrone sulfate was determined using a validated LC-MS/MS method over a concentration range of 20.0760 to 5098.6680 pg/mL.

(b) (4) manufactured the 25 mcg estradiol vaginal insert (Test product, Lot No. PN0089-04). Novo Nordisk A/S manufactured the Reference product (Vagifem® 25 mcg, Lot No. CE70169).

Per the application, trial samples were analyzed for estradiol and estrone using a validated LC-MS/MS method over a concentration range of 1.9960 to 703.1640 pg/mL and 9.9080 to 3490.5920 pg/mL, respectively. Estrone sulfate was determined using a validated LC-MS/MS method over a concentration range of 20.0760 to 5098.6680 pg/mL. The PK parameters for the estradiol, estrone, and estrone sulfate concentrations at each sampling time were evaluated by analysis of variance (ANOVA) with sequence, subjects-within-sequence, period, and treatment as factors, using a general linear models approach. The ANOVA for areas and peak concentrations were conducted on natural log (ln) transformed values. The 90% confidence intervals (CIs) on the geometric mean area and  $C_{max}$  ratios for the Test product compared to the Reference product were constructed to compare the bioavailability of the Test product to that of the Reference product. Results for both baseline-adjusted and unadjusted data are provided. All 36 women completed both treatment periods and were eligible for PK evaluation.

A summary of the PK parameters of Test product and Reference product for estradiol baseline-adjusted is provided in Table 6. A summary of the PK parameters of Test product and Reference product for estradiol baseline-unadjusted is provided in Table 7.

Table 6: Summary of Pharmacokinetic Parameters for Estradiol Baseline-Adjusted for Test Product (25 mcg TX-004HR) and Reference Product (25 mcg Vagifem®) (N=36)

Pharmacokinetic Parameter	Arithmetic Mean $\pm$ SD	Coefficient of Variation
<b>Test Product (Tx-004HR)</b>		
- $C_{max}$ (pg/mL)	25.33 $\pm$ 12.55	49.5
- AUC <sub>0-24</sub> (pg.hr/mL)	99.85 $\pm$ 57.91	58.0
- $t_{max}$ (hr)	1.92 $\pm$ 0.50	26.1

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(b) (4) (estradiol vaginal insert)

Reference Product (Vagifem®)		
- C <sub>max</sub> (pg/mL)	51.53 ± 33.23	64.5
- AUC <sub>0-24</sub> (pg.hr/mL)	350.5 ± 163.0	46.5
- t <sub>max</sub> (hr)	12.50 ± 5.66	45.3

Source: Adapted from NDA 208564, Clinical Trial Report for ESTR-1K-500-12, Table 10, page 46 of 88 and Table 11, page 47 of 88.

Abbreviations: SD = standard deviation; AUC<sub>0-24</sub> – area under the concentration-time curve 24 hours; C<sub>max</sub> = peak concentration; t<sub>max</sub> = time to reach peak concentration

Table 7: Summary of Pharmacokinetic Parameters for Estradiol Baseline-Unadjusted for Test Product (25 mcg TX-004HR) and Reference Product (25 mcg Vagifem®) (N=36)

Pharmacokinetic Parameter	Arithmetic Mean ± SD	Coefficient of Variation
<b>Test Product (Tx-004HR)</b>		
- C <sub>max</sub> (pg/mL)	31.03 ± 12.30	39.6
- AUC <sub>0-24</sub> (pg.hr/mL)	218.7 ± 103.6	47.4
- t <sub>max</sub> (hr)	1.92 ± 0.50	26.1
<b>Reference Product (Vagifem®)</b>		
- C <sub>max</sub> (pg/mL)	59.84 ± 34.39	57.5
- AUC <sub>0-24</sub> (pg.hr/mL)	545.4 ± 344.3	63.1
- t <sub>max</sub> (hr)	12.50 ± 5.66	45.3

Source: Adapted from NDA 208564, Clinical Trial Report for ESTR-1K-500-12, Table 13 and Table 14, page 50 of 88.

Abbreviations: SD = standard deviation; AUC<sub>0-24</sub> – area under the concentration-time curve 24 hours; C<sub>max</sub> = peak concentration; t<sub>max</sub> = time to reach peak concentration

Per the application, geometric least square means, intra-subject CV%, Test/Reference ratio, power, and 90% CI were determined for C<sub>max</sub> and AUC<sub>0-24</sub> for baseline-adjusted and baseline-unadjusted data for estradiol, estrone, and estrone sulfate. Table 8 shows the reported comparative bioavailability results for estradiol baseline-adjusted in Trial ESTR-1K-500-12. Table 9 shows the reported comparative bioavailability results for estradiol baseline-unadjusted in Trial ESTR-1K-500-12. Reported results for estrone and estrone sulfate can be viewed in the Clinical Trial Report for Trial ESTR-1K-500-12 in the application.

Table 8: Statistical Results of 25 mcg TX-004HR Versus 25 mcg Vagifem for Estradiol Baseline-Adjusted (N=36)

Pharmacokinetic Parameter	Geometric Least Square Mean		Intra Subject CV%	T/R Ratio (%)	90% Confidence Interval	% Power
	TX-004HR (Test)	Vagifem (Reference)				
C <sub>max</sub> (pg/mL)	23.08	42.70	54.0	54.1	44.2 – 66.1	57.1
AUC <sub>0-24</sub> (pg.h/mL)	89.21	292.1	70.4	30.5	23.7 – 39.3	42.2

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(b) (4) (estradiol vaginal insert)

Source: Adapted from NDA 208564, Clinical Trial Report for Trial ESTR-1K-500-12, Table 28, page 65 of 88.

Abbreviations: AUC<sub>0-24</sub> = area under the concentration-time curve to 24 hours; C<sub>max</sub> = peak concentration; CV = coefficient of variation.

Table 9: Statistical Results of 25 mcg TX-004HR Versus 25 mcg Vagifem for Estradiol Baseline-Unadjusted (N=36)

Pharmacokinetic Parameter	Geometric Least Square Mean		Intra Subject CV%	T/R Ratio (%)	90% Confidence Interval	% Power
	TX-004HR (Test)	Vagifem (Reference)				
C <sub>max</sub> (pg/mL)	29.07	52.06	43.3	55.8	47.4 – 65.9	72.2
AUC <sub>0-24</sub> (pg.h/mL)	192.3	483.8	43.9	39.8	33.6 – 47.0	71.2

Source: Adapted from NDA 208564, Clinical Trial Report for Trial ESTR-1K-500-12, Table 29, page 65 of 88.

Abbreviations: AUC<sub>0-24</sub> = area under the concentration-time curve to 24 hours; C<sub>max</sub> = peak concentration; CV = coefficient of variation.

No deaths, serious adverse events, or other significant adverse events were reported during this clinical trial. Laboratory results (clinical chemistry and hematology) were within normal ranges or were found to be not clinically significant. All 36 women completed this trial.

The applicant concludes that the systemic exposure of 25 mcg TX-004HR was lower than that observed with 25 mcg Vagifem® “and within the normal range for healthy postmenopausal women.”

### **Clinical Reviewer’s Comments:**

The reported CV% for estradiol was 46% to 58%, less variable than reported in Trial ESTR-1K-500-12. The C<sub>max</sub> and AUC for 25 mcg TX-004HR showed approximately one-third to two-thirds of the systemic exposure of 25 mcg Vagifem (for baseline-adjusted estradiol, the T/R ratios (90% CIs) for C<sub>max</sub> and AUC were 54% (44% to 66%) and 31% (24% to 39%), respectively). Similarly lower plasma levels are reported for baseline-unadjusted estradiol plasma concentrations.

This reviewer agrees that the results reported in Trial ESTR-1K-500-12 show that the systemic exposure of 25 mcg TX-004HR is lower than 25 mcg Vagifem® in the healthy postmenopausal female women participating in this clinical trial

### **Trial ESTR-2036-14**

This was an open-label, single-dose, single period trial to assess the relative bioavailability of a 25 mcg dose estradiol vaginal insert. Plasma concentrations of estradiol, estrone and estrone sulfate in 16 healthy postmenopausal women, 44 to 58

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years of age, who had previously participated in Trial ESTR-1K-500-12 were assessed to determine the effect of absorption in women who remained upright following intravaginal insertion of the estradiol vaginal insert. In Trials ESTR-1K-499-12 and ESTR-1K-500-12, trial participants were required to remain in a supine position for 4 hours after dosing and to refrain from strenuous activity until they were checked out of the clinical facility.

The primary objective in this clinical trial was to evaluate the impact of normal daily activities for 4 hours post-dose versus remaining in the supine position for 4 hours post-dose (as in Trials ESTR-1K-499-12 and ESTR-1K-500-12) on the measured concentration of TX-004HR in the plasma samples collected. Trial participants could remain seated or were ambulatory for the first 4 hours post-dose, and were restricted from lying down except as directed by the investigator in case of an adverse event.

A total of 13 blood samples were taken at prescribed time points per the trial protocol: -1.00, -0.50, 0.00, 1.00, 2.00, 4.00, 6.00, 8.00, 10.00, 12.00, 14.00, 18.00 and 24.00 hours with reference to the time of insertion into the vagina. Plasma samples were analyzed at (b) (4)

Trial participant specific baseline concentrations were corrected prior to PK analysis. The method for baseline correction was arithmetic, with the mean of the predose concentrations (samples collected at -1.00, -0.50, and 0.00 timepoints) being subtracted from all the postdose concentrations. Per the protocol, if a negative concentration value resulted after baseline correction, this was set to zero. In addition, the baseline-adjusted predose concentration (0-hour) was also set to zero. Data were analyzed using both the uncorrected and baseline corrected data. If, after baseline adjustment, a subject had negative concentrations at all sample times that were set to zero in at least one period, this woman was excluded from statistical evaluations for the given parameter. Per the Clinical Trial Report in the application, all study participants had valid concentration values and no trial participant was excluded from calculations.

Per the Clinical Trial Report, for estradiol baseline-adjusted, the mean (SD)  $C_{max}$  was 36.45 (20.31) pg/mL, and the mean (SD)  $AUC_{0-24}$  was 104.43 (60.85) pg·h/mL (see Table 10). For estradiol baseline-unadjusted, the mean (SD)  $C_{max}$  was 41.58 (19.48) pg/mL, and the mean (SD)  $AUC_{0-24}$  was 123.27 (62.86) pg·h/mL (see Table 11). Reported results for estrone and estrone sulfate can be viewed in the Clinical Trial Report for Trial ESTR-2036-14 in the application.

Table 10: Summary of PK Parameters of 25 mcg TX-004HR for Estradiol Baseline-Adjusted (N=16)

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Pharmacokinetic Parameter	Arithmetic Mean (SD)	Coefficient of Variation	Median	Minimum	Maximum	Geometric Mean
C <sub>max</sub> (pg/mL)	36.45 (20.31)	55.7	35.3	0.0	75.0	35.05
AUC <sub>0-24</sub> (pg·h/mL)	104.4 (60.85)	58.3	103	0.0	226	98.03
t <sub>max</sub> (h)	2.14 (1.68)	78.8	2.00	1.00	8.00	1.83

Source: Adapted from NDA 208564, Clinical Trial Report for Trial ESTR-2036-14, Table 9, page 41 of 61.

Abbreviations: C<sub>max</sub> – maximum concentration; AUC<sub>0-24</sub> – area under the concentration-time curve to 24 hours;

t<sub>max</sub> – time to reach peak concentration

Table 11: Summary of PK Parameters of 25 mcg TX-004HR for Estradiol Baseline-Unadjusted (n=16)

Pharmacokinetic Parameter	Arithmetic Mean (SD)	Coefficient of Variation	Median	Minimum	Maximum	Geometric Mean
C <sub>max</sub> (pg/mL)	41.58 (19.48)	46.8	36.2	17	75.0	37.43
AUC <sub>0-24</sub> (pg·h/mL)	123.3 (62.86)	51.0	111	30	250	108.3
t <sub>max</sub> (h)	2.00 (1.71)	85.5	2.00	0.00	8.00	1.83

Source: Adapted from NDA 208564, Clinical Trial Report for Trial ESTR-2036-14, Table 10, page 43 of 61.

Abbreviations: C<sub>max</sub> – maximum concentration; AUC<sub>0-24</sub> – area under the concentration-time curve to 24 hours;

t<sub>max</sub> – time to reach peak concentration

No deaths, serious adverse events, or other significant adverse events were reported during this trial. Laboratory evaluations (clinical chemistry and hematology) were obtained pre-dose and 24 hours post-dose. Results were reported as within normal range or as not clinically significant by the investigator.

Per the applicant, the results of Trial ESTR-2036-14 suggest: “1) activity level or body position do not affect the vaginal absorption of TX-004HR, and 2) that vaginal absorption with 25 mcg of TX-004HR is modest and does not increase estradiol levels beyond those within the normal range for postmenopausal women.”

### **Clinical Reviewer’s Comments:**

Clinical Pharmacology requested data on the number of women who sat after administration of the estradiol vaginal insert versus the number of women who were ambulatory after administration of the estradiol vaginal insert. This information was provided on October 10, 2016.

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The applicant noted that Trial ESTR-2036-14 did not collect whether the woman was seated, ambulatory, or a combination of seated or ambulatory after insertion of the 25 mcg estradiol vaginal insert. Only that, it was known, that the woman did not recline during the 4 hours after insertion.

Per the Clinical Pharmacology Review, dated April 7, 2017, "..., activity level for a subject seated is different from being ambulatory; therefore, subjects from study ESTR-2036-14 should not be combined into one seated/ambulatory group. Without data on the exact positioning of each subject, it is not possible to accurately assess how activity or body positioning can affect estradiol exposure from study ESTR-2036-14."

See the Clinical Pharmacology Review, dated April 7, 2017, for a full discussion of the pharmacokinetic findings in the TX-004HR (estradiol vaginal insert) development program.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 12: Listing of Clinical Trials in the TX-004 HR (Estradiol Vaginal Insert) Development Program

<b>Trial Identifier Type of Trial</b>	<b>Objective(s) of the Trial</b>	<b>Trial Design and Type of Control</b>	<b>Test Product Dosage regimen: Route of Administration</b>	<b>Number of Enrolled Postmenopausal Women</b>	<b>Duration of Treatment</b>
ESTR-1K-499-12 Phase 1 PK	Evaluation of the systemic bioavailability of TX-004HR (10 mcg estradiol vaginal insert) versus 10 mcg of Vagifem (estradiol vaginal insert)	Randomized, 2-treatment, 2-period, 2-way crossover Open-label	10 mcg TX-004HR (estradiol vaginal insert) single dose intravaginally  10 mcg Vagifem (estradiol vaginal insert) single dose intravaginally	36	2 Dosing Periods 3 Days per Period
ESTR-1K-500-12 Phase 1 PK	Evaluation of the systemic bioavailability of TX-004HR (25 mcg estradiol vaginal insert) versus 25 mcg of Vagifem (estradiol vaginal insert)	Randomized, 2-treatment, 2-period, 2-way crossover Open-label	25 mcg TX-004HR (estradiol vaginal insert) single dose intravaginally  25 mcg Vagifem (estradiol vaginal insert) single dose intravaginally	36	2 Dosing Periods 3 Days per Period
ESTR-2036-14 Phase 1 PK	Evaluation of the systemic bioavailability of	Randomized, single-arm, single-dose	25 mcg TX-004HR (estradiol vaginal insert) single dose	16	1 Dosing Period

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	TX-004HR (25 mcg estradiol vaginal insert)	Open-label	intravaginally		3 Days per Period
TXV13-01 Phase 2 Efficacy and Safety	Evaluation of efficacy and safety dose response in postmenopausal women with VVA	Randomized, Double-blind Placebo-controlled	Placebo vaginal insert	26	14 Days
			10 mcg TX-004HR (estradiol vaginal insert)	24	
TXV14-01 Phase 3 Efficacy and Safety  Primary	Evaluation of the efficacy and safety of TX-004HR (estradiol vaginal Insert) for the treatment of moderate to severe dyspareunia due to menopause	Randomized, Double-blind, Placebo-controlled	Placebo vaginal insert	192	12 Weeks
			4 mcg TX-004HR (estradiol vaginal insert)	191	
			10 mcg TX-004HR (estradiol vaginal insert)	191	
			25 mcg TX-004HR (estradiol vaginal insert)	190	

## 5.2 Review Strategy

The available clinical data in primary 12-week, phase 3, safety and efficacy clinical Trial TXV14-01 provide the basis for consideration regarding the efficacy of TX-004HR (4 mcg, 10 mcg, and 25 mcg) vaginal inserts for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Phase 2, 14-day Trial TXV13-01 is not considered supportive of efficacy for this indication, but is considered supportive of the safety data in this NDA application.

Trial TXV14-01 is the single safety and efficacy trial conducted in support of moderate to severe dyspareunia as the most bothersome symptoms of vulvar and vaginal atrophy.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Trial TXV14-01

#### 5.3.1.1 Objectives

**Primary:**

The primary objective of Trial TXV14-01 was “to assess the safety and efficacy of three doses of TX-004HR (4 mcg, 10 mcg, and 25 mcg) compared with placebo at 12 weeks on vaginal superficial cells, vaginal parabasal cells, vaginal pH, and the symptom of moderate to severe dyspareunia (vaginal pain associated with sexual activity) as the most bothersome symptom (MBS) associated with VVA.”

**Secondary Objectives:**

The secondary objectives of Trial TXV14-01 were to:

- Assess the efficacy of vaginal superficial cells, vaginal parabasal cells, vaginal pH, and moderate to severe dyspareunia (vaginal pain associated with sexual activity) defined as the MBS of 3 doses of estradiol vaginal insert (4 mcg, 10 mcg, and 25 mcg) compared with placebo at 2, 6, and 8 weeks.
- Assess the efficacy of three doses of estradiol vaginal insert (4 mcg, 10 mcg, and 25 mcg) compared with placebo at 2, 6, 8, and 12 weeks on vaginal dryness and on vulvar and/or vaginal itching or irritation associated with VVA.
- Assess hormone concentration of estradiol, estrone, and estrone conjugates at Screening 1A, Days 1, 14, and 84 of treatment in a subset of subjects (PK sub-study) for the 4 mcg, 10 mcg, and 25 mcg dose groups (PK subtrial).
- Assess visual evaluation of the vaginal mucosa at 2, 6, 8, and 12 weeks.
- Assess sexual function by the Female Sexual Function Index (FSFI) at 12 weeks.

5.3.1.2 Enrollment Criteria

**Inclusion Criteria:**

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

1. Postmenopausal women between 40 and 75 years old (at the time of Randomization) with at least:
  - 12 months of spontaneous amenorrhea (women <55 years of age with history of hysterectomy without bilateral oophorectomy prior to natural menopause must have had FSH levels > 40 mIU/mL); OR
  - 6 months of spontaneous amenorrhea with FSH levels > 40 mIU/mL; OR
  - At least 6 weeks postsurgical bilateral oophorectomy.
2. ≤ 5% superficial cells on vaginal cytological smear.
3. Vaginal pH > 5.0.
4. Moderate to severe symptom of vaginal pain associated with sexual activity considered the most bothersome vaginal symptom by the subject at Screening Visit 1A.
5. Moderate to severe symptom of vaginal pain associated with sexual activity at Screening Visit 1B.
6. Women should be sexually active (for example, have sexual activity with vaginal penetration within approximately one month of Screening Visit 1A).
7. Women should anticipate having sexual activity (with vaginal penetration) during the conduct of the trial.
8. For women with an intact uterus: Women must have had an acceptable result from an evaluable Screening endometrial biopsy. The endometrial biopsy reports by the two central pathologists at Screening must each specify one of the following: secretory endometrium; endometrial tissue other (including benign,

inactive, or atrophic fragments of endometrial epithelium, glands, stroma, etc); endometrial tissue insufficient for diagnosis; no endometrium identified; or no tissue identified. However, at least one pathologist must identify sufficient tissue to evaluate the biopsy. Additionally, the endometrial biopsy reports by the two central pathologists of Other Findings at Screening must each specify one of the following: endometrial polyp not present; benign endometrial polyp; or polyp other.

9. Women who have a Body Mass Index (BMI) less than or equal to 38 kg/m<sup>2</sup>. BMI values were rounded to the nearest integer (example, 32.4 rounds down to 32, while 26.5 rounds up to 27).
10. In the opinion of the investigator, the woman would comply with the protocol and had a high probability of completing the study.

**Exclusion Criteria:**

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

1. Use of the following:
  - a. Oral estrogen-, progestin-, androgen-, or selective estrogen receptor modulator (SERM)-containing drug products within 8 weeks before Screening Visit 1A (can enter washout);
  - b. Use of transdermal hormone products within 4 weeks before Screening Visit 1A (can enter washout);
  - c. Use of vaginal hormone products (rings, creams, gels) within 4 weeks before Screening Visit 1A (can enter washout);
  - d. Use of intrauterine progestins within 8 weeks before Screening Visit 1A (can enter washout);
  - e. Use of progestin implants/injectables or estrogen pellets/injectables within 6 months before Screening Visit 1A (cannot enter washout);
  - f. Use of vaginal lubricants or moisturizers within 7 days before the Screening Visit 1B vaginal pH assessment.
2. A history or active presence of clinically important medical disease that might confound the study or be detrimental to the woman; examples include:
  - a. Hypersensitivity to estrogens;
  - b. Endometrial hyperplasia;
  - c. Undiagnosed vaginal bleeding;
  - d. Have a history of a chronic liver or kidney dysfunction/disorder (for example, Hepatitis C or chronic renal failure);
  - e. Thrombophlebitis, thrombosis, or thromboembolic disorders;
  - f. Cerebrovascular accident, stroke, or transient ischemic attack;
  - g. Myocardial infarction or ischemic heart disease;
  - h. Malignancy or treatment for malignancy, within the previous 5 years, with the exception of basal cell carcinoma of the skin or squamous cell carcinoma of the skin. A history of estrogen dependent neoplasia, breast

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- cancer, melanoma, or any gynecologic cancer, at any time, excludes the subject;
- i. Endocrine disease (except for controlled hypothyroidism or controlled non-insulin dependent diabetes mellitus).
3. Recent history of known alcohol or drug abuse.
  4. History of sexual abuse or spousal abuse that, in the opinion of the PI, may interfere with the subject's assessment of vaginal pain with sexual activity.
  5. Current history of heavy smoking (more than 15 cigarettes per day) or use of e-cigarettes.
  6. Use of an intrauterine device within 12 weeks before Screening Visit 1A.
  7. Use of an investigational drug within 60 days before Screening Visit 1A.
  8. Any clinically important abnormalities on Screening physical exam, assessments, ECG, or laboratory tests, such as:
    - a. Unresolved cervical cytologic smear report of atypical glandular cells of undetermined significance (AGUS) or atypical squamous cells of undetermined significance (ASCUS). Cervical cytologic smear report of low-grade squamous intraepithelial lesion (LSIL) or greater, CIN1 or greater, or any reported dysplasia; women with ASCUS were eligible only if high risk human papillomavirus (HPV) result was negative.
    - b. Unresolved findings suspicious for malignancy on the breast exam; incomplete mammogram result (BI-RADS 0) or unresolved findings suggestive of malignant changes or findings requiring short interval follow-up on the pre-study mammogram (women must have mammography result of BI-RADS 1 or 2 to enroll). Mammogram could have been performed within 9 months prior to Visit 2 (Randomization) with documentation available. (The site had to obtain a copy of the official report for the woman's study file, and it must be verified that the mammogram itself was available if needed for additional assessment).
    - c. In subjects with intact uterus: have a Screening endometrial biopsy sample that was found by both primary pathologists to have endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified. (With the approval of the Medical Monitor, the Screening endometrial biopsy could be repeated once.)
    - d. In subjects with intact uterus: an endometrial biopsy report by one central pathologist at Screening with one of the following:
      - Endometrial hyperplasia, endometrial cancer or; proliferative endometrium, weakly proliferative endometrium, disordered proliferative pattern OR
      - Endometrial polyps with hyperplasia, glandular atypia of any degree (for example, atypical nuclei), or cancer.
    - e. Vulvar or vaginal inflammatory condition such as a contact or allergic dermatitis, lichen sclerosis, or other pathological findings;
    - f. Presence of suspicious vulvar or vaginal lesions for dysplasia, malignancy, or other pathology other than atrophy;

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- g. Painful genital warts or localized areas of ulceration;
  - h. A history of active, chronic pelvic pain;
  - i. Interstitial cystitis;
  - j. Serum alanine aminotransferase (ALT) or serum aspartate aminotransferase (AST) greater than 1.5 times the upper limit of normal for the laboratory used;
  - k. Fasting total cholesterol greater than 300 mg/dL (7.77 mmol/L) or triglycerides greater than 300 mg/dL (3.39 mmol/L);
  - l. Fasting blood glucose greater than 125 mg/dL (6.94 mmol/L) with a hemoglobin A1C of greater than or equal to 6.5%;
  - m. Uncontrolled hypertension; women with elevated sitting blood pressure, greater than 140 mm Hg systolic or greater than 90 mm Hg diastolic and may not be using more than 2 antihypertensive medications for the treatment of hypertension;
  - n. A clinically significant abnormal 12-lead ECG (such as myocardial infarction or other findings suggestive of ischemia).
9. Be known to be pregnant or had a positive urine pregnancy test. (Note: A pregnancy test was not required for women who have had bilateral tubal ligation, bilateral oophorectomy, hysterectomy, or were 55 years old or greater and had experienced cessation menses for at least 1 year).
10. Current use of marijuana.

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

Medications necessary for the well-being of the woman was allowed at the discretion of the investigator with the exception of:

- Investigational drugs other than estradiol vaginal insert
- Estrogen-, progestin-, androgen- (for example DHEA), or SERM-containing medications other than estradiol vaginal insert
- Medications, remedies, and supplements known to treat vulvar/vaginal atrophy
- Vaginal lubricants and moisturizers (for example, Replens) be discontinued 7 days prior to Visit 1B vaginal pH assessment
- All medications excluded in exclusion criterion 1

### 5.3.1.3 Trial Design and Conduct

Clinical Trial TXV14-01 entitled: "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial to Evaluate the Safety and Efficacy of TX-004HR in Postmenopausal Women with Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy" was multicenter (total of 100 investigative sites; 89 centers randomized at least one woman in the US and Canada), randomized (764 women randomized), double-blind, placebo-controlled clinical trial conducted between November 1, 2014 (first woman enrolled) and September 30, 2015 (last woman completed the trial) to support the indication "Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause."

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Seven hundred and sixty-four (764) healthy postmenopausal women, 40 to 75 years of age, who had  $\leq 5\%$  superficial cells on a lateral wall vaginal smear, a vaginal pH  $> 5.0$ , and who had self-identify moderate to severe dyspareunia as their MBS of VVA at Baseline, were randomized in a 1:1:1:1 ratio to receive:

- 4 mcg estradiol vaginal insert [191 women randomized (batch number: PN0089-10); 175 (91.6%) completers]; 1 insert daily for 2 weeks, then 1 insert twice weekly for 10 weeks
- 10 mcg estradiol vaginal insert [191 women randomized (batch number: PN 0089-08); 174 (91.1%) completers]; 1 insert daily for 2 weeks, then 1 insert twice weekly for 10 weeks
- 25 mcg estradiol vaginal insert [190 women randomized (batch number: PN 0089-09); 177 (93.2%) completers]; 1 insert daily for 2 weeks, then 1 insert twice weekly for 10 weeks
- Placebo vaginal insert [192 women randomized (batch number: PN089-07); 178 (92.7%) completers]; 1 insert daily for 2 weeks, then 1 insert twice weekly for 10 weeks

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

1. Vaginal cell maturation:

Vaginal smears were collected from the lateral vaginal walls according to standard procedure at Screening 1B and Weeks 2, 5, 8, and 12 (or early termination) and sent to a central laboratory. The percentage of superficial, parabasal, and intermediate cells were determined. All on-therapy/early termination vaginal cytology results were blinded to the applicant, investigators and the trial participants. The mean change from Baseline to Week 12 (proportion of superficial and parabasal cells) was evaluated.

2. Vaginal pH:

A pH indicator strip was applied to the lateral vaginal wall at Screening 1B and Weeks 2, 5, 8, and 12 (or early termination) until it became wet, taking care to avoid cervical mucus known to affect vaginal pH. The color of the strip was immediately compared with a colorimetric scale and the measurement recorded. The mean change from Baseline to Week 12 was evaluated.

3. Self-assessment of vaginal symptoms:

The self-assessment of symptoms was evaluated by use of the VVA Symptom Self-Assessment Questionnaire at Screening Visit 1B and at Visit 3 (Week 2, Day  $14 \pm 3$  days), Visit 4 (Week 6, Day  $42 \pm 3$  days), Visit 5 (Week 8, Day  $56 \pm 3$  days), and Visit 6 (Week 12, Day  $84 \pm 3$  days). The mean change from Baseline (Screening Visit 1B, Day 1) to Week 12 in moderate to severe dyspareunia was evaluated as the primary efficacy endpoint.

#### 5.3.1.4 Assessment of Efficacy

##### **Primary Efficacy Endpoints:**

The co-primary efficacy endpoints for Trial TXV14-01 were the change from Baseline to Week 12 in:

- the percentage of vaginal superficial cells compared to placebo
- the percentage of vaginal parabasal cells compared to placebo
- vaginal pH as compared to placebo
- the severity of the MBS of dyspareunia associated with VVA as compared to placebo

##### **Secondary Efficacy Endpoints:**

- change from Baseline to Weeks 2, 6, and 8 in the percentage of vaginal superficial cells compared to placebo
- change from Baseline to Weeks 2, 6, and 8 in the percentage of vaginal parabasal cells compared to placebo
- change from Baseline to Weeks 2, 6, and 8 in vaginal pH compared to placebo
- change from Baseline to Weeks 2, 6, and 8 on the severity of the MBS of dyspareunia (vaginal pain associated with sexual activity) associated with VVA as compared to placebo
- change from Baseline to Weeks 2, 6, 8, and 12 on the severity of vaginal dryness and vulvar and/or vaginal itching or irritation associated with VVA as compared to placebo
- change in visual evaluation of the vaginal mucosa from Baseline to Weeks 2, 6, 8, and 12 compared to placebo
- change from Baseline in the Female Sexual Function Index (FSFI) at Week 12 compared to placebo

Additional analyses included subgroup analyses, a responder analysis, and a product acceptability questionnaire.

#### 5.3.1.5 Assessment of Safety

The safety variable in Trial TXV14-02 included:

- Adverse events
- Clinical laboratory tests [hematology (CBC including White blood cell count and differential, red blood cell count, hemoglobin, hematocrit and platelet count), serum chemistry (sodium, potassium, chloride, total cholesterol, BUN, iron, albumin, total protein, AST, ALT, alkaline phosphatase, creatinine, calcium, phosphorus, uric acid, total bilirubin, glucose and triglycerides), FSH, urinalysis (appearance, specific gravity, protein, pH)]

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- Vital signs
- Physical examination findings including breast and pelvic examinations
- 12-Lead ECGs
- Endometrial biopsy
- Pap smears
- Mammogram (can be performed within 9 months prior to initial dose with documentation available)

### ***Adverse Events:***

Information was collected, throughout the trial, on vital signs, physical examination, gynecological examination including a Pap smear, mammogram (unless performed within 9 months prior to Day 1 with written documentation), and clinical laboratory tests (hematology including a complete blood count; coagulation parameters including prothrombin time, activated partial thromboplastin time; blood chemistry including glucose, electrolytes, BUN, creatinine, AST, ACT, alkaline phosphate, total bilirubin, total serum protein, LDH; lipid profile including total cholesterol, triglyceride, HDL, LDL, lipoprotein B; and urinalysis). Adverse events (AEs) were recorded for safety evaluation and then coded into system organ class and preferred terms using MedDRA version 18.0.

### ***Endometrial Assessment:***

For non-hysterectomized women, an endometrial biopsy was done at Screening to document the endometrial histological status and to exclude a woman with endometrial pathology from trial participation. At Screening, endometrial biopsies were read centrally by two pathologists. If at least one pathologist assessed the endometrial biopsy as endometrial hyperplasia, endometrial cancer, proliferative endometrium, weakly proliferative endometrium, or disordered proliferative pattern, or if at least one pathologist identified an endometrial polyp with hyperplasia, glandular atypia of any degree (for example, atypical nuclei), or cancer the woman was excluded from the study. Additionally, at least one pathologist had to identify sufficient tissue to evaluate the biopsy for trial eligibility. With the approval of the Medical Monitor, the Screening endometrial biopsy may have been repeated once when an initial endometrial biopsy was performed and both of the primary pathologists reported endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified, and if the subject had met all other protocol-specified eligibility criteria. Endometrial biopsies were also performed at Week 12/End-of-Treatment (if trial participant received 10 weeks of trial medication).

Per the application, three independent pathologists with expertise in gynecologic pathology, blinded to treatment and to each other's readings, determined the diagnosis for endometrial biopsy slides during the conduct of the Trial TXV14-01. All End-of-Treatment/Early Termination and on-treatment unscheduled endometrial biopsies were centrally read by three pathologists.

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Each pathologist's report was classified into one of the following three categories:

- Category 1: non hyperplasia / non malignancy - includes proliferative endometrium, weakly proliferative endometrium, disordered proliferative pattern, secretory endometrium, endometrial tissue other [that is, benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc], endometrial tissue insufficient for diagnosis, no endometrium identified, no tissue identified, other.
- Category 2: hyperplasia- includes simple hyperplasia with or without atypia and complex hyperplasia with or without atypia.
- Category 3: malignancy – endometrial malignancy.

Consensus was reached when two of the three pathologist readers agreed on any of the above categories. The final diagnosis was based on agreement of two of the three reads. If all three readings were disparate, the final diagnosis was based on the most severe of the three readings.

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

### 5.3.1.6 Statistical Methodology

All trial participants who were randomly assigned and had at least one dose of trial medication formed the intent-to-treat (ITT) population. The modified intent-to-treat (MITT) population was the primary efficacy population with supportive efficacy analyses conducted on the efficacy evaluable (EE) population. MITT population was defined as all ITT trial participants who received the treatment to which they were randomized, had baseline values for all co-primary variables, and had at least one post-baseline value for any of the following co-primary variables at any visit (superficial cells, parabasal cells, vaginal pH, or MBS of dyspareunia).

The EE population was defined as: 1) met MITT population criteria; 2) completed the study; 3)  $\geq 80\%$  overall study drug compliant based on diary; 4) baseline superficial cells  $\leq 5\%$ ; 5) baseline vaginal pH  $> 5.0$ ; 6) moderate to severe dyspareunia identified as MBS at baseline; 7) no concomitant prohibited medications taken during the treatment period (list provided by sponsor prior to unblinding); 8) must have taken the correct study drug as randomized; and 9) have no other major protocol deviations (list provided by sponsor prior to unblinding).

The PK population included all trial participants randomized to the PK subtrial. Women were included in the PK population if they had sufficient dosing for PK evaluation at Day 14, regardless of completion status or compliance at the end of the trial.

### 5.3.1.7 Results

#### **Demographics:**

Demographic characteristics in Trial TXV14-01 recorded at Baseline for the ITT population are summarized by treatment group in Table 13. The demographic characteristics are similar across the three active treatment groups and the placebo treatment group. The overall mean age of trial participants was 59.1 years and ranged from 40 to 75 years. The majority of women were White (86.6%; 662 of 764 total trial participants) across all treatment groups with 11.6% (89 of 764 total trial participants) Black or African Americans. The overall mean BMI was 26.7 kg/m<sup>2</sup> with consistency across the four treatment groups.

Table 13: Demographics of the Intent-to-Treat (ITT) Population in Phase 3 Trial Txv14-01

Parameter	TX-004HR 4 mcg (N=191)	TX-004HR 10 mcg (N=191)	TX-004HR 25 mcg (N=190)	Placebo (N=192)	Total (N=764)
Age (years)					
- Mean (SD)	59.8 (5.90)	58.5 (6.29)	58.9 (6.26)	59.3 (6.07)	59.1 (6.24)
- Median	59	58	58	59	59
- Min, Max	41, 75	42, 75	40, 74	43, 73	40, 75
Race, n (%)					
- White	167 (87.4)	168 (88.0)	165 (86.8)	162 (84.4)	662 (86.6)
- Black / African American	20 (10.5)	21 (11.0)	24 (12.6)	24 (12.5)	89 (11.6)
- Asian	3 (1.6)	2 (1.0)	1 (0.5)	1 (0.5)	7 (0.9)
- Other	10(0.5)	0 (0.0)	0 (0.0)	5 (2.6)	6 (0.8)
Height (cm)					
- Mean (SD)	162.7 (6/86)	162.9 (6.93)	162.3 (6.37)	162.2 (6.30)	162.5 (6.62)
- Median	162.6	162.6	162.6	162.5	162.6
- Min, Max	114.7, 179.0	142.9, 182.9	149.0, 178.3	142.2, 180.0	142.2, 182.9
Weight (kg)					
- Mean (SD)	70.4 (14.26)	71.1 (13.49)	70.6 (13.7)	70.4 (13.6)	70.6 (13.74)
- Median	69.6	68.6	69.4	68.75	69.1
- Min, Max	42.1, 118.1	45.4, 119.8	45.4, 118.4	44.5, 109.8	42.1, 119.8
BMI (kg.m <sup>2</sup> )					
- Mean (SD)	26.5 (4.87)	26.8 (4.68)	26.7 (4.79)	26.7 (4.59)	26.7 (4.73)
- Median	26	26	26	26	26
- Min, Max	18, 38	18, 37	17, 38	18, 38	17, 38

Source: Adapter from NDA 208564, Clinical Trial Report for Trial TXV14-01, Table 15 on page 73 of 3533.  
Abbreviation: SD = standard deviation, Min = minimum, Max = maximum, BMI = body mass index.

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

Demographic data were similar across treatment groups. The Black or African American trial participants, while significantly less than White trial participants, represent 11.6% of the trial population. This signifies an acceptable percentage in a US trial population for the stated indication.

**Disposition of Participating Women:**

The disposition of the ITT and Safety populations in 12-week, phase 3 Trial TXV14-01 is summarized in Table 14.

Table 14: Trial Participant Disposition for the Intent-to-Treat (ITT) and Safety Populations in Phase 3 Trial TXV14-01

	<b>TX-004HR 4 mcg (N=191)</b>	<b>TX-004HR 10 mcg (N=191)</b>	<b>TX-004HR 25 mcg (N=190)</b>	<b>Placebo (N=192)</b>	<b>Total (N=764)</b>
Number of completers, n (%)	175 (91.6)	174 (91.1)	177 (93.2)	178 (92.7)	704 (92.1)
Number discontinued, n (%)	16 (8.4)	17 (8.9)	13 (6.8)	14 (7.3)	60 (7.9)
Adverse Event	1 (1.0)	3 (1.6)	4 (2.1)	5 (2.6)	14 (1.8)
Lack of Efficacy	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	3 (0.4)
Lost to Follow-Up	3 (1.6)	3 (1.6)	2 (1.1)	4 (2.1)	12 (1.6)
Protocol Violation	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)	4 (0.5)
Investigator Decision	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	3 (0.4)

Source: Adapted from NDA 208564, Clinical Trial Report for Trial TXV14-01, Table 10 on page 69 of 3533.

**Clinical Reviewer’s Comments:**

As shown in Table 14, the majority (92.1%) of total trial participant completed this 12-week trial. The percentages of completers across the three active treatment groups and the placebo treatment were similar. More discontinuations occurred in the 4 mcg and 10 mcg estradiol vaginal insert treatment groups than in the 25 mcg estradiol and placebo vaginal insert treatment groups, apparently due to a combination of adverse events and lack of efficacy as reasons for discontinuation in the two lower estradiol vaginal insert treatment groups. However, adverse events as reasons for discontinuation were higher in the 25 mcg estradiol treatment group and the placebo treatment group. Overall, adverse events as the reason for discontinuation were low (1.8%, 14 of 674 randomized women). Adverse events are discussed in Section 7 Safety of this review.

**Primary Efficacy Analyses:**

Two study populations were analyzed in Trial TXV14-01. The MITT population was the primary efficacy population. It was defined as all ITT subjects who received the treatment to which they were randomized, had baseline values for all co-primary variables, and had at least one post-baseline value for any of following four co-primary variables at any visit (superficial cells, parabasal cells, vaginal pH, and MBS of dyspareunia). Vaginal smears, vaginal pH or responses on the VVA symptoms questionnaire obtained within 7 days after the last dose of trial medication was considered on-therapy. Data collected more than 7 days after the last dose was considered post-therapy and was excluded from the analysis.

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(b) (4) (estradiol vaginal insert)

The efficacy-evaluable (EE) population was defined as: 1) met MITT population criteria; 2) completed the study (defined as having completed the study through 12 weeks per the EOS eCRF); 3)  $\geq 80\%$  overall study drug compliant based on diary; 4) baseline superficial cells  $\leq 5\%$ ; 5) baseline vaginal pH  $> 5.0$ ; 6) moderate to severe dyspareunia identified as MBS at baseline; 7) no concomitant prohibited medications that could impact the assessment of the primary endpoints taken during the treatment period; 8) must have taken the correct study drug as randomized; 9) have no other major protocol deviations. Table 15 demonstrated the two populations previously defined.

Table 15: Populations in Phase 3 Trial TXV14-01

	<b>TX-004HR 4 mcg (N=191)</b>	<b>TX-004HR 10 mcg (N=191)</b>	<b>TX-004HR 25 mcg (N=190)</b>	<b>Placebo (N=192)</b>	<b>Total (N=764)</b>
Number Randomized and in the ITT/Safety populations	191	191	190	192	764
Included in the MITT Population	186	188	186	187	747
Included in the EE Population	172	171	176	176	695

Source: Adapted from NDA 208564, Clinical Trial Report for Trial RXV14-01, Table 14 on page 73 of 3533.

The primary efficacy analysis was conducted on the MITT subjects with supportive efficacy analyses conducted on the EE population. For analysis purposes, a subject must have completed all visits, up to and including Visit 6 (Week 12), to be considered as having completed the study (completer).

To account for the multiple comparisons of testing placebo to each of the three doses of the estradiol vaginal insert (4 mcg, 10 mcg and 25 mcg) and the multiple testing of the four co-primary endpoints, the procedural testing started by examining the highest dose (25 mcg) for each of the co-primary endpoints in the following order:

- 1) vaginal superficial cells,
- 2) vaginal parabasal cells,
- 3) vaginal pH, and
- 4) severity of the MBS of dyspareunia.

If all of the p-values for each of the four co-primaries were significant ( $p \leq 0.05$ ) then the hypothesis testing continued on to the next lowest dose (10 mcg) for each of the co-primaries, as described above. If all of the four co-primary endpoints were significant ( $p \leq 0.05$ ) for 10 mcg estradiol vaginal insert, then the hypothesis testing continued for the next lowest dose (4 mcg). If at any point the hypothesis testing yielded a non-significant result, the testing was stopped.

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(b) (4) (estradiol vaginal insert)

Primary and secondary efficacy endpoints were measured at Baseline and at Weeks 2, 6, 8 and 12. The analysis examined change from baseline. The analyses of covariance (ANCOVAs) were based on mixed-effect model repeated measures (MMRM) where the random effect was subject and the two fixed effects were treatment group and Visit (2, 6, 8 and 12 weeks). Baseline measures and age were used as covariates. ANCOVAs were therefore not calculated independently for each study collection period. The analyses started with the full model and with an interaction term for Visit (Week 2, 6, 8, and 12) with treatment.

The following Baseline data for the four co-primary endpoints were submitted in the NDA application for the MITT population. See Table 16.

Table 16: Baseline Data for the Four Co-Primary Endpoints for the MITT Population

Parameter at Baseline	TX-004HR 4 mcg (N=186)	TX-004HR 10 mcg (N=188)	TX-004HR 25 mcg (N=198)	Placebo (N=187)	Total (N=747)
Percentage of superficial cells- Mean (SD)	1.3 (1.24)	1.2 (1.23)	1.3 (1.16)	1.3 (1.31)	1.3 (1.23)
Percentage of parabasal cells- Mean (SD)	52.3 (39.21)	51.3 (37.96)	53.5 (38.33)	52.0 (39.22)	52.3 (38.61)
Vaginal pH- Mean (SD)	6.34 (0.871)	6.27 (0.832)	6.33 (0.914)	6.33 (1.042)	6.32 (0.917)
MBS dyspareunia by severity- Mean (SD)	2.7 (0.48)	2.6 (0.48)	2.7 (0.44)	2.7 (0.46)	2.7 (0.46)

Source: Adapted from NDA 208564, Clinical Trial Report for Trial TXV14-01, Table 19 on page 78 of 3533, Table 20 on page 79 of 2533, and Table 21 on page 79 of 3533.

Abbreviations: MITT = modified intent-to-treat, SD = standard deviation, MBS = most bothersome symptom.

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

Per the data represented in Table 16, the percentage of superficial cells and parabasal cells on the Baseline lateral wall vaginal smears were consistent across treatment groups. Likewise, vaginal pH at Baseline was consistent across all treatment groups. The overall mean Baseline severity score for dyspareunia was 2.7. The majority of trial participants reported severe dyspareunia at Baseline (68.7%) while 31.3% reported moderate dyspareunia at Baseline.

Per the statistical analysis plan (SAP), the Least Square (LS) mean change from Baseline of each active treatment group from the placebo treatment group was calculated for each co-primary endpoint. The following Table 17 shows the LS mean change from Baseline to Week 12 for the MITT population.

Table 17: Co-Primary Efficacy Summary: Least-Square (LS) Mean Change from Baseline to Week 12 in Trial TXV14-012 (MITT Population)

	TX-004HR	TX-004HR	TX-004HR	
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(b) (4) (estradiol vaginal insert)

Parameter	4 mcg (N=186)	10 mcg (N=188)	25 mcg (N=198)	Placebo (N=187)
Percent Change in Superficial Cells (n)	170	171	174	172
- LS Mean (SE)	17.50 (1.542)	16.72 (1.540)	23.20 (1.529)	5.63 (1.537)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
Percent Change in Parabasal Cells (n)	170	171	174	172
- LS Mean (SE)	-40.63 (1.755)	-44.07 (1.751)	-45.55 (1.745)	-6.73 (1.750)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
Change in Vaginal pH (n)	170	171	174	174
- LS Mean (SE)	-1.32 (0.066)	-1.42 (0.066)	-1.34 (0.066)	-0.28 (0.066)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
Change in Severity of Dyspareunia (n)	151	154	159	163
- LS Mean (SE)	-1.52 (0.071)	-1.69 (0.071)	-1.69 (0.071)	-1.28 (0.070)
- MMRM P-value vs. placebo	0.0149	<0.0001	<0.0001	--

Source: Adapted from NDA 208564, Clinical Trial Report for Trail TXV14-01, Table 22 on page 80 of 3533.

Abbreviations: MITT = modified intent-to-treat, LS = least square, SE = standard error, MMRM = mixed model repeated measures.

A summary of the observed and mean changes from Baseline to Week 12 in the Co-Primary Endpoints in Trial TXV14-01 are presented in Table 18.

Table 18: Summary of Observed and Mean Changes from Baseline to Week 12 in the Co-Primary Endpoints in Trial TXV14-01 (MITT Population)

	TX-004HR 4 mcg (N=186)	TX-004HR 10 mcg (N=188)	TX-004HR 25 mcg (N=198)	Placebo (N=187)
<b>Superficial Cells</b>				
Baseline (n)	186	188	186	187
- Mean (SD)	1.3 (1.24)	1.2 (1.23)	1.3 (1.16)	1.3 (1.31)
Week 12 (n)	170	171	174	172
- Mean (SD)	18.7 (19.54)	18.5 (19.95)	24.9 (24.23)	1.0 (14.70)
Change from Baseline (n)	170	171	174	172
- Mean (SD)	17.5 (19.33)	17.3 (19.76)	23.6 (24.17)	5.7 (14.27)
- LS Mean (SE)	17.50 (1.542)	16.72 (1.540)	23.20 (1.529)	5.63 (1.537)
- MMRM p-value vs. placebo	<0.0001	<0.0001	<0.0001	--
<b>Parabasal Cells</b>				
Baseline (n)	186	188	186	187
- Mean (SD)	52.3 (39.21)	51.3 (37.96)	53.5 (38.33)	52.0 (39.22)
Week 12 (n)	170	171	174	172
- Mean (SD)	12.0 (22.32)	7.8 (37.84)	6.6 (16.62)	45.2 (40.27)
Change from Baseline (n)	170	171	174	172
- Mean (SD)	-41.1 (41.57)	-43.8 (37.84)	-46.2 (39.99)	-6.3 (29.76)
- LS mean (SE)	-40.63 (1.755)	-44.07 (1.751)	-45.55 (1.745)	-6.73 (1.750)
- MMRM p-value vs. placebo	<0.0001	<0.0001	<0.0001	--

<b>Vaginal pH</b>				
Baseline (n)	186	188	186	187
- Mean (SD)	6.34 (0.871)	5.2 (0.832)	6.33 (0.914)	6.33 (1.042)
Week 12 (n)	170	171	174	174
- Mean (SD)	5.03 (0.961)	1.86 (0.737)	4.98 (0.871)	6.07 (1.373)
Change from Baseline (n)	170	171	174	174
- Mean (SD)	-1.33 (1.111)	-1.41 (1.027)	-1.37 (1.143)	-0.26 (1.048)
- LS mean (SE)	1.32 (0.066)	-1.42 (0.066)	-1.34 (0.066)	-0.28 (0.066)
- MMRM p-value vs. placebo	<0.0001	<0.0001	<0.0001	--
<b>Severity of MBS Dyspareunia</b>				
Baseline (n)	186	188	186	187
- Mean (SD)	2.7 (0.48)	2.6 (0.48)	2.7 (0.44)	2.7 (0.46)
Week 12 (n)	151	154	159	163
- Mean (SD)	1.1 (0.98)	0.9 (0.92)	1.0 (0.99)	1.4 (1.02)
Change from Baseline (n)	151	154	159	163
- Mean (SD)	-1.54 (1.044)	-1.68 (0.956)	-1.72 (0.935)	-1.28 (1.039)
- LS mean (SE)	-1.52 (0.071)	-1.69 (0.071)	-1.69 (0.071)	-1.28 (0.070)
- MMRM p-value vs. placebo	0.0149	<0.0001	<0.0001	--

Source: Adapted from NDA 208564, Clinical Trial Report, Table 25 on page 82 of 3533, Table 24 on page 81 of 3533, Table 26 on page 83 of 3533, and Table 27 on page 84 of 3533.

Abbreviations: MITT = modified intent-to-treat, LS = least square, SE = standard error, MMRM = mixed model repeated measures.

**Clinical Reviewer's Comments:**

The results reported in Trial TXV14-01, shown in the tables above, demonstrated that all three doses (4 mcg, 10 mcg, and 12 mcg) of estradiol vaginal insert are effective for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

Because trial participants with either no reported sexual activity at Week 12 (n=68, 9.1% of trial participants) or missing data on dyspareunia at Week 12 (n=52, 7.0% of trial participants) were excluded from MMRM analysis of MBS dyspareunia, the Statistical Reviewer requested that the applicant provide additional sensitivity analysis using last observation carried forward (LOCF) to handle the missing data. Table 19 represents the data in Table 14.2.1.4X received in the Clinical Information Amendment verified by the Statistical Reviewer's analysis.

Table 19: MBS of Dyspareunia: Change in Severity from Baseline to Week12 (MITT Population, LOCF)

	<b>TX-004HR 4 mcg</b>	<b>TX-004HR 10 mcg</b>	<b>TX-004HR 25 mcg</b>	<b>Placebo</b>
<b>Baseline (n)</b>	186	188	186	187
- Mean	2.7 (0.48)	2.6 (0.48)	2.7 (0.44)	2.7 (0.46)
- Median	3	3	3	3
- Min, Max	2,3	2, 3	2, 3	2,3

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(b) (4) (estradiol vaginal insert)

<b>Week 12 (n)</b>	178	176	174	183
- Mean (SD)	1.18 (0.97)	1.03 (0.95)	1.03 (0.97)	1.45 (1.03)
- Median	1	1	1	1
- Min, Max	0, 3	0, 3	0, 3	0, 3
<b>Change from Baseline</b>				
- LS Mean (SE)	-1.50 (0.07)	-1.64 (0.07)	-1.67 (0.07)	-1.25 (0.07)
- Diff. from Placebo (95% CI) <sup>1</sup>	-0.25 (-0.44, -0.05)	-0.38 (-0.58, -0.19)	-0.42 (-0.62, -0.22)	-
- P-value vs. Placebo <sup>2</sup>	0.0156	0.0002	<0.0001	-

Source: Adapted from Statistical Review dated April 4, 2017, Table 6, page 12 of 22.

<sup>1</sup> Difference from placebo = TX-004HR (Week 12 mean – baseline mean) – Placebo (Week 12 mean – baseline mean).

<sup>2</sup> ANCOVA: Treatment as the main factor and baseline value as the covariate.

**Clinical Reviewer's Comments:**

Table 19 shows a similar statistically significant reduction in the severity of MBS dyspareunia for all three dose of the estradiol vaginal insert as is demonstrated in Table 18.

Per the applicant, severity of MBS dyspareunia improved at Week 12 by 2 to 3 levels as shown in the following table.

Table 20: MBS of Dyspareunia: Change in Severity from Baseline to Week 12 (MITT Population)

Change in Severity	TX-004HR 4 mcg (N=186) n (%)	TX-004HR 10 mcg (N=188) n (%)	TX-004HR 25 mcg (N=198) n (%)	Placebo (N=187) n (%)
- 3 less pain	32 (17.2)	34 (18.1)	32 (17.2)	24 (12.8)
- 2 less pain	45 (24.2)	55 (29.3)	71 (38.2)	43 (23.0)
- 1 less pain	49 (26.3)	46 (24.5)	35 (18.8)	53 (28.3)
- 0 no change	22 (11.8)	19 (10.1)	21 (11.3)	41 (21.9)
- 1 more pain	1 (1.6)	0 (0)	0 (0)	0 (0)
- No sex with vaginal penetration	20 (10.8)	19 (10.1)	17 (9.1)	12 (6.4)
- Missing	15 (8.1)	15 (8.1)	10 (5.4)	12 (6.4)
- Row Mean Scores	0.0317	0.0006	0.0001	--

Source: Adapted from NDA 208564, Clinical Trial Report for Trial TXV14-01, Table 28 on page 85 of 3533.

**Clinical Reviewer's Comments:**

Table 20 shows that the severity of dyspareunia improved by 2 to 3 levels in 41.4% of women treated with 4 mcg estradiol vaginal insert, 47.4% of women treated with 10 mcg estradiol vaginal insert, and 55.4% of women treated with 25 mcg estradiol vaginal insert. However, Table 20 also shows that approximately 12% of trial participants reported no change in the severity of their dyspareunia in this clinical trial. The results reported in Table 20 need to

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(b) (4) (estradiol vaginal insert)

be balanced with the number of missing data in Trial TXV14-01 and with the number of trial participants reporting no sex with penetration 30 days prior to the Week 12 assessment. For the primary analysis, missing/invalid data were not imputed; instead, MMRM was fit using all the available information for estimating the treatment affect.

The Statistical Reviewer requested that the applicant re-conduct this categorical data analysis without deleting trial participants with missing data for the MITT population. Table 21 shows this sensitivity analysis using all available data for trial participants with at least one post-baseline measurement via LOCF.

Table 21: MBS of Dyspareunia: Change in Severity from Baseline to Week 12 (MITT Population)

Change in Severity MITT Population	TX-004HR 4 mcg 178 n (%)	TX-004HR 10 mcg 176 n (%)	TX-004HR 25 mcg 174 n (%)	Placebo 183 n (%)
- 3 less pain	34 (18.3)	35 (18.6)	34 (18.3)	26 (13.9)
- 2 less pain	54 (29.0)	61 (32.4)	76 (40.9)	49 (26.2)
- 1 less pain	58 (31.2)	56 (29.8)	41 (22.0)	58 (31.0)
- 0 no change	28 (15.1)	24 (12.8)	23 (12.4)	48 (25.7)
- 1 more pain	4 (2.2)	0 (0)	0 (0)	2 (1.1)
- P-value <sup>1</sup>	0.0501	0.0014	0.0001	--

Source: Adapted from Statistical Review dated April 4, 2017, Table 8, page 13 of 22.

<sup>1</sup> Trial participants with any post-treatment data are included via LOCF.

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

A statistically significant reduction in the severity of MBS dyspareunia is noted in the 10 mcg and 25 mcg estradiol vaginal insert treatment groups. The 0.4 mcg estradiol vaginal insert treatment group showed a marginally statistically significant reduction.

### **Secondary Efficacy Analyses:**

The analysis of secondary endpoints (see Subsection 5.3.1.4 of this review for a full listing of secondary endpoints) at Weeks 2, 6, and 8 were also performed and appear consistent with the changes observed at Week 12 for the primary endpoints:

- Statistical significance was noted at Weeks 2, 6, and 8 for vaginal superficial epithelial cells, vaginal parabasal epithelial cells, and vaginal pH for the 4 mcg, 10 mcg and 25 mcg estradiol vaginal insert (p<0.0001 at all-time points for all three of these evaluations).
- The change in severity of dyspareunia is reported as statistically significant at Weeks 2, 6, and 8 (reported as p=0.0260, p=0.0069, and p=0.0003, respectively, for 4 mcg estradiol vaginal insert; p=0.0019, p=0.0009, and p<0.0001,

respectively for the 10 mcg estradiol vaginal insert; and  $p=0.105$ ,  $p<0.001$ , and  $p<0.0001$ , respectively, for the 25 mcg estradiol vaginal insert.

- The change in the severity of vaginal dryness was evaluated at Weeks 2, 6, 8, and 12. Per the application, there was a statistically significant difference at each time point for the 10 mcg estradiol vaginal insert and the 25 mcg estradiol vaginal insert. The 4 mcg estradiol vaginal insert did not show statistically significant improvement in vaginal dryness until Week 6.
- The change in the severity of vulvar and vaginal irritation/itching was also evaluated at Weeks 2, 6, 8, and 12. At Week 12, p-values for 4 mcg, 10 mcg, and 25 mcg estradiol vaginal insert were reported as 0.0503, 0.0055, and 0.0263, respectively. Earlier timepoints showed no improvement in vaginal irritation/itching except at Week 8 for the 10 mcg estradiol vaginal insert ( $p=0.0356$ ).
- The change in the investigator's visual evaluation of the vaginal mucosa was reported at Weeks 2, 6, 8, and 12 as no atrophy, mild atrophy, moderate atrophy, and severe atrophy, scored as 0, 1, 2, and 3, and included an assessment of vaginal color, vaginal epithelial integrity, vaginal secretions, and vaginal epithelial surface thickness. Results of the mean change in all four categories demonstrated statistical significance at all time points.
- Changes from Baseline to Week 12 in FSFI total score and domains compared to placebo are also reported. Per the application, the 25 mcg estradiol vaginal insert demonstrated statistically significant improvements compared to placebo for: Total Score, Arousal, Lubrication, Pain, and Satisfaction. The 10 mcg estradiol vaginal insert showed statistical improvement compared to placebo for: Total Score, Lubrication, and Pain. There was no reported difference between the 4 mcg estradiol vaginal insert and placebo in the FSFI.

**Clinical Reviewer's Comments:**

TherapeuticsMD was advised that no outcomes from secondary analyses would be taken under consideration when reaching a decision regarding the effectiveness of estradiol vaginal insert to relieve moderate to severe dyspareunia. (b) (4)

***Analyses of Other Endpoints:***

Other additional analyses included a responder analysis, subgroup analyses, and product acceptability questionnaire:

***Responder Analysis:***

Per the protocol, a responder was defined as any trial participant who had at least two of the following at Week 12: 1) vaginal superficial cells > 5%; 2) vaginal pH < 5.0; 3) improvement from Baseline in MBS of at least one numerical category. Table 22 shows the number of responders meeting the protocol definition.

Table 22: Summary of Responder Analysis at Week 12 (Efficacy Evaluable Population): Treatment Versus Placebo in Trial TXV14-01

	<b>TX-004HR 4 mcg (N=172) n (%)</b>	<b>TX-004HR 10 mcg (N=171) n (%)</b>	<b>TX-004HR 25 mcg (N=176) n (%)</b>	<b>Placebo (N=176) n (%)</b>
Responder	113 (65.7)	126 (73.7)	132 (75)	55 (31.3)
Non-Responder	43 (25.0)	31 (18.1)	36 (20.5)	114 (64.8)
Cannot be Determined	16 (9.3)	14 (8.2)	8 (4.5)	7 (4.0)
Fisher Exact Test	<0.0001	<0.0001	<0.0001	--

Source: Adapted from NDA 208564; Clinical Trial Report, Table 40 on page 98 of 3553.

**Clinical Reviewer’s Comments:**

The definition of responder for the conducted responder analyses was not previously agreed-upon with the Agency. The above Table 21 shows that a majority of trial participants met the protocol-specified definition of a responder. The percentage of responders is statistically significant for each of the three estradiol vaginal insert treatment groups when compared to placebo.

In Trial TXV14-01, trial participants were asked to rate the acceptability of the product at Week 12 or Early Termination using a five question questionnaire as follows:

1. Was the product easy to use?
2. How would you rate the ease of insertion of the capsule?
3. Level of satisfaction with the product.
4. How do you compare the treatment you received in this study to previous medication or therapies for your vulvar and vaginal atrophy symptoms?
5. Would you consider using this form of treatment again?

Responses to these five questions are tabulated in the following Table 23.

Table 23: Summary of Acceptability of Product Administration Questionnaire in Trial TXV14-01 (Randomized Population)

	<b>TX-004HR 4 mcg (N=191) n (%)</b>	<b>TX-004HR 10 mcg (N=191) n (%)</b>	<b>TX-004HR 25 mcg (N=190) n (%)</b>	<b>Placebo (N=192) n (%)</b>
Was the product easy to use?				
- Yes	171 (89.2)	172 (90.1)	175 (92.1)	164 (85.4)
- No	10 (5.2)	9 (4.7)	9 (4.7)	21 (10.9)
- Missing	10 (5.2)	10 (5.2)	6 (3.2)	7 (3.6)
- Fisher Exact Test	0.0595	0.0349	0.0347	--
How would you rate the ease of insertion of the capsule?				
- Excellent	78 (41.4)	83 (43.5)	83 (43.7)	65 (33.9)
- Good	77 (40.3)	72 (37.7)	74 (38.9)	79 (41.1)
- Fair	20 (10.5)	23 (12)	18 (9.5)	25 (13)
- Poor	5 (2.6)	3 (1.6)	9 (4.7)	16 (8.3)

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(b) (4) (estradiol vaginal insert)

- Missing CMH Test vs. Placebo	10 (5.2) 0.0105	10 (5.2) 0.0039	6 (3.2) 0.0201	7 (3.6) --
Level of satisfaction with the product.				
- Very satisfied	74 (38.7)	84 (44)	83 (43.7)	41 (21.4)
- Satisfied	57 (29.8)	55 (28.8)	62 (32.6)	68 (35.4)
- Unsure	23 (12)	28 (14.7)	21 (11.1)	39 (20.3)
- Dissatisfied	19 (9.9)	9 (4.7)	12 (6.3)	20 (10.4)
- Very Dissatisfied	8 (4.2)	5 (2.6)	6 (3.2)	17 (8.9)
- Missing	10 (5.2)	10 (5.2)	6 (3.2)	7 (3.6)
- CMH Test vs. Placebo	0.0009	<0.0001	<0.0001	--
How do you compare the treatment you received in this study to previous medications or therapies for your VVA symptoms?				
- Very much prefer present treatment	63 (33)	57 (29.8)	70 (36.8)	44 (22.9)
- Somewhat prefer present treatment	25 (13.1)	19 (9.9)	25 (13.2)	24 (12.5)
- No preference	14 (7.3)	15 (7.9)	15 (7.9)	21 (10.9)
- Somewhat prefer previous treatment	7 (3.7)	10 (5.2)	9 (4.7)	12 (6.3)
- Very much prefer previous treatment	10 (5.2)	12 (6.3)	9 (4.7)	23 (12)
- Previously not used treatment	62 (32.5)	68 (35.6)	56 (29.5)	61 (31.8)
- Missing	10 (5.2)	10 (5.2)	6 (3.2)	7 (3.6)
- CMH Test vs. Placebo	0.0010	0.0212	0.0003	--
Would you consider using this form of treatment again?				
- Yes, definitely	109 (57.1)	95 (49.7)	111 (58.4)	79 (41.1)
- Yes, probably	30 (15.7)	48 (25.1)	42 (22.1)	41 (21.4)
- Unsure	20 (10.5)	19 (9.9)	14 (7.4)	27 (14.1)
- No, probably not	14 (7.3)	15 (7.9)	14 (7.4)	21 (10.9)
- No, definitely not	8 (4.2)	4 (2.1)	3 (1.6)	17 (8.9)
- Missing	10 (5.2)	10 (5.2)	6 (3.2)	7 (3.6)
- CMH Test vs. Placebo	0.0015	0.0015	<0.0001	--

Source: Adapted from NDA 208564, Clinical Trial Report for Trial TXV14-01, Table 41 on page 98 of 3533; Table 42 on page 99 of 3533, Table 43 on page 99 of 3533, Table 44 on page 100 of 3533, and Table 45 on page 100 of 3533.

Abbreviations: CMH = Cochran-Mantel-Haenszel

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

Overall, trial participants found this digitally administered product acceptable indicating they would definitely/probably consider using the estradiol vaginal insert again (72.8% to 80.5% in active treatment groups compared with 62.5% in the placebo treatment group). Approximately 90% of treated women reported that the product was easy to use.

### **Analyses of Subpopulations:**

Subgroup analyses were performed based upon:

- Age using the following tertiles: ≤ 56 years, ≥ 57 to ≤ 61 years, and ≥ 62 years
- Body Mass Index (BMI) analysis by the following tertiles: ≤ 24 kg/m<sup>2</sup>, ≥ 25 to ≤ 28 kg/m<sup>2</sup>, and ≥ 29 kg/m<sup>2</sup>
- Uterine status, pregnancy status and vaginal birth status

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(b) (4) (estradiol vaginal insert)

Analyses of the change from Baseline to Week 12 in percentages of parabasal and superficial cells, vaginal pH, and the MBS of dyspareunia for the subgroups were performed. Table 24 shows the least square mean change from Baseline to Week 12 by age. Table 25 shows the least square mean change from Baseline to Week 12 by BMI.

Table 24: Summary of Least Square (LS) Mean Change from Baseline to Week 12 by Age

	<b>TX-004HR 4 mcg (N=186)</b>	<b>TX-004HR 10 mcg (N=188)</b>	<b>TX-004HR 25 mcg (N=186)</b>	<b>Placebo (N=187)</b>
<b>Superficial Cells</b>				
≤ 56 years (youngest tertile), (n)	<b>51</b>	<b>67</b>	<b>70</b>	<b>56</b>
- LS Mean (SE)	17.23 (2.846)	14.93 (2.503)	22.45 (2.453)	7.31 (2.726)
- MMRM P-value vs. placebo	0.0122	0.0403	<0.0001	--
≥ 57 to ≤ 61 years (middle tertile) (n)	<b>57</b>	<b>54</b>	<b>47</b>	<b>56</b>
- LS Mean (SE)	18.74 (2.7)	19.62 (2.758)	28.18 (2.941)	5.22 (2.719)
- MMRM P-value vs. placebo	0.0005	0.0002	<0.0001	--
≥ 62 years (oldest tertile) (n)	<b>62</b>	<b>50</b>	<b>57</b>	<b>60</b>
- LS Mean	16.75 (2.438)	16.18 (2.712)	19.96 (2.555)	4.05 (2.489)
- MMRM P-value vs. placebo	0.0003	0.001	<0.001	--
<b>Parabasal Cells</b>				
≤ 56 years (youngest tertile), (n)	<b>51</b>	<b>67</b>	<b>70</b>	<b>56</b>
- LS Mean (SE)	-35.02 (2.917)	-36.42 (2.582)	-38.69 (2.541)	-9.11 (2.794)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
≥ 57 to ≤ 61 years (middle tertile) (n)	<b>57</b>	<b>54</b>	<b>47</b>	<b>56</b>
- LS Mean (SE)	-46.76 (3.012)	-47.64 (3.062)	-45.26 (3.262)	-12.30 (3.033)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
≥ 62 years (oldest tertile) (n)	<b>62</b>	<b>50</b>	<b>57</b>	<b>60</b>
- LS Mean	-40.26 (3.045)	-49.33 (3.372)	-53.65 (3.209)	-0.02 (3.113)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
<b>Vaginal pH</b>				
≤ 56 years (youngest tertile), (n)	<b>51</b>	<b>67</b>	<b>70</b>	<b>56</b>
- LS Mean (SE)	-1.36 (0.113)	-1.30 (0.100)	-1.38 (0.098)	-0.48 (0.108)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
≥ 57 to ≤ 61 years (middle tertile) (n)	<b>57</b>	<b>54</b>	<b>47</b>	<b>58</b>
- LS Mean (SE)	-1.37 (0.116)	-1.58 (0.118)	-1.42 (0.126)	-0.34 (0.116)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
≥ 62 years (oldest tertile) (n)	<b>62</b>	<b>50</b>	<b>57</b>	<b>60</b>
- LS Mean	-1.23 (0.112)	-1.4 (0.125)	-1.24 (0.118)	-0.05 (0.115)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
<b>MBS Dyspareunia</b>				
≤ 56 years (youngest tertile), (n)	<b>50</b>	<b>61</b>	<b>65</b>	<b>52</b>
- LS Mean (SE)	-1.58 (0.122)	-1.77 (0.112)	-1.86 (0.108)	-1.25 (0.119)
- MMRM P-value vs. placebo	0.0539	0.0015	0.0002	--
≥ 57 to ≤ 61 years (middle tertile) (n)	<b>50</b>	<b>49</b>	<b>47</b>	<b>53</b>
- LS Mean (SE)	-1.42 (0.121)	-1.63 (0.121)	-1.79 (0.125)	-1.39 (0.118)
- MMRM P-value vs. placebo	0.8366	0.1488	0.0189	--
≥ 62 years (oldest tertile) (n)	<b>51</b>	<b>44</b>	<b>47</b>	<b>58</b>
- LS Mean	-1.52 (0.126)	-1.66 (0.138)	-1.38 (0.135)	-1.19 (0.122)
- MMRM P-value vs. placebo	0.058	0.0099	0.2888	--

Source: Adapted from NDA 208564, Clinical Trial Report for Trial TXV14-01, Table 47 and 48 on page 102 of 3533, Table 49 and 50 on page 103 of 3533.

Abbreviations: LS = least square, SE = standard error, MMRM = Mixed Model Repeated Measures.

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(b) (4) (estradiol vaginal insert)

**Clinical Reviewer’s Comments:**

Consistently positive results were observed across all age subgroups and all dosage strength of estradiol vaginal insert as compared for the co-primary endpoints of an increase in superficial cells, a decrease in parabasal cells, and a reduction in vaginal pH. This is not the case for the LS mean change in the MBS dyspareunia, however, which demonstrated inconsistencies (numeric improvements not statistically significant) across the age subgroups and dosage strengths of estradiol vaginal insert. Small subgroup sample sizes may have influences these reported results.

Table 25 shows the least square mean change from Baseline to Week 12 by BMI.

Table 25: Summary of Least Square (LS) Mean Change from Baseline to Week 12 by BMI

	<b>TX-004HR 4 mcg (N=186)</b>	<b>TX-004HR 10 mcg (N=188)</b>	<b>TX-004HR 25 mcg (N=186)</b>	<b>Placebo (N=187)</b>
<b>Superficial Cells</b>				
≤ 24 kg/m <sup>2</sup> (lowest tertile), (n)	<b>67</b>	<b>63</b>	<b>56</b>	<b>61</b>
- LS Mean (SE)	18.78 (2.425)	18.33 (2.515)	24.75 (2.648)	3.49 (2.543)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
≥ 25 to ≤ 28 kg/m <sup>2</sup> (middle tertile) (n)	<b>47</b>	<b>56</b>	<b>63</b>	<b>58</b>
- LS Mean (SE)	15.91 (2.913)	19.04 (2.671)	23.43 (2.535)	7.04 (2.628)
- MMRM P-value vs. placebo	0.0243	0.00014	<0.0001	--
≥ 29 kg/m <sup>2</sup> (highest tertile) (n)	<b>56</b>	<b>52</b>	<b>55</b>	<b>53</b>
- LS Mean (SE)	17.73 (2.655)	12.85 (2.751)	21.04 (2.693)	6.35 (2.756)
- MMRM P-value vs. placebo	0.0031	0.0962	0.0002	--
<b>Parabasal Cells</b>				
≤ 24 kg/m <sup>2</sup> (lowest tertile), (n)	<b>67</b>	<b>63</b>	<b>56</b>	<b>91</b>
- LS Mean (SE)	-51.68 (2.863)	-54.49 (2.968)	-52.86 (3.111)	-4.99 (2.969)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
≥ 25 to ≤ 28 kg/m <sup>2</sup> (middle tertile) (n)	<b>47</b>	<b>56</b>	<b>63</b>	<b>58</b>
- LS Mean (SE)	-42.56 (3.293)	-43.54 (3.031)	-47.08 (2.89)	-8.23 (2.981)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
≥ 29 kg/m <sup>2</sup> (highest tertile) (n)	<b>56</b>	<b>52</b>	<b>55</b>	<b>53</b>
- LS Mean (SE)	-25.52 (2.899)	-32.68 (2.995)	-35.73 (2.951)	-7.43 (3.014)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
<b>Vaginal pH</b>				
≤ 24 kg/m <sup>2</sup> (lowest tertile), (n)	<b>67</b>	<b>63</b>	<b>56</b>	<b>61</b>
- LS Mean (SE)	-1.54 (0.095)	-1.52 (0.099)	-1.49 (0.104)	-0.17 (0.099)
- MMRM P-value vs. placebo	<0.001	<0.0001	<0.0001	--
≥ 25 to ≤ 28 kg/m <sup>2</sup> (middle tertile) (n)	<b>47</b>	<b>56</b>	<b>63</b>	<b>60</b>
- LS Mean (SE)	-1.3 (0.137)	-1.5 (0.125)	-1.22 (0.119)	-0.29 (0.112)
- MMRM P-value vs. placebo	<0.0001	<0.0001	<0.0001	--
≥ 29 kg/m <sup>2</sup> (highest tertile) (n)	<b>56</b>	<b>52</b>	<b>54</b>	<b>53</b>
- LS Mean (SE)	-1.08 (0.113)	-1.23 (0.116)	-1.31 (0.115)	-0.40 (0.117)
- MMRM P-value vs. placebo	<0.0001	<0.001	<0.0001	--
<b>MBS Dyspareunia</b>				
≤ 24 kg/m <sup>2</sup> (lowest tertile), (n)	<b>58</b>	<b>56</b>	<b>51</b>	<b>56</b>
- LS Mean (SE)	-1.48 (0.113)	-1.60 (0.117)	-1.72 (0.117)	-1.14 (0.115)
- MMRM P-value vs. placebo	0.0340	0.0055	0.0006	--
≥ 25 to ≤ 28 kg/m <sup>2</sup> (middle tertile) (n)	<b>45</b>	<b>52</b>	<b>58</b>	<b>57</b>

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(b) (4) (estradiol vaginal insert)

- LS Mean (SE)	-1.51 (0.131)	-1.78 (0.124)	-1.77 (0.117)	-1.48 (0.118)
- MMRM P-value vs. placebo	0.8404	0.0829	0.0756	--
≥ 29 kg/m <sup>2</sup> (highest tertile) (n)	<b>48</b>	<b>46</b>	<b>50</b>	<b>50</b>
- LS Mean (SE)	-1.56 (0.125)	-1.71 (0.239)	-1.57 (0.124)	-1.21 (0.125)
MMRM P-value vs. placebo	0.0509	0.0052	0.0403	--

Source: adapted from NDA 208564, Clinical Trial Report for Trial TXV14-01, Table 52 on page 104 of 3533, Table 55 on page 105 of 3533, and Table 54 and Table 55 on page 106 of 3533.

Abbreviations: LS = least square, SE = standard error, MMRM = Mixed Model Repeated Measures.

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

Here too, positive results were observed across all BMI tertiles and all dosage strength of estradiol vaginal insert as compared for the co-primary endpoints of an increase in superficial cells, a decrease in parabasal cells, and a reduction in vaginal pH except for the highest BMI tertile for the 10 mcg estradiol vaginal insert treatment group. Similar inconsistent and unexplained results are reported for MBS dyspareunia as was observed in the age subgroup analysis. Non-statistically significant results are reported in the middle tertile across all dosage strengths which is opposite from the statistically significant results reported for the lowest and highest BMI tertiles. The meaning of these findings is unclear.

The results of the co-primary efficacy endpoints for the MITT population by uterine status (intact or non-intact), prior pregnancy, and vaginal birth can be viewed in the Clinical Trail Report for Trial TXV14-01 in the application.

### **Analysis of Clinical Information Relevant to Dosing Recommendations:**

Per the application, the initial dose selection for the single phase 3 clinical trial was based on the results from phase 1 PK Trials ESTR-1K-499-12 and ESTR-1K-500-12 and the 14-day phase 2 clinical Trial TXV13-01. No dedicated phase 2 dose finding trial was conducted. In the two PK trials estradiol, estrone, and estrone sulfate exposures at both the 10 mcg dose and the 25 mcg dose were significantly lower for the estradiol vaginal insert than that of the comparison product (Vagifem<sup>®</sup> 10 mcg and 25 mcg vaginal insert, respectively). In phase 2 Trial TXV13-01, the 10 mcg estradiol vaginal insert showed greater improvement in increasing the percentage of superficial cells, reducing the percentage of parabasal cells and reducing vaginal pH compared to the placebo vaginal insert. Based on these results, the applicant included the 10 mcg and 25 mcg doses as well as a lower 4 mcg dose of the estradiol vaginal insert in the phase 3 clinical trial.

The reported differences in outcome analyses of the recommended co-primary endpoint for a VVA indication are discussed beginning on page 54 in this review.

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

All three doses of the estradiol vaginal insert (4 mcg, 10 mcg and 25 mcg) demonstrated statistically significant improvements compared with placebo in the co-primary endpoints evaluated. Overall, the 10 mcg and 25 mcg estradiol vaginal inserts performed "better" (smaller p-values) than the 4 mcg estradiol

vaginal insert, but absolute differences are small and unlikely to be clinically meaningful.

***Discussion of Persistence of Efficacy and/or Tolerance Effects:***

The efficacy and safety of 4 mcg, 10 mcg, and 25 mcg estradiol vaginal inserts were only evaluated in a single 12-week clinical trial (Trial TXV14-01). No long-term general and endometrial safety and chronic drug exposure data is available for review in this NDA application.

**Clinical Reviewer's Comments:**

Single primary phase 3 Trial TXV14-01, submitted in support of approval of the 4 mcg, 10 mcg (b) (4) estradiol vaginal inserts for the treatment of moderate to severe dyspareunia, is a 12-week clinical trial. Trial TXV14-01 complies with the Agency's 2003 draft Clinical Evaluation Guidance. Trial TXV14-01 is appropriate and adequate to provide efficacy data for the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal inserts.

Trial TXV14-01 is neither appropriate nor adequate, given it limited 12-weeks of drug exposure, to provide sufficient long-term safety and chronic-use exposure data for the 4 mcg, 10 mcg and 25 mcg estradiol vaginal inserts. Therefore, this application does not contain adequate safety data for evaluation of a chronic use product for approval for the treatment of moderate to severe dyspareunia in a postmenopausal woman.

The absence of long-term general and endometrial safety data as well as chronic-use drug exposure data is a significant deficiency for this NDA application. From a clinical standpoint, no decision on approval should be made in the absence of this critical safety evaluation for the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal inserts.

## **6 Review of Efficacy**

### **Efficacy Summary**

(b) (4) (estradiol vaginal insert) 4 mcg, 10 mcg, 25 mcg administered intravaginally once daily for two weeks, then twice weekly for 10 weeks demonstrated statistically significant improvement over placebo in a single 12-week clinical trial (TXV14-01). Efficacy of 4 mcg, 10 mcg, and 25 mcg of estradiol vaginal inserts for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy in postmenopausal women, is supported by the available efficacy evidence presented in 12-week Trial TXV14-01.

Trial TXV14-01 does not provide adequate general and endometrial safety data for a chronic use product due to the limited 12-week of drug exposure.

## 6.1 Indication

The proposed indication in this application reads, "Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause."

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

Should the proposed product be granted approval, the proposed indication in NDA 208564 is acceptable. This is the indication that will eventually be reflected in product labeling.

### 6.1.1 Methods

The data presented in the single, 12-week efficacy and safety phase 3 clinical trial (Trial TXV14-01) was reviewed in its entirety. See Subsection 5.3.1.

### 6.1.2 Demographics

See discussion of the trial demographics for the single, 12-week Trial TXV14-01 in Subsection 5.3.1.7.

### 6.1.3 Subject Disposition

See discussion of the disposition of women enrolled in Trial TXV14-01 in Subsection 5.3.1.7.

### 6.1.4 Analysis of Primary Endpoint(s)

See discussion of the primary efficacy analyses for 12-week, phase 3 Trial TXV14-01 in Subsection 5.3.1.7.

### 6.1.5 Analysis of Secondary Endpoints(s)

See discussion of the secondary efficacy analyses for 12-week, phase 3 Trial TXV14-01 in Subsection 5.3.1.7.

### 6.1.6 Other Endpoints

No other endpoints for 12-week, phase 3 Trial TXV14-01 will be discussed.

### 6.1.7 Subpopulations

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(b) (4) (estradiol vaginal insert)

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See discussion of the subpopulation analyses for 12-week, phase 3 Trial TXV14-01 in Subsection 5.3.1.7.

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

The reported differences in outcome analyses for the three estradiol vaginal insert doses used in Trial TXV14-01 can be found in Subsection 5.3.1.7 in this review.

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

Efficacy was evaluated in a single, 12-week, phase 3 clinical trial (Trial TXV14-01). No long-term general or endometrial safety or chronic use exposure clinical trial was conducted to examine persistence of efficacy and/or tolerance effects.

### 6.1.10 Additional Efficacy Issues/Analyses

No additional primary efficacy analyses are considered in this review.

## 7 Review of Safety

### Safety Summary

The safety population in this NDA consist of 902 healthy postmenopausal women with and without a uterus, exposed to 4 mcg, 10 mcg, or 25 mcg estradiol vaginal insert (N=684) or placebo vaginal insert (n=218) in five clinical trials conducted during the estradiol vaginal insert clinical development program. A total of 72 healthy postmenopausal women received either 10 mcg or 25 mcg estradiol vaginal inserts (36 at each dosage strength, respectively) in two phase 1, single dose clinical trials, 16 healthy postmenopausal received one additional single dose of 25 mcg estradiol vaginal insert in a separate phase 1 clinical trial, 24 healthy postmenopausal women received 10 mcg estradiol vaginal inserts in one, 14-day, phase 2 clinical trial, and a total of 572 healthy postmenopausal women received 4 mcg (n=191), 10 mcg (n=191), or 25 mcg (n=190) in a single, 12-week, phase 3 clinical trial.

No long-term general and endometrial safety data or chronic use drug exposure data was obtained during the estradiol vaginal insert development program. The maximum time of exposure to estradiol vaginal inserts in the estradiol vaginal insert development program was 12-weeks in Trial TXV14-01. Therefore, this NDA application does not provide data on chronic exposure at 6 months and 12-months for the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal inserts. The 12-week safety data from Trial TXV14-01 is inadequate to assess long-term general and endometrial safety data of the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal inserts to support an indication for the treatment of

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(b) (4) (estradiol vaginal insert)

moderate to severe dyspareunia, a symptom of valvar and vaginal atrophy, due to menopause.

The 120-Day Safety Update Report received November 4, 2016 (dated November 4, 2016) states, "No studies are ongoing and no new safety information has become known to TherapeuticsMD since the application was submitted."

### 7.1 Methods

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

The NDA application contains an Integrated Summary of Safety (ISS). Where applicable, safety data from the single phase 2, 14-day clinical trial (Trial TXV13-01) and the single phase 3, 12-week clinical trial (Trial TXV14-01) are integrated and include adverse events (AEs), vital signs, and physical examination findings. The safety population in these trials is defined as all randomized subjects who received at least one dose of trial medication. Analysis was based on the actual treatment the subject received.

See Table 12 of this review for the completed clinical trials in the estradiol vaginal insert clinical development program. Table 12 shows that the five clinical trials were performed on very similar populations of postmenopausal women with VVA.

There were a total of 814 postmenopausal women randomized into the single phase 2 Trial TXV13-01 and the single phase 3 Trial TXV14-01 (596 in estradiol vaginal insert treatment groups and 218 in placebo vaginal insert treatment groups), 752 women (92.4%) completed these two clinical trials, and 62 women (7.6%) discontinued prematurely. See Table 26 for the number and percentages of completer in these two clinical trials.

Table 26: Safety Population for Combined Phase 2 and Phase Trials

	<b>TX-004HR 4 mcg (N=191)</b>	<b>TX-004HR 10 mcg (N=215)</b>	<b>TX-004HR 25 mcg (N=190)</b>	<b>Placebo (N=218)</b>	<b>Total (N=814)</b>
Number of completers, n (%)	175 (91.6)	198 (92.1)	177 (93.2)	202 (92.7)	752 (92.4)
Number of discontinuations, n (%)	16 (8.4)	17 (7.9)	13 (6.8)	16 (7.3)	62 (7.6)

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 2 on page 13 of 80.

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

Overall, 92.4% of postmenopausal women completed their participation in the estradiol vaginal insert development program. Less than 10% (7.6%) discontinued their participation. Discontinuations are discussed in Subsection 7.3.3 Dropouts and/or Discontinuations of this review.

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The application includes a summary of the demographics and other Baseline characteristics of the safety population in Trials TXV13-01 and TXV14-01. These two combined trials had very similar populations of postmenopausal women with VVA. See Table 27.

Table 27: Demographics for Combined Phase 2 and Phase 3 Clinical Trials (Safety Population)

	<b>TX-004HR 4 mcg (N=191)</b>	<b>TX-004HR 10 mcg (N=215)</b>	<b>TX-004HR 25 mcg (N=190)</b>	<b>Placebo (N=218)</b>	<b>Total (N=814)</b>
<b>Age (years)</b>					
Mean (SD)	58.9 (5.90)	58.9 (6.33)	58.9 (6.26)	59.7 (6.25)	59.3 (6.20)
Median	59.0	59.0	58.0	59.5	59.0
Min, Max	41, 75	42, 75	40, 74	43, 75	40, 75
<b>Race, n (%)</b>					
White	167 (87.4)	189 (87.9)	165 (86.8)	186 (85.3)	707 (86.9)
Black/African American	10 (10.5)	23 (10.7)	24 (12.6)	26 (11.9)	93 (11.4)
Asian	3 (1.6)	3 (1.4)	1 (0.5)	1 (0.5)	8 (1.0)
Other	1 (0.5)	0 (0.0)	0 (0.0)	5 (2.3)	6 (0.7)
<b>Anthropometric Measurements (Mean)</b>					
Height (cm)	162.7 (6.86)	162.8 (6.74)	162.3 (6.37)	162.3 (6.27)	162.5 (6.56)
Weight (kg)	70.4 (14.26)	71.0 (13.32)	70.6 (13.70)	70.7 (13.26)	70.7 (13.59)
Body Mass Index (kg/m <sup>2</sup> )	26.5 (4.87)	26.8 (4.60)	26.7 (4.79)	26.8 (4.45)	26.7 (4.67)
<b>Oophorectomy</b>					
Yes	51 (26.7)	59 (27.4)	45 (23.7)	47 (21.6)	202 (24.8)
No	140 (73.3)	156 (72.6)	145 (76.3)	171 (78.4)	612 (75.2)
<b>Years Since Menopause</b>					
Mean (SD)	14.2 (8.97)	14.4 (9.18)	13.7 (9.37)	13.9 (9.22)	14.1 (9.17)

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 4 on page 14 of 80.

Abbreviations: SD = standard deviation, cm = centimeter, kg = kilogram, kg/m<sup>2</sup> = kilogram per meter squared.

**Clinical Reviewer's Comments:**

Similar age distributions are observed in all treatment groups. The safety population consisted mainly of White women (86.9%) followed by Black/African American women (11.4%). The demographics and Baseline characteristics are similar in the different treatment groups.

7.1.2 Categorization of Adverse Events

An adverse event (AE) is defined as the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered casually related to the product. Any medical condition diagnosed from the results of Screening procedures was not considered an AE, but was recorded as medical history.

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Per the application, all AEs that occurred after enrolled, before treatment, during treatment, or within 15 days following the cessation of treatment, whether or not they were related to the trial medication, were recorded on Case Report Forms. All AEs were followed up until satisfactory resolution.

A serious adverse event (SAE) or reaction was any untoward medical occurrence that at any dose:

- Results in death
  - Was life-threatening (the trial participant was at immediate risk of death from the AE as it occurred).
  - Requires in-patient hospitalization or prolongation of existing hospitalization;
  - Results in persistent or significant disability or incapacity;
  - Is a congenital anomaly or birth defect;
- Is an important medical event that may jeopardize the woman or may require medical intervention to prevent one of the outcomes listed above. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the woman and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatments in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. Adverse events resulting in hospitalization are considered serious.

It was the investigator's responsibility to notify the Institutional Review Board (IRB) in accordance with the IRB's safety reporting procedures of all SAEs that occurred at his or her site. Investigators were also to be notified of all unexpected, serious, drug related events (7 or 15 Day Safety Reports) that occurred during the clinical trial. Sites that used a local IRB were responsible for notifying their IRB of the additional SAEs. The applicant or designee was to notify the central IRB of expedited safety reports on behalf of the sites.

All AEs were coded to standard preferred terms (PTs) and system organ class (SOC) categories as defined in Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0. AEs from the phase 2 Trial TXV13-01 were originally coded to MedDRA, Version 16.0 but were updated to Version 18.0, to be consistent with the phase 3 Trial TXV14-01 for the purposes of this ISS.

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

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In the application, phase 2 Trial TXV13-01 and phase 3 Trial TXV14-01 are pooled for reporting adverse events, vital signs and findings on physical examination. Safety results for each of the five trials conducted in the estradiol vaginal insert development program are available in the individual clinical trial reports in the application. Laboratory data is discussed in Subsection 7.5.2 of this review.

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

The pooling of AEs after only 14 days of exposure in Trial TXV13-01 with AEs after 12-weeks of exposure in Trial TXV14-01 is not ideal. The most informative safety information for short-term evaluations of AEs is obtained from 12-week safety and efficacy clinical trials.

## 7.2 Adequacy of Safety Assessments

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

DBRUP generally follows the ICH guidelines for patient exposure when a drug product is used on a chronic basis such as for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. The ICH E1 guidelines recommend exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures must occur at the dose or dose range believed to be efficacious.

DBRUP recommends that a safety trial of at minimum 12 months duration be conducted to assess the long-term general and endometrial safety and drug exposure of estrogen-alone products in compliance with the ICH E1 guidelines.

Per the application, a total of 596 postmenopausal women received at least one dose of estradiol vaginal insert in the combined phase 2 and phase 3 trials. In phase 2 Trial TXV13-01, 24 postmenopausal women received the 10 mcg estradiol vaginal insert for 14 days. In phase 3 Trial TXV14-01, 191 postmenopausal women received 4 mcg estradiol vaginal insert for 12 weeks (daily for 2 weeks, then twice weekly for 10 weeks), 191 postmenopausal women received 10 mcg estradiol vaginal insert for 12 weeks (daily for 2 weeks, then twice weekly for 10 weeks), and 190 postmenopausal women received 25 mcg estradiol vaginal insert for 12 weeks (daily for 2 weeks, then twice weekly for 10 weeks).

The mean duration of exposure to estradiol vaginal inserts was 31.6 doses over 74.8 days in combined phase 2 and phase 3 trials as shown in Table 28.

Table 28: Summary of Treatment Exposure for Combined Trials TXC13-01 and TXV14-01 (Safety Population)

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	<b>TX-004HR 4 mcg (N=191)</b>	<b>TX-004HR 10 mcg (N=215)</b>	<b>TX-004HR 25 mcg (N=190)</b>	<b>Placebo (N=218)</b>	<b>Total (N=814)</b>
Mean number of doses taken (SD)	32.8 (5059)	30.4 (8.38)	32.9 (5.82)	30.7 (8.41)	31.6 (7.34)
Mean duration of exposure (days) (SD)	78.5 (15.29)	70.8 (27.03)	79.5 (15.96)	71.3 (26.93)	74.8 (22.71)
Mean estradiol exposure (mcg) (SD)	131.2 (22.34)	304.2 (83.78)	823.0 (145.50)	0 (0)	--

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 3 on page 13 of 80.

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

In the Clinical Information Amendment received October 11, 2016, the applicant confirms that the proposed indication (treatment of moderate to severe dyspareunia due to menopause) is for a chronic use indication in postmenopausal women, and that the NDA application does not provide exposure data at 6 months and 12 months for the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal inserts.

The mean duration of exposure in combined 14-day phase 2 Trial TXV13-01 and 12-week phase 3 Trial TXV14-01 is only 74.8 days [standard deviation (SD) of 22.71 days]. By combining the phase 2 and phase 3 trials, the total exposure may have been artificially reduced, however. The mean duration of exposure in the single, 12-week, phase 3 Trial TXV14-01 is 78.8 (SD 16.97), similar to but greater than 74.8 (SD 22.71) days in combined phase 2 and 3 clinical trials.

A mean duration of exposure of 78.8 days duration in 12-week Trial TXV14-01 is insufficient to adequately advise on the long-term safety of estradiol vaginal inserts for the proposed indication.

As shown in Table 28, calculated mean estradiol exposure, based on daily use for two weeks, then twice weekly use for 10 weeks, demonstrates an increase in total estradiol exposure accordingly with the increase in actual dose for 4 mcg, 10 mcg, and 25 mcg estradiol vaginal inserts.

### 7.2.2 Explorations for Dose Response

Dose response was not evaluated in 14-day Trial TXV13-01. Trial TXV13-01 compared only one dose of estradiol vaginal insert (10 mcg) with the placebo vaginal insert.

Phase 3, 12-weeks Trial TXV14-01 evaluated the dose response of the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal insert compared with the placebo vaginal insert. All three doses demonstrated statistically significant results for the evaluated co-primary endpoints. See Subsection 5.3.1.7.

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

No dedicated dose finding trial to select potentially efficacious doses to study in a proof-of-efficacy trial was conducted prior to phase 3 Trial TXV14-01, which was a dose ranging trial. The ISS includes information on dose related AEs, SAEs, and TEASs. See Subsections 7.3.2 and 7.4.1.

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

See the Pharmacology/Toxicology Review for a full discussion of preclinical testing. No clinical findings emerged necessitating special animal and/or *in vitro* testing.

### 7.2.4 Routine Clinical Testing

The clinical evaluations conducted in the two double-blind, placebo-controlled clinical trials in the ISS (15-Day, phase 2 Trial TXV13-01 and 12-Week, phase 3 Trial TXV14-01) had adequate routine clinical testing to evaluate adverse outcomes arising from the use of estrogen-alone in healthy postmenopausal women for treatment of symptoms of vulvar and vaginal atrophy.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

Previous *in vitro* and *in vivo* studies have indicated that systemic estrogens are metabolized partially by cytochrome P450 3A4.

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

Per the Clinical Pharmacology Review, dated April 7, 2017, "On October 10, 2016, the Applicant stated that they acknowledge concomitant use of TX-004HR and vaginal antifungals can increase or decrease estrogen exposure. The Applicant believes their draft labeling is consistent with other estrogen products (class labeling) with higher systemic exposure and includes ketoconazole and Itraconazole (CYP3A4 inhibitors) that may increase estrogen exposure. The rationale provided by the Applicant addresses the potential metabolic interaction between estradiol and CYP3A4 inhibitors." "The Applicant did not address how physical interactions with excipients from TX-004HR vaginal insert and other vaginal products can affect estrogen bioavailability. From a safety perspective, the proposed product is an immediate release product that has demonstrated low systemic exposure and clearance within 24 hours; therefore, a PMR will not be required."

See the Clinical Pharmacology Review, dated April 7, 2017, for additional information.

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

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Four (4) estrogen-alone products are currently approved for the proposed indication in this NDA application (see Table 1 in this review). Numerous other estrogen (estrogen-alone and estrogen plus progestin) products are approved for a general indication for the treatment of moderate to severe symptoms of vulvar and vaginal due to menopause (see Subsection 9.4 in this review). All approved estrogen-alone and estrogen plus progestin products have estrogen class labeling which provides Warnings and Precautions with the use of estrogens in a postmenopausal population. Cardiovascular disorders, malignant neoplasms, probable dementia, gallbladder disease, hypercalcemia/hypocalcemia, visual abnormalities, hypertriglyceridemia, hypothyroidism, exacerbation of endometriosis, and fluid retention are Warnings and Precautions for estrogen-alone products in estrogen class labeling.

Unless data from well-designed clinical trials support that a distinction should be made, estrogen class labeling is applied to each estrogen-alone product in the class regardless of dose, route of administration, and duration of use. The Boxed Warning in estrogen-alone class labeling presents, among other warning of the safety findings from the Women's Health Initiative (WHI) clinical subtrials, the warning on the risk of endometrial cancer with unopposed estrogen use:

“There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed or recurring abnormal genital bleeding [see *Warnings and Precautions (5.3)*].”

Section 5.3 Malignant Neoplasms, *Endometrial Cancer*, in approved estrogen-alone product labeling, provides the following additional safety information:

“The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk with the use of estrogens for less than 1 year. The greater risk appears to be associated with prolonged use, with increased risks 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.”

Safety of the endometrium is supported by the results of one or more 52-week or greater clinical trial(s); results are included in Section 5.3 of estrogen class labeling.

See Subsection 7.3.5.1, “Endometrial Safety” for a discussion of the findings and the acceptability of the endometrial safety evaluation obtained in 12-week Trial TVX14-01 in the clinical development program for the estradiol vaginal insert.

## 7.3 Major Safety Results

### 7.3.1 Deaths

There were no deaths during the estradiol vaginal insert development program.

### 7.3.2 Nonfatal Serious Adverse Events

In the application, no SAEs were reported in the three phase 1 clinical trials or in phase 2 Trial TXV13-01. Eight (8) subjects experienced a total of 9 treatment-emergent SAEs in 12-week, phase 3 Trial TXV14-01. See Table 29.

Table 29: Serious Adverse Events by System Organ Class and Preferred Term  
(Safety Population in 12-Week Trial TXV14-01)

System Organ Class Preferred Term	TX-004HR 4 mcg (N=191)	TX-004HR 10 mcg (N=215)	TX-004HR 25 mcg (N=190)	Placebo (N=218)	Total (N=814)
Trail Participants with at least one SAE	0 (0)	3 (1.4)	4 (2.1)	1 (0.5)	8 (1.0)
Cardiac disorder					
- Atrial fibrillation	0 (0)	0 (0)	1 (0.5)	0 (0)	1 (0.1)
- Sinus node dysfunction	0 (0)	1 (0.5)	0 (0)	0 (0)	1 (0.1)
Gastrointestinal disorders					
- Appendicitis	0 (0)	0 (0)	1 (0.5)	0 (0)	1 (0.1)
Infections and infestations					
- Endophthalmitis	0 (0)	0 (0)	1 (0.5)	0 (0)	1 (0.1)
Injury, poisoning, and procedural disorders					
- Ankle fracture	0 (0)	1 (0.5)	0 (0)	0 (0)	1 (0.1)
Musculoskeletal and connective tissue disorders					
- Arthralgia	0 (0)	1 (0.5)	0 (0)	0 (0)	1 (0.1)
Neoplasms benign, malignant and unspecified					
- Malignant melanoma	0 (0)	1 (0.5)	0 (0)	0 (0)	1 (0.1)
Nervous system disorders					
- Cervical myelopathy	0 (0)	0 (0)	0 (0)	1 (0.5)	1 (0.1)
Respiratory, thoracic and mediastinal disorders					
- Chronic obstructive pulmonary disease	0 (0)	0 (0)	1 (0.5)	0 (0)	1 (0.1)

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 11 on page 19 of 80.

Abbreviation: SAE = serious adverse event.

Note: If a woman had more than one treatment-emergent AE that coded to the same preferred term she was counted only once for that preferred term.

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

As shown in Table 29, a small percentage of women in the estradiol vaginal insert development program experienced serious adverse events, 1% overall (8

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of 814 trial participants). All of the SAEs shown in Table 29 occurred in 12-week Trial TXV14-01. One woman in the 10 mcg estradiol vaginal insert treatment group experienced two SAEs (ankle fracture and sinus node dysfunction); all others experienced only one SAE. None of these reported SAEs were considered related to trial medication by the investigator.

The women who experienced these SAEs are identified as follows.

One (1) woman in the placebo vaginal insert treatment group experienced a SAE:

1. Number (b) (6) – A woman 63 years of age experienced intense pain in her left shoulder and neck with pain going down her arm on trial Day 85 (82 days of trial medication). She was seen in the Emergency Room: blood work, ECG, and MRI of brain were normal. The MRI of her cervical spine showed multilevel degenerative changes and the woman was admitted to the hospital. A lumbar puncture, performed on trial Day 87, was negative. A repeat MRI of the brain showed a small, curvilinear focus of T2 hyperintensity in the medial aspect of the anterior temporal lobe, and she was treated with intravenous methylprednisolone which improved her pain. Her SAE was ongoing at the end-of-trial. The investigator and medical monitor assessed this SAE as severe and not related to trial medication. This woman completed the clinical trial.

Three (3) woman in the 10 mcg estradiol vaginal insert treatment group experienced SAEs:

1. Number (b) (6) – A woman 66 years of age experienced arthralgia described as worsening of pain due to severe degenerative disease in the left knee. Relevant medical history included severe bilateral knee degenerative arthritis, chondroplasty of medial patella femoral compartments, and right knee arthroscopic surgery. She was hospitalized on trial Day 79 and a left total knee arthroplasty was performed. She was discharged without sequelae on trial Day 80. The investigator assessed this SAE as severe and not related to trial medication. This woman completed the clinical trial.
2. Number (b) (6) – A woman 56 years of age was found to have an ulcer appearing 5 mm lesion on the upper left labia (almost to the clitoris) on trial Day 42. On trial Day 51, a blood sample for syphilis and herpes simplex 1 and 2 and a biopsy of the lesion was collected. The results for syphilis and herpes were negative. The biopsy showed ulcerated malignant melanoma. She was discontinued from the trial on trial Day 58 (55 days of trial medication) and seen at the University of Michigan. It was determined that the woman had stage 1B melanoma and a wide local excision with 1-2 cm margin with sentinel lymph node biopsy was performed, with recommended follow-ups every 6 months for 3 years. The investigator and Medical Monitor assessed this SAE as severe and not related to trial medication.

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3. Number (b) (6) – A woman 69 years of age experience nausea, vomiting and diarrhea, and a syncopal episode on trial Day 35. At the hospital, a right ankle x-ray showed a bimalleolar fracture (requiring open reduction and internal fixation). A head computed tomography (CT) scan was within normal. Her CBC, basic metabolic panel and cardiac enzymes were normal. A chest x-ray showed her heart size was the upper limit of normal, and a focal opacity anterior to the spine in the lateral view. Her ECG showed sinus rhythm with right bundle branch block, QRS duration 146 milliseconds, and asystolic episodes. A pacemaker was implanted on Day 38. She was discharged from the hospital on Day 41. Relevant medical history included treated hyperlipidemia and past history of smoking. The investigator assessed the ankle fracture as moderate in severity and not related to trial medication. The investigator and medical monitor assessed the sick sinus syndrome as severe and not related to trial medication. This woman completed the clinical trial.

Four (4) women in the 25 mcg estradiol vaginal insert treatment group experienced SAEs:

1. Number (b) (6) – A woman 60 years of age experienced a left corneal ulcer on trial Day 6. A penetrating keratoplasty graft was performed on trial Day 7. Subsequently, she experienced acute endophthalmitis (beta hemolytic strep), periorbital edema, preseptal cellulitis, and blindness in the left eye on trial Day 10. She was discharged from the hospital on trial Day 14. The acute endophthalmitis of left eye resolved on trial Day 77. Relevant medical history included partial left eye blindness. This woman received one dose of trial medication. The investigator assessed the acute endophthalmitis as severe and the associated events as moderate in severity, and not related to trial medication. This woman was “discontinued” on trial Day 140. Her SAE was ongoing.
2. Number (b) (6) – A woman 55 years of age with a history of QT<sub>c</sub> ranges from 510-540 ms with bifascicular block experienced pre-syncopal episodes for one week with dyspnea. She stopped trial medication on Day 39. She was seen in the hospital on trial Day 43 and found to be in complete heart block with a ventricular rate of 30 beats per minute and admitted. On trial Day 48, an ECG showed a normal sinus rhythm, right bundle branch block, left anterior fascicular block, bifascicular block, and septal and lateral infarcts (reported 2012 ECG). At early discontinuation on trial Day 71, her ECG on was clinically significant showing sinus rhythm, abnormal left axis deviation, S1, S2, S3 pattern; left anterior fascicular block; right bundle branch block; bifascicular block: QRS(T) contour abnormality; consider anteroseptal myocardial damage. Her SAE was ongoing at end-of-trial. The investigator and medical monitor assessed the SAE as severe and not related to trail medication.
3. Number (b) (6) – A woman 58 years of age with a history of chronic obstructive pulmonary disease (COPD) experienced progressive shortness of breath during Screening and was hospitalized and treated for one day prior to her first dose of

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trail medication. She experienced an acute exacerbation of her COPD on trial Day 54 and was hospitalized and treated on trial Day 55. She was discharge on trial Day 59 in stable conditions. The investigator and medical monitor assessed this SAE as severe and not related to trial medication. This woman completed the clinical trial.

- Number (b) (6) – A woman 71 years of age experienced severe right lower quadrant abdominal pain and diarrhea on trial Day 33. She was admitted to the hospital and a laparoscopic appendectomy was performed. She was discharged on trial Day 34. The investigator assessed this SAE as severe and not-related to trial medication. This woman completed the clinical trial.

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

This reviewer agrees with the investigators' assessments for these 8 women who received treatment up to 12-weeks in the estradiol vaginal insert development program. These reported AEs in this 12-week clinical trial do not raise safety concerns for estradiol vaginal inserts.

No long-term (at least 12-month) clinical trial was conducted in the estradiol vaginal insert clinical development program to allow for an evaluation of AEs observed over a longer time period.

### 7.3.3 Dropouts and/or Discontinuations

Table 30 shows trial participant disposition in the combined phase 2 Trial TXV13-01 and phase 3 Trial TXV14-01 for the safety population.

Table 30: Safety Population Disposition in Combined Phase 2 and Phase 3 Clinical Trials

	<b>TX-004HR 4 mcg (N=191)</b>	<b>TX-004HR 10 mcg (N=215)</b>	<b>TX-004HR 25 mcg (N=190)</b>	<b>Placebo (N=218)</b>	<b>Total (N=814)</b>
Completed Trials, n (%)					
- Yes	175 (91.6)	198 (92.1)	177 (93.2)	202 (92.7)	752 (92.4)
- No	16 (8.4)	17 (7.9)	13 (6.8)	16 (7.3)	62 (7.6)
Reason for Discontinuations, n (%)					
- Adverse Event	2 (1.0)	3 (1.4)	4 (2.1)	6 (2.8)	15 (1.8)
- Lack of Efficacy	2 (1.0)	2 (0.9)	0 (0.0)	0 (0.0)	4 (0.5)
- Withdrew Consent	6 (3.1)	7 (3.3)	5 (2.6)	6 (2.8)	24 (2.9)
- Lost to Follow-up	3 (1.6)	3 (1.4)	2 (1.1)	4 (1.8)	12 (1.5)
- Protocol Violation	2 (1.0)	1 (0.5)	1 (0.5)	0 (0.0)	4 (0.5)
- Investigator Decision	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)	3 (0.4)

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 2 on page 13 of 80.

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As shown in Table 30 in these combined clinical trials, the percentage of women who discontinued from the estradiol vaginal insert treatment groups and the placebo treatment group are similar. The largest percentage of discontinuations occurred in the 4 mcg treatment group, driven by “withdrew consent” and “lost to follow-up” as reasons for discontinuation. “Withdrew Consent” accounted for the largest numbers of discontinuations across all treatment groups.

In the single phase 3 Trial TXV14-01, 14 women discontinued from Trial TXV14-01 due to a treatment-emergent adverse event (TEAE; nine women treated with estradiol vagina inserts and five women treated with placebo vaginal insert). One woman in the placebo treatment group in phase 2 Trial TXV13-01 discontinued due to a TEAE. Table 31 shows the reasons for discontinuations in the ISS.

Table 31: Adverse Events Leading to Discontinuation in the ISS

System Organ Class Preferred Term	TX-004HR 4 mcg (N=191)	TX-004HR 10 mcg (N=215)	TX-004HR 25 mcg (N=190)	Placebo (N=218)	Total (N=814)
Any AE leading to discontinuation n (%)	2 (1.0)	3 (1.4)	4 (2.1)	6 (2.8)	15 (1.8)
Cardiac disorder - Atrial fibrillation	0 (0)	0 (0)	1 (0.5)	0 (0)	1 (0.1)
Eye disorders - Blindness unilateral	0 (0)	0 (0)	1 (0.1)	0 (0)	1 (0.1)
General disorders and administrative site conditions - Chest pain - Edema peripheral	0 (0) 1 (0.5)	0 (0) 0 (0)	1 (0.5) 0 (0)	0 (0) 0 (0)	1 (0.1) 1 (0.1)
Infections and infestations - Endophthalmitis - Periorbital cellulitis - Sinusitis	0 (0) 0 (0) 0 (0)	0 (0) 0 (0) 0 (0)	1 (0.5) 1 (0.5) 1 (0.5)	0 (0) 0 (0) 0 (0)	1 (0.1) 1 (0.1) 1 (0.1)
Musculoskeletal and connective tissue disorders - Muscle spasm - Muscle twitching	0 (0) 1 (0.5)	1 (0.5) 0 (0)	0 (0) 0 (0)	0 (0) 0 (0)	1 (0.1) 1 (0.1)
Neoplasms benign, malignant and unspecified - Malignant melanoma	0 (0)	1 (0.5)	0 (0)	0 (0)	1 (0.1)
Nervous system disorders - Headache - Paresthesia	1 (0.5) 0 (0)	0 (0) 0 (0)	0 (0) 0 (0)	0 (0) 1 (0.5)	1 (0.1) 1 (0.1)
Psychiatric disorders - Affect liability	0 (0)	0 (0)	0 (0)	1 (0.5)	1 (0.1)
Renal and urinary disorders - Dysuria	0 (0)	1 (0.5)	0 (0)	0 (0)	1 (0.1)
Reproductive system and breast disorders - Vulvovaginal burning	0 (0)	0 (0)	0 (0)	2 (0.9)	2 (0.2)
Skin and subcutaneous tissue disorders - Alopecia - Chloasma	0 (0) 1 (0.5)	0 (0) 0 (0)	0 (0) 0 (0)	1 (0.5) 0 (0)	1 (0.1) 1 (0.1)

Vascular disorders - Aortic calcification	0 (0)	0 (0)	0 (0)	1 (0.5)	1 (0.1)
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Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 12 on page 21 of 80.

**Clinical Reviewer’s Comments:**

The most common TEAE leading to discontinuation in combined phase 2 Trial TXV13-01 and phase 3 Trial TXV14-01 is vulvovaginal burning reported in two placebo participants (0.2%). More detailed information follows on these trial participants.

Six (6) women in the placebo estradiol vaginal insert treatment group discontinued due to TEAEs:

1. Number (b) (6) in Trial TXV-14-01 – A woman 63 years of age experienced vulvovaginal burning starting on trial Day 1. She received no treatment. The investigator assessed this AE as moderate in severity and probably related to trial medication. This woman discontinued on trial Day 17.
2. Number (b) (6) in Trial TXV-14-01 – A woman 54 years of age experienced affect lability starting on trial Day 1. She received no treatment. Relevant medical history included depression. The investigator assessed this AE as mild in intensity and not related to trial medication. This woman discontinued on trial Day 48.
3. Number (b) (6) in Trial TXV-14-01 – A woman 47 years of age experienced vulvovaginal burning sensation starting on trial Day 2 and resolving on trial Day 7. She received not treatment. The investigator assessed this AE as moderate in severity and not related to trial medication. This woman discontinued on trial Day 17.
4. Number (b) (6) in Trial TXV-14-01 – A woman 70 years of age experienced alopecia starting on trial Day 31. She received no treatment. The investigator assessed this AE as moderate in severity and possibly related to trial medication. This woman discontinued on trial Day 53.
5. Number (b) (6) in Trial TXV-14-01 – A woman 52 years of age who reported on trial Day 16 that she was having a cardiac catheterization due to aortic calcification identified on the Screening ECG (reported after randomization). Relevant medial history included hypercholesterolemia, aortic valve disease, and current smoker. The investigator assessed this AE as severe in intensity and not related to trial medication. This woman discontinued on trial Day 30.
6. Number (b) (6) in Trial TXV13-01 – A woman of unknown age experienced vulvovaginal discomfort that resolved. The investigator assessed this AE as moderate and not related to trial medication. This woman also experienced right calf tingling sensation (paresthesia) that resolved. The investigator assessed this AE as moderate and not related to trial medication. This woman discontinued the clinical trial on Day 8.

Two (2) women in the 4 mcg estradiol vaginal insert discontinued due to TEAEs:

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1. Number (b) (6) – A woman 53 years of age discontinued due to worsening of chloasma and headache starting on trial Day 6 and resolving on trial Day 8. Relevant medical history included chloasma since 2000. The investigator assessed this AE as mild in severity and possibly related to the trial medication. This woman also experienced peripheral edema starting and resolving on trial Day 6. The investigator assessed this AE as mild in severity and possibly related to the trial medication. This woman discontinued on trial Day 8.
2. Number (b) (6) – A woman 54 years of age experienced muscle twitching starting on trial Day 51. The investigator assessed this AE as moderate in severity and not related to the trial medication. She also experienced insomnia on trial Day 61 and was prescribed 50 mg trazadone. This woman discontinued on trial Day 69.

Three (3) women in the 10 mcg estradiol vaginal insert treatment group discontinued due to TEAEs:

1. Number (b) (6) – A woman 64 years of age experienced dysuria starting on trial Day 2. She was prescribed 800 mg sulfamethoxazole/160 mg trimethoprim for trial Day 6 to trial Day 10, then again on trial Day 18 to trial Day 22. The investigator assessed this AE as severe in intensity and probably related to the trial medication. She also experienced hematuria trial Day 2 to trial Day 6. The investigator assessed this AE as moderate in severity and probably related to the trial medication. This woman discontinued on trial Day 28.
2. Number (b) (6) – A woman 68 years of age experienced muscle spasm (bilateral leg cramps) starting on trial Day 11 and resolving on trial Day 33. The investigator assessed this AE as mild in intensity and possibly related to the trial medication. She also experienced headaches beginning on trial Day 16 that resolved on trial Day 39. The investigator assessed this AE as mild in severity and possibly related to the trial medication. This woman discontinued on trial Day 47.
3. Number (b) (6) – A woman 56 years of age was found to have an ulcer appearing 5 mm lesion on the upper left labia (almost to the clitoris) on trial Day 42. On trial Day 51, a blood sample for syphilis and herpes simplex 1 and 2 and a biopsy of the lesion was collected. The results for syphilis and herpes were negative. The biopsy showed ulcerated malignant melanoma. She was discontinued from the trial on trial Day 58 (55 days of trial medication) and seen at the University of Michigan. It was determined that the woman had stage 1B melanoma and a wide local excision with 1-2 cm margin with sentinel lymph node biopsy was performed, with recommended follow-ups every 6 months for 3 years. The investigator and Medical Monitor assessed this AE as severe and not related to trial medication.

Four (4) women in the 25 mcg estradiol vaginal insert treatment group discontinued due to TEAEs:

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1. Number (b) (6) – A woman 59 years of age experienced chest pain on trial Day 64 and was admitted to the hospital Emergency Room for tests, including ECGs, echocardiogram with a bubble test, magnetic resonance imaging (MRI) of the brain, magnetic resonance angiography (MRA) of the head and neck, bilateral lower extremity ultra sound and blood work. All results were considered normal except for slightly elevated D-dimer values, an echocardiogram showing mildly decreased left ventricular diastolic compliance/mild mitral and tricuspid regurgitation, and the MRA showing an area of stenosis in the distal aspect of the right vertebral artery. The AE resolved on trial Day 65. The investigator assessed this AE as moderate in severity and not related to the trial medication. Relevant medical history included anxiety, depression, hypertension, mitral valve prolapse, and hyperlipidemia. This woman discontinued on trial Day 87.
2. Number (b) (6) – A woman 52 years of age experienced sinusitis on trial Day 2 which resolved on trial Day 19. She was prescribed amoxicillin 500 mg BID. The investigator assessed this AE as mild in severity and not related to trial medication. This woman discontinued on trial Day 22.
3. Number (b) (6) – A woman 55 years of age with a history of QT<sub>c</sub> ranges from 510-540 ms with bifascicular block, post pacemaker placement, experienced pre-syncope episodes for one week with dyspnea. She stopped trial medication on Day 39. She was seen in the hospital on trial Day 43 and found to be in complete heart block with a ventricular rate of 30 beats per minute and admitted. On trial Day 48, an ECG showed a normal sinus rhythm, right bundle branch block, left anterior fascicular block, bifascicular block, and septal and lateral infarcts (reported 2012 ECG). At early discontinuation on trial Day 71, her ECG was clinically significant showing sinus rhythm, abnormal left axis deviation, S1, S2, S3 pattern; left anterior fascicular block; right bundle branch block; bifascicular block: QRS(T) contour abnormality; consider anteroseptal myocardial damage. The investigator and medical monitor assessed the SAE as severe and not related to trail medication.
4. Number (b) (6) – A woman 60 years of age experienced a left corneal ulcer on trial Day 6. A penetrating keratoplasty graph was performed on trial Day 7. Subsequently, she experienced acute endophthalmitis (beta hemolytic strep), periorbital edema, preseptal cellulitis, and blindness in the left eye on trial Day 10. She was discharged from the hospital on trial Day 14. The acute endophthalmitis and blindness of her left eye resolved on trial Day 77. Relevant medical history included partial left eye blindness. This woman received one dose of trial medication. The investigator assessed the acute endophthalmitis as severe and the associated events as moderate in severity, and not related to trial medication. This woman was “discontinued” on trial Day 140.

### **Clinical Reviewer’s Comments:**

Overall, this reviewer agrees with the investigators’ assessments of the above reported AEs as unrelated to trial medication.

### 7.3.4 Significant Adverse Events

The following four (4) narratives are provided in the application for AEs the applicant considered of special interest in Trial TXV13-01:

#### Cervical Dysplasia:

1. Number (b) (6) – A woman 47 years of age, with a surgical history of hysterectomy and bilateral oophorectomy due to menorrhagia, who received 14 daily doses of 10 mcg estradiol vaginal inserts. A finding of Atypical Squamous Cells of Undetermined Significance (ASCUS) was reported on her vaginal cytology smear at end-of-treatment (Screening Pap smear was reported normal). She was informed of these finding by follow-up phone call and was advised to follow-up with her private gynecologist to repeat the smear in 3 months. A post-hoc reassessment of slides by “an independent pathologist” was reported as “non-dysplastic features, changes associated with estrogen therapy.”
2. Number (b) (6) – A woman 66 years of age, postmenopausal for approximately 20 years, received 14 daily doses of 10 mcg estradiol vaginal inserts. A finding of ASCUS was reported on her vaginal cytology smear at end-of-treatment (Screening Pap smear was reported normal with mild inflammation). The investigator assessed the severity of the event as mild and possibly related to trial medication. Clinical site personnel were unsuccessful in reaching this woman by phone so a copy of the vaginal smear results were mailed to her advising her to follow-up with her private gynecologist. A post-hoc reassessment of the slides “by an independent pathologist” was reported as “non-dysplastic features, changes associated with estrogen therapy.”
3. Number (b) (6) – A woman 56 years of age, with a surgical history of hysterectomy and bilateral oophorectomy due to fibroids, who received 14 daily doses of 10 mcg estradiol vaginal inserts. A finding of ASCUS was reported on her vaginal cytology smear at end-of-treatment (Screening smear was reported as normal). The investigator assessed the severity of the event as mild and possibly related to trial medication. She was informed of these finding by follow-up phone call and was advised to follow-up with her private gynecologist to repeat the smear in 3 months. A post-hoc reassessment of slides by “an independent pathologist” was reported as “non-dysplastic features, changes associated with estrogen therapy.”
4. Number (b) (6) – A woman 56 years of age, with a surgical history of hysterectomy and bilateral oophorectomy due to atypical endocervical cells, who received 14 daily doses of 10 mcg estradiol vaginal inserts. A finding of Low grade Squamous Intraepithelial Lesion (LSIL) was reported on her vaginal cytology smear at end-of-treatment (Screening smear was reported as normal). The investigator assessed the severity of the event as mild and possibly related to trial medication. She was informed of these finding by follow-up phone call and was advised to follow-up with her private gynecologist for colposcopy, human

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papilloma virus (HPV) testing, and tissue studies. The woman reported, in a second telephone call, that her colposcopy examination and HPV test were negative, and that her gynecologist attributed the “abnormality to the vaginal atrophy.” A post-hoc reassessment of slides by “an independent pathologist” was reported as “non-dysplastic features, changes associated with estrogen therapy.”

### **Clinical Reviewer’s Comments:**

All four of the 10 mcg estradiol vaginal insert-treated women listed above had an abnormal finding reported on a vaginal wall smear (ASCUS or LSIL) and a normal Baseline Pap smear. The applicant coded the cases of ASCUS (numbers (b) (6), (b) (6), and (b) (6)) as “cervical dysplasia” and the case of LSIL (Number (b) (6)) as “vaginal dysplasia” due to the surgical history of hysterectomy.

All four of these cases should have been classified by the investigator and/or applicant as probably related to trial medication.

The following narratives are provided in the application for AEs the applicant considered of special interest in Trial TXV14-01:

### **Cervical Dysplasia:**

1. Number (b) (6) – A woman 64 years of age, randomized to the 10 mcg estradiol vaginal insert treatment group, with a surgical history of hysterectomy, right salpingo-oophorectomy, uterine prolapse, and HPV infection (2010) who experienced “cervical dysplasia” starting on trial Day 85. Her Screening Pap smear was reported normal. Her Pap smear on trial Day 85 revealed LSIL. A colposcopy and biopsy was performed post-trial Day 155. Reported results were negative for dysplasia and malignancy. The investigator assessed the event as mild and not related to 10 mcg estradiol vaginal inserts. This woman completed the clinical trial.
2. Number (b) (6) – A woman 62 years of age, randomized to the 10 mcg estradiol vaginal insert treatment group, experienced “cervical dysplasia” starting on trial Day 85. Her Screening Pap smear was reported normal. Her Pap smear on trial Day 85 revealed LSIL. Her HPV test was negative. A colposcopy with endocervical curettage was performed post-trial Day 107. Reported results were negative for dysplasia and malignancy. The investigator assessed the event as mild in severity and not related to trial medication. This woman completed the clinical trial.
3. Number (b) (6) – A woman 55 years of age, randomized to the placebo estradiol vaginal insert treatment group, experienced “cervical dysplasia” starting on trial Day 83. Her Screening Pap smear was reported normal. Her Pap smear on trial Day 83 revealed LSIL. A colposcopy performed post-trial Day 154 reported results negative for dysplasia and malignancy. A HPV test was requested but not performed. The investigator assessed the AE as mild in

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severity and possibly related to trial medication. This woman completed the clinical trial.

4. (b) (6) – A woman 55 years of age, randomized to the placebo estradiol vaginal insert treatment group experienced LSIL (mild dysplasia) on her end-of-trial Pap smear. Her Screening Pap smear was reported normal. A HPV test was performed and reported as negative. A colposcopy performed post-trial Day 105 reported results negative for dysplasia and malignancy. The investigator did not classify this AE. This woman completed the clinical trial.

### **Clinical Reviewer’s Comments:**

Two trial participants randomized to the 10 mcg estradiol vaginal insert treatment group and two trial participants randomized to the placebo vaginal insert treatment group in 12-week Trial TXV14-01 were diagnosed with LSIL “cervical dysplasia” during trial participation. All four of these trial participants had a colposcopy performed with negative reported results for dysplasia or malignancy. Unfortunately, HPV testing was not consistently applied for these four trial participants. HPV is a common sexually transmitted virus that can cause cervical dysplasia.

### **Vaginal Hemorrhage:**

1. Number (b) (6) – A woman 57 years of age, randomized to the 4 mcg estradiol vaginal insert treatment group, experienced intermittent vaginal spotting starting on trial Day 6 and lasting 13 days. Her Screening endometrial biopsy was reported as endometrial tissue “Other”. Her end-of-trial endometrial biopsy on trial Day 84 was reported as follows:
  - First pathologist = endometrial tissue “Other”, no endometrial polyp
  - Second pathologist = endometrial tissue “Other”, no endometrial polyp
  - Third pathologist = no endometrial tissue identified, no endometrial polypThe investigator assessed the TEAE as mild and possibly related to trial medication. This woman completed the clinical trial.
2. Number (b) (6) – A woman 54 years of age, randomized to the 4 mcg estradiol vaginal insert treatment group, experienced “light” vaginal bleeding starting on trial Day 90 and lasting 3 days. Her Screening endometrial biopsy was reported as endometrial tissue “Other”. Her end-of-trial endometrial biopsy on trial Day 84 was reported as follows:
  - First pathologist = endometrial tissue “Other”, no endometrial polyp
  - Second pathologist = endometrial tissue “Other”, no endometrial polyp
  - Third pathologist = endometrial tissue “Other”, no endometrial polypThe investigator assessed the TEAE as mild and possibly related to trial medication. This woman completed the clinical trial.
3. Number (b) (6) – A woman 58 years of age, randomized to the 10 mcg estradiol vaginal insert treatment group, experienced vaginal spotting that started and resolved on trial Day 23 and again on post-trial Day 87 resolved on Day 90.

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Her Screening endometrial biopsy was reported as endometrial tissue “Other”. Her end-of-trial endometrial biopsy on trial Day 85 was reported as follows:

- First pathologist = endometrial tissue “Other”, no endometrial polyp
- Second pathologist = endometrial tissue “Other”, no endometrial polyp
- Third pathologist = endometrial tissue “Other”, no endometrial polyp

The investigator assessed these two TEAE as mild and possibly related to trial medication. This woman completed the clinical trial.

4. Number (b) (6) – A woman 64 years of age, randomized to the 25 mcg estradiol vaginal insert treatment group, experienced vaginal bleeding that started and resolved on trial Day 6. Her Screening endometrial biopsy was reported as endometrial tissue “Other”. Her end-of-trial endometrial biopsy on trial Day 84 was reported as follows:

- First pathologist = endometrial tissue “Other”, no endometrial polyp
- Second pathologist = endometrial tissue “Other”, no endometrial polyp
- Third pathologist = no endometrial tissue identified, no endometrial polyp, benign cervical polyp

The investigator assessed this TEAE as mild and possibly related to trial medication. This woman completed the clinical trial.

5. Number (b) (6) – A woman 57 years of age, randomized to the placebo vaginal insert treatment group, experienced two episodes of vaginal bleeding: first episode started on trial Day 8 resolved on trial Day 14, second episode started and resolved on trial Day 19. Her Screening endometrial biopsy was reported as endometrial tissue “Other” by the first pathologist and tissue insufficient for diagnosis by the second pathologist. Her end-of-trial endometrial biopsy on trial Day 89 was reported as follows:

- First pathologist = endometrial tissue “Other”, no endometrial polyp
- Second pathologist = endometrial tissue “Other”, no endometrial polyp
- Third pathologist = endometrial tissue “Other”, no endometrial polyp

The investigator assessed this TEAE as mild and probably related to trial medication. This woman completed the clinical trial.

6. Number (b) (6) – A woman 64 years of age, randomized to the placebo estradiol vaginal insert treatment group, experienced vaginal spotting that started on trial Day 2 and lasted 93 days. Her Screening endometrial biopsy was reported as endometrial tissue “Other”. Her end-of-trial endometrial biopsy on trial Day 86 was reported as follows:

- First pathologist = no endometrium identified, no endometrial polyp
- Second pathologist = endometrial tissue “Other”, no endometrial polyp
- Third pathologist = endometrial tissue “Other”, no endometrial polyp

The investigator assessed this TEAE as mild and probably related to trial medication. This woman completed the clinical trial.

7. Number (b) (6) – A woman 65 years of age, randomized to the placebo estradiol vaginal insert treatment group, experienced vaginal spotting that started on trial Day 1 and lasted 1 day. Her Screening endometrial biopsy was reported

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as endometrial tissue “Other”. Her end-of-trial endometrial biopsy on trial Day 84 was reported as follows:

- First pathologist = no endometrium identified, no endometrial polyp
- Second pathologist = no endometrium identified, no endometrial polyp
- Third pathologist = no endometrium identified, no endometrial polyp

The investigator assessed this TEAE as mild and possibly related to trial medication. This woman completed the clinical trial.

### **Clinical Reviewer’s Comments:**

Vaginal “spotting” and “bleeding” occurred similarly across all dosage strength of the estradiol vaginal insert [4 mcg (2 cases), 10 mcg (1 case), and 25 mcg (1 case)] as well as in the placebo vaginal insert treatment group (3 cases). All were self-limiting and resolved. No cases of endometrial hyperplasia or carcinoma were reported. These cases of vaginal spotting/bleeding do not raise safety concerns for the treatment groups in this 12-week clinical trial.

### Breast Mass:

1. Number (b) (6) – A woman 69 years of age, randomized to the placebo vaginal insert treatment group, experienced a left breast mass starting on post-trial Day 90. Her Screening mammogram was reported as normal. A diagnostic mammogram with computer aided detection and an ultrasound of the left breast performed on post-trial Day 93 were negative - BIRADS category 1. The investigator assessed this TEAE as mild in severity and not related to trial medication. This woman completed the clinical trial.

### **Clinical Reviewer’s Comments:**

This one case of a breast mass in the placebo vaginal insert treatment group does not raise safety concerns.

## 7.3.5 Submission Specific Primary Safety Concern

### 7.3.5.1 Endometrial Safety

A major concern with the use of hormonal therapy for the treatment of symptoms due to menopause is the risk of endometrial hyperplasia/cancer in non-hysterectomized postmenopausal women receiving estrogen-alone therapy.

In phase 3 Trial TXV14-01, endometrial biopsies were performed at Screening 1B and at Week 12/End-of-Treatment (after at least 10 weeks of trial drug exposure). An endometrial safety population (ES) was *a priori* defined for the evaluation of potential endometrial changes. To be included in the ES population, the trial participant had to have:

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- Had a pretreatment endometrial biopsy and an endometrial biopsy performed within 30 days of her last dose of trial medication with no exclusionary protocol violations
- Taken at least 80% of the assigned trial medication over the 12-week dosing period
- Not taken any prohibited concomitant medication that may impact endometrial safety

To ensure uniformity in interpretation, TherapeuticsMD established a chartered Pathology Committee (TXV14-01 Pathology Committee Charter) consisting of four independent pathologists to assess the endometrial biopsy samples in a blinded fashion. Three of these four pathologists served as the primary, independent, blinded pathologists. The fourth independent, blinded pathologist was added to cover in the absence of one of the three primary pathologists (in case of illness or other absence from work).

Endometrial biopsies collected at Screening were read centrally by two blinded pathologists. The woman was excluded from trial participation if one of these two pathologists assessed the Screening endometrial biopsy sample as endometrial hyperplasia, endometrial cancer, proliferative endometrium, weakly proliferative endometrium, or disordered proliferative pattern, or if one of these two pathologist identified an endometrial polyp with hyperplasia, glandular atypia of any degree (atypical nuclei), or cancer in the woman. Additionally, at least one pathologist had to identify sufficient tissue to evaluate the biopsy for study eligibility. With the approval of the Medical Monitor, the Screening endometrial biopsy may have been repeated once if both Screening pathologists reported endometrial tissue insufficient for diagnosis, no endometrium identified, or no tissue identified, and if the subject had met all other protocol-specified eligibility criteria.

At Week 12 (or Early Termination) endometrial biopsies and on-treatment unscheduled endometrial biopsies were assessed by three independent, blinded pathologists. Each pathologist's report was classified into one of the following three categories:

- Category 1: non-hyperplasia / non-malignancy - included proliferative endometrium, weakly proliferative endometrium, disordered proliferative pattern, secretory endometrium, endometrial tissue "other" [that is, benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc], endometrial tissue insufficient for diagnosis, no endometrium identified, no tissue identified.
- Category 2: hyperplasia - included simple hyperplasia with or without atypia and complex hyperplasia with or without atypia.
- Category 3: malignancy - endometrial malignancy.

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The final diagnosis was based on agreement of two of the three pathologists. If all three pathologists reported a different category, the final diagnosis was based on the most severe category identified.

Per protocol, the end-of-treatment endometrial biopsy could be repeated once if all three pathologists reported one of the following: 1) endometrial tissue insufficient for diagnosis, 2) no endometrium identified, or 3) no tissue identified. If the same histology findings were reported on the repeat endometrial biopsy, a TVU was performed. If the endometrial thickness was  $\leq 4$  mm, no further evaluation was required. If the endometrial thickness was  $> 4$  mm, a hysteroscopy with endometrial sampling was performed.

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

The Agency's draft 2003 Clinical Evaluation Guidance for Industry recommends that standardized criteria as provided in Blaustein's pathology text (Pathology of the Female Genital Tract) be used for the diagnosis of endometrial hyperplasia or cancer.<sup>4</sup> Histologic Characteristics of the Endometrium under Blaustein's Pathology of the Female Genital Tract is divided into the following individual histologic characteristics: 0) No tissue; 1) Tissue insufficient for diagnosis; 2) Atrophic; 3) Inactive; 4) Proliferative: a. Weekly proliferative, b. Active proliferative, and c. Disordered proliferative; 5) Secretory: a. Cyclic type, b. Progestational type (including stromal decidualization); 6) Menstrual type; 7) Simple hyperplasia without atypia; 8) Simple hyperplasia with atypia; 9) Complex hyperplasia without atypia; 10) Complex hyperplasia with atypia; 11) Carcinoma (specify type). No grouping of the 11 individual histologic characteristics is recommended.

In the NDA application, however, the applicant's presents the final reported histological findings of the three independent pathologists as a category rather than reporting the individual histologic characteristics of the endometrium reported by each of the three independent pathologists for each trial participant with a uterus who had an endometrial biopsy at end-of-treatment. On September 21, 2016, DBRUP requested that the applicant provide a copy of each endometrial biopsy report generated by each of the three pathologists for each trial participant with a uterus. TherapeuticsMD provided the requested information on October 20, 2016.

The applicant's Category 2 and 3 classifications, shown above, comply with the Agency's 2003 Clinical Evaluation Guidance. Category 2: hyperplasia includes simple hyperplasia with or without atypia and complex hyperplasia with or without

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<sup>4</sup> The standardized criteria for histologic evaluation, and the Agency's 2003 draft clinical evaluation guidance can be viewed at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/WomensHealthResearch/UCM133343.pdf>

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atypia (Blaustein's histologic characteristics numbers 7, 8, 9, and 10). Category 3: malignancy includes carcinoma (Blaustein's histologic characteristics number 11).

The applicant's Category 1 classification does not fully comply with the Agency's draft 2003 Clinical Evaluation Guidance for Industry, however. Category 1 classification does not clearly identify the presence of secretory endometrium or menstrual type endometrium which is included in "endometrial tissue "other" [that is, benign, inactive or atrophic fragments of endometrial epithelium, glands, stroma, etc.]"

### Endometrial Biopsy Histology Results:

There were 425 trial participants with uteri in 12-week Trial TXV14-01. Of these women, 390 had end-of-trial/follow-up endometrial biopsies performed. Eleven (11) women were not included in the ES population for the following reasons:

- Four (4) women were non-compliant per protocol [Numbers (b) (6) (25 mcg, endometrial tissue benign), (b) (6) (placebo, endometrial tissue benign), (b) (6) (25 mcg, endometrial tissue benign), and (b) (6) (25 mcg, endometrial tissue benign)]
- Three (3) women were excluded because they took prohibited medications [Numbers (b) (6) (4 mcg, endometrial tissue benign), (b) (6) (10 mcg, endometrial tissue benign), and (b) (6) (4 mcg, endometrial tissue benign)]
- Two (2) women were excluded because they did not have an end-of-trial biopsy performed within 30 days of last dose of trial medication [Numbers (b) (6) (10 mcg, endometrial tissue benign) and (b) (6) (placebo treatment group, endometrial tissue "Other", benign endometrial polyp)].
- One (1) woman [Number (b) (6) (4 mcg, no endometrium identified)] had no tissue identified on three endometrial biopsy reads. She refused a repeat biopsy; therefore, a TVU was performed with a reported double-wall thickness of 3.1 mm.
- One woman [Number (b) (6) (25 mcg, no endometrium identified) with a prior hysterectomy had a "biopsy performed in error".

### Clinical Reviewer's Comments:

This reviewer is unsure what "tissue" was sampled in trial participant Number (b) (6) which resulting in a finding of "no endometrium identified".

In the application, a total 379 women with uteri had endometrial biopsies performed and submitted for review (the ES population):

- 4 mcg estradiol vaginal insert = 87
- 10 mcg estradiol vaginal insert = 91
- 25 mcg estradiol vaginal insert = 94

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- Placebo vaginal insert = 107

Reported biopsy results by category: Category 1 (non-hyperplastic/non-malignant), Category 2 (hyperplasia – simple and complex), and Category 3 (endometrial malignancy) are shown in Table 32.

Table 32: Endometrial Biopsy Results by Applicant Defined Category in Trial TXV14-01

Category, n (%)	TX-004HR 4 mcg (N=87)	TX-004HR 10 mcg (N=91)	TX-004HR 25 mcg (N=94)	Placebo (N=107)	Total (N=379)
<b>Baseline</b> - Non-hyperplasia/ Non-malignant	87 (100)	91 (100)	94 (100)	107(100)	379 (100)
<b>Week 12/End-of-Trial<sup>a</sup></b> - Non-hyperplasia/ Non-malignant	87 (100)	91 (100)	94 (100)	107(100)	379 (100)
- Hyperplasia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
- Malignancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 17 on page 30 of 80.

<sup>a</sup> For inclusion trial participants have taken at least 10 weeks of trial medication.

Three women included in Category 1 (non-hyperplasia/non-malignant) had histologic finding at Week 12 that demonstrate estrogenic effects on the endometrium at Week 12 in Trial TXV14-01. See the descriptions below of the cases summarized in Table 33.

1. Number (b) (6) – A woman 52 years of age, randomized to the 10 mcg estradiol vaginal insert treatment group, experienced vaginal bleeding that started on post-trial Day 92 and resolved on post-trial Day103. Her Screening endometrial biopsy was reported as endometrial tissue “Other”. Her end-of-trial endometrial biopsy on trial Day 92 was reported as follows:
  - First pathologist = proliferative endometrium, no endometrial polyp, benign endocervical polyp identified
  - Second pathologist = disordered proliferative pattern, no endometrial polyp
  - Third pathologist = endometrial tissue “Other”, no endometrial polypNo investigator assessment of this TEAE is provided in the application. This woman completed the clinical trial.
2. Number (b) (6) – A woman 52 years of age, randomized to the 25 mcg estradiol vaginal insert treatment group, whose end-of-trial endometrial biopsy revealed endometrial proliferation. Her Screening endometrial biopsy was reported as endometrial tissue “Other”. She had no reported vaginal bleeding or spotting. Her end-of-trial endometrial biopsy on trial Day 90 was reported as follows:

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- First pathologist = weakly proliferative endometrium, no endometrial polyp, benign endocervical polyp identified
- Second pathologist = weakly proliferative endometrium, no endometrial polyp
- Third pathologist = complex hyperplasia without atypia, no endometrial polyp

No investigator assessed of this TEAE is provided in the application. This woman completed the clinical trial.

3. Number (b) (6) – A woman 54 years of age, randomized to the 25 mcg estradiol vaginal insert treatment group, whose end-of-trial endometrial biopsy revealed endometrial proliferation. Her Screening endometrial biopsy was reported as endometrial tissue “Other”. She had no reported vaginal bleeding or spotting. Her end-of-trial endometrial biopsy on trial Day 83 was reported as follows:

- First pathologist = endometrial tissue “Other”, no endometrial polyp
- Second pathologist = weakly proliferative endometrium, no endometrial polyp
- Third pathologist = proliferative endometrium, no endometrial polyp

No investigator assessment of this TEAE is provided in the application. This woman completed the clinical trial.

Table 33: Summary of Trial Participants with a Diagnosis of Endometrial Proliferation on Endometrial Biopsy in 12-Week Trial TXV14-01

Trial Participant Number	Treatment	Histology Findings (b) (4)	Histology Findings (b) (4)	Histology Findings (b) (4)	Histology Findings (b) (4) (Alternate)	Final Histology Findings in the Application
(b) (6)	10 mcg estradiol vaginal insert	Proliferative endometrium	Disordered Proliferative pattern	Endometrial tissue (Other)	N/A	Non-hyperplasia/Non-malignant
(b) (6)	25 mcg estradiol vaginal insert	N/A	Weakly proliferative endometrium	Weakly proliferative endometrium	Complex hyperplasia without atypia	Non-hyperplasia/Non-malignant
(b) (6)	25 mcg estradiol vaginal insert	Endometrial tissue (Other)	Weakly proliferative endometrium	Proliferative endometrium	N/A	Non-hyperplasia/Non-malignant

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 18 On page 30 of 80.

Abbreviation: N/A = not applicable.

### **Clinical Reviewer’s Comments:**

This reviewer concurs that, per protocol, the three final histology findings shown in Table 33 represent non-hyperplasia/non-malignant findings according to the applicant’s Category 1 grouping of histologic findings.

However, the Agency’s 2003 draft Clinical Evaluation Guidance for Industry recommends that histologic description of endometrial biopsy findings utilize standardized criteria as provided in Blaustein’s pathology text (Pathology of the

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Female Genital Tract) without grouping into categories as presented in this NDA. This allows for a more complete description of the individual histologic characteristics of the endometrium reported in each endometrial biopsy sample collected in a clinical trial.

The three reported cases of proliferative endometrium in a 12-week clinical trial are unexpected. Even more so unexpected is the finding of disordered proliferative endometrium on an endometrial biopsy sample after only 12-weeks of estrogen-alone exposure. In participant Number (b) (6) in the above table, all three pathologists reported different histologic finding, therefore, the final diagnosis in trial participant Number (b) (6) is disordered proliferative endometrium. Disordered proliferative endometrium is thought to be the precursor for endometrial hyperplasia.

The absence of long-term safety data of at least 12-months in a woman with a uterus is very concerning to this reviewer. Unopposed estrogen, including estradiol, use in a postmenopausal woman with a uterus increases the risk of endometrial hyperplasia/cancer. The limited 12-week safety data in Trial TXV14-01, available in this application, is inadequate to assess long-term general and endometrial safety of the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal inserts.

### Endometrial Polyps:

At Baseline in Trial TXV14-01, a total of 13 endometrial polyps were identified which were all reported as benign (4 in trial participants randomized to the 4 mcg estradiol vaginal insert treatment group, 4 in trial participants randomized to the 10 mcg estradiol vaginal insert treatment group, 2 in trial participants randomized to the 25 mcg estradiol vaginal insert treatment group, and 3 in trial participants randomized to the placebo estradiol vaginal insert treatment group). Per protocol, endometrial polyps were categorized as benign, hyperplasia with atypia, hyperplasia without atypia, carcinomatous, or other. These participants were not excluded from trial participation.

At Week 12 in Trial TXV14-01, the following benign polyps were identified by at least two of the pathologists: one (1) in the 4 mcg estradiol vaginal insert treatment group [her polyp was present at screening (Number (b) (6))], and three (3) in the 25 mcg estradiol vaginal insert treatment group.

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

It is not uncommon to identify a benign endometrial polyp in an asymptomatic woman. We know, however, that endometrial polyps can indicate effect on the endometrium. Endometrial polyps are estrogen-sensitive and grow in response to circulating estrogen levels. The three polyps confirmed at the 25 mcg estradiol vaginal insert treatment group versus no polyps identified in the placebo vaginal insert treatment group in 12-week Trial TCV14-01 may represent a signal for estrogenic effect.

## 7.4 Supportive Safety Results

Refer to Subsection 7.3.5.1 for a discussion of safety of the endometrium with the use of estradiol vaginal inserts.

### 7.4.1 Common Adverse Events

An overview of AEs for the combined phase 2 Trial TXV13-01 and phase 3 Trial TXV14-01 is presented in Table 34.

Table 34: Overview of Adverse Events for Combined Phase 2 and Phase 3 Trials in the Safety Population – Presented as Number and Percentage

	<b>TX-004HR 4 mcg (N=191)</b>	<b>TX-004HR 10 mcg (N=215)</b>	<b>TX-004HR 25 mcg (N=190)</b>	<b>Placebo (N=218)</b>	<b>Total (N=814)</b>
Any woman with reported AE	113 (59.2)	115 (53.5)	107 (56.3)	127 (58.3)	462 (56.8)
Any woman with reported TEAE	97 (50.8)	104 (48.4)	93 (48.9)	114 (52.3)	408 (50.1)
Any woman with drug related TEAE <sup>a</sup>	38 (19.9)	37 (17.2)	34 (17.9)	49 (22.5)	158 (19.4)
Any woman with SAE	0 (0)	3 (1.4)	4 (2.1)	1 (0.5)	8 (1.0)
Any TEAE leading to discontinuation	2 (1.0)	3 (1.4)	4 (2.1)	6 (2.8)	15 (1.8)
Any woman with drug related TEAE leading to discontinuation	1 (0.5)	2 (0.9)	0 (0)	3 (1.4)	6 (0.7)

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 5 on page 16 of 80.

<sup>a</sup> Recorded by the investigator as “possibly related”, “probably related”, or “definitely related”.

#### **Clinical Reviewer’s Comments:**

The percentage of women reporting TEAEs are similar across all treatment groups. While SAEs occurred more frequently in the 10 mcg and 25 mcg estradiol vaginal insert treatment groups than in the 4 mcg or placebo vaginal insert treatment groups, this does not appear to represent a clear dose response.

Common TEAEs occurring in  $\geq 3$  percent of any treatment group are summarized in Table 35.

Table 35: Summary of Treatment-Emergent Adverse Events Occurring in  $\geq 3$  Percent in Any Treatment Group in the Safety Population

<b>System Organ Class Preferred Term</b>	<b>TX-004HR 4 mcg (N=191)</b>	<b>TX-004HR 10 mcg (N=215)</b>	<b>TX-004HR 25 mcg (N=190)</b>	<b>Placebo (N=218)</b>	<b>Total (N=814)</b>
Infections and infestations, n (%) - Nasopharyngitis	5 (2.6)	6 (2.8)	7 (3.7)	10 (4.6)	28 (3.4)

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- Urinary tract infection	5 (2.6)	5 (2.3)	8 (4.2)	4 (1.8)	22 (2.7)
Musculoskeletal and connective tissue disorders, n (%)					
- Back pain	9 (4.7)	1 (0.5)	4 (2.1)	8 (3.7)	22 (2.7)
Nervous system disorders, n (%)					
- Headaches	12 (6.3)	14 (6.5)	6 (3.2)	15 (6.0)	47 (5.8)
Reproductive system and breast disorders, n (%)					
- Vaginal discharge	5 (2.6)	7 (3.3)	4 (2.1)	13 (6.0)	29 (3.6)
- Vulvovaginal pruritus	4 (2.1)	4 (1.9)	7 (3.7)	10 (4.6)	25 (3.1)
Respiratory, thoracic, and mediastinal disorders, n (%)					
- Oropharyngeal pain	1 (0.5)	0 (0)	6 (3.2)	1 (0.5)	8 (1.0)

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 7 on page 17 of 80.

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

Reported TEAEs such as back pain, headache, vaginal discharge, and vulvovaginal pruritus are known to occur with estrogen products.

TEAEs were graded as mild, moderate and severe, and assessed as “not related”, “possibly related”, “probably related”, and “definitely related” by the clinical site investigators. Per the application, the majority of TEAEs in all treatment groups were assessed as “not related”. See Table 36.

Table 36: Investigator Assessment of Relationship of Treatment-Emergent Adverse Event to Trial Medications for Combined Phase 2 and Phase 3 Trials

Relationship to Trial Medication	TX-004HR 4 mcg (N=191)	TX-004HR 10 mcg (N=215)	TX-004HR 25 mcg (N=190)	Placebo (N=218)	Total (N=814)
None	59 (30.9)	67 (31.2)	59 (31.1)	65 (29.8)	250 (30.7)
Possible	29 (15.2)	24 (11.2)	21 (11.1)	37 (17.0)	111 (13.6)
Probable	9 (4.7)	12 (5.6)	13 (6.8)	12 (5.5)	46 (5.7)
Definitely	0 (0)	1 (0.5)	0 (0)	0 (0)	1 (0.1)

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 8 on page 18 of 80.

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

Per this application, there were numerically fewer women in the estradiol vaginal insert treatment groups assessed with drug-related TEAEs than in the placebo vaginal insert treatment group. This reported finding is unclear to this reviewer.

The most frequently treatment-related TEAEs (classified as “possible related” and “probably related”) observed in  $\geq 3$  percent of women in any treatment group are shown in Table 37.

Table 37: Drug Related Treatment-Emergent Adverse Events Occurring in ≥ 3 Percent of Any Treatment Group in the Safety Population

System Organ Class Preferred Term	TX-004HR 4 mcg (N=191)	TX-004HR 10 mcg (N=215)	TX-004HR 25 mcg (N=190)	Placebo (N=218)	Total (N=814)
Nervous system disorders, n (%)					
- Headache	7 (3.7)	5 (2.3)	3 (1.6)	6 (2.8)	21 (2.6)
Reproductive system and breast disorders, n (%)					
- Vaginal discharge	5 (2.6)	7 (3.3)	4 (2.1)	12 (5.5)	28 (3.4)
- Vulvovaginal pruritus	2 (1.0)	4 (1.9)	5 (2.6)	8 (3.7)	19 (2.3)

Source: Adapted from NDA 208564, Integrated Summary of Safety, Table 9 on page 18 of 80.

**Clinical Reviewer’s Comments:**

As shown in Table 37, drug-related headaches occurred numerically more frequently in the lowest 4 mcg estradiol vaginal insert treatment group compared to the placebo vaginal insert treatment group and the higher (10 mcg and 25 mcg) estradiol vaginal inserts. Vaginal discharge and vulvovaginal pruritus, however, occurred more frequently in women in the placebo estradiol vaginal insert treatment group, possible related to an improvement in the vaginal maturation index and vaginal pH in the active treatment groups demonstrated in this NDA application.

7.4.2 Laboratory Findings

Samples for clinical laboratory measurements (hematology, chemistry, and urinalysis) were obtained at Screening and Week 12 in 12-week Trial TXV14-01, but only at Screening in 15-day Trial TXV13-01. Therefore, no integration of laboratory measurements was included in the NDA application. Per the application, no clinically relevant changes in laboratory measurements requiring treatment were evident in Trial TXV13-01.

Each clinical laboratory parameter for the Safety population in Trial TXV14-01 was summarized using descriptive statistics (including mean and SD, median, minimum, and maximum) for each time point and change from Baseline. Shifts in laboratory values and potentially clinically important (PCI) findings are summarized in the application.

Three (3) hematology-related TEAEs were reported:

- Number (b) (6) in the placebo vaginal insert treatment group = anemia
- Number (b) (6) in the placebo vaginal insert treatment group = decreased platelet count
- Number (b) (6) in the 25 mcg estradiol vaginal insert treatment group = eosinophilia

One (1) placebo-treated woman had a worsening of her pre-existing dyslipidemia that the investigator assessed as mild and not related to trial medication.

**Clinical Reviewer's Comments:**

No safety issues are raised, as a result of these reported changes in laboratory measurements, following 12-weeks of drug exposure in Trial TXV14-01.

#### 7.4.3 Vital Signs

There were four (4) reports of increased blood pressure during Trials TXV13-01 [Number (b) (6) in the active treatment group (10 mcg estradiol vaginal insert, assessed as mild in severity and possibly related)] and TXV14-01 [Number (b) (6) (4 mcg estradiol vaginal insert, assessed as mild in severity and possibly related), Number (b) (6) (10 mcg estradiol vaginal insert, assessed as mild in severity and not related), and Number (b) (6) (placebo vaginal insert, assessed as mild in severity and possibly related)].

Two (2) additional trial participants in Trial TXV14-01 developed hypertension, both in the 4 mcg estradiol vaginal insert treatment group, both considered mild in severity by the investigator.

**Clinical Reviewer's Comments:**

No safety issues are raised from these reports of increased blood pressure/hypertension in 12-week Trial TXV14-01.

#### 7.4.4 Electrocardiograms (ECGs)

ECG assessments were performed in 12-week Trial TXV14-01 at Baseline and Week 12/End-of-Treatment.

There were two ECG findings at Week 12 reported as abnormal - clinically significant:

- Number (b) (6) in the placebo vaginal insert treatment group had a reported abnormal, not clinically significant, finding at Screening. Her End-of-Treatment ECG on trial Day 92 was also reported as abnormal. A repeat ECG by her cardiologist was reported as within normal limits.
- Number (b) (6) in the 25 mcg estradiol vaginal insert treatment had a history of QT<sub>c</sub> ranges from 510-540 ms with bifascicular block at Screening. Her case is discussed in Subsection 7.3.2 Nonfatal Serious Adverse Events in this review.

#### 7.4.5 Special Safety Studies/Clinical Trials

Refer to Subsection 7.3.5.1 for a discussion of safety of the endometrium with the use of estradiol vaginal inserts.

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### 7.4.6 Immunogenicity

No human immunogenicity studies were submitted in the NDA application.

## 7.5 Other Safety Explorations

### 7.5.1 Dose Dependency for Adverse Events

No clear dose response for adverse effects was observed across the 4 mcg, 10 mcg, and 25 mcg estradiol vaginal insert treatment groups. Differences in certain reported AEs related to dose were observed as follows:

- At Week 12 end-of-trial endometrial biopsies in Trial TXV14-01, two cases of proliferative endometrium were reported in the 25 mcg estradiol vaginal insert treatment group as compared to no cases of proliferative endometrium in the placebo vaginal insert treatment group
- At Week 12 end-of-trial endometrial biopsies in Trial TXV14-01, one case of disordered proliferative endometrium was reported in the 10 mcg estradiol vaginal insert treatment group as compared to no cases of disordered proliferative endometrium in the placebo vaginal insert treatment group.
- At Week 12 end-of-trial endometrial biopsies in Trial TXV14-01, four benign endometrial polyps were reported [one in the 4 mcg estradiol vaginal insert treatment group (also evident in the Screening endometrial biopsy), and three in the 25 mcg estradiol vaginal insert treatment group] as compared to no polyps in the placebo vaginal insert treatment group.

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

As previously stated, the three reported cases of proliferative endometrium in a 12-week clinical trial of estrogen-alone exposure in a woman with a uterus are both unexpected and concerning to this reviewer. No long-term safety data is available in the application to determine if continued drug exposure (for example, at least 12-months of general and endometrial safety data) would alter these findings reported at 12-weeks of drug exposure. This applicant needs to provide long-term general and endometrial safety data and chronic use exposure data to address this reviewer's concerns before any decision can be reached regarding approval of the 4 mcg, 10 mcg, (b) (4) estradiol vaginal insert for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

### 7.5.2 Time Dependency for Adverse Events

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A single 12-week clinical trial is submitted in this application. This 12-week drug exposure interval is inadequate to fully assess time dependency of adverse events for this potential chronically-administered product.

### 7.5.3 Drug-Demographic Interactions

No other pharmacokinetic studies have been conducted with TX-004HR estradiol vaginal inserts.

See Subsection 7.1.7 Subpopulations for subgroup analyses based on age and BMI.

### 7.5.4 Drug-Disease Interactions

No other pharmacokinetic studies have been conducted with TX-004HR estradiol vaginal inserts.

### 7.5.5 Drug-Drug Interactions

No pharmacodynamic drug interaction studies have been conducted with TX-004HR estradiol vaginal inserts.

Per the Clinical Pharmacology Review, dated April 7, 2017, “There is no potential for drug-food interaction as the drug product is proposed for vaginal administration. However, there is a potential for local drug-drug interaction (DDI) in the vaginal space (e.g., the presence of active/inactive ingredients from a second vaginally applied product may alter the release and absorption potential of estradiol). The Applicant did not conduct drug interaction studies with commonly use vaginal products such as antifungals. This type of assessment is important in determining if an interaction between estradiol/inactive ingredients from TX-004HR and active/inactive ingredients from other vaginal products within the vaginal space can affect systemic estrogen exposure and potentially impacting safety.”

#### **Clinical Reviewer’s Comments:**

On April 27, 2017, Clinical Pharmacology ultimately determined that no DDI studies would be required for this drug product.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

The applicant did not conduct a long-term general and endometrial safety trial (with duration greater than a year) that would be necessary to determine the risks of endometrial cancer and other malignant neoplasms caused or promoted by the use of unopposed estrogens. See Subsection 7.3.5.1 Endometrial Safety.

### 7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported during the TX-004HR estradiol vaginal insert development program.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The TX-004HR development program addresses an indication which is applicable only to postmenopausal women.

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdose, drug abuse, withdrawal or rebound potential was demonstrated in the application.

## 7.7 Additional Submissions / Safety Issues

See Subsections 7.2.6 and 7.3.5.1 for discussions of the importance of evaluation of the endometrium for the class of estrogen-alone products and this proposed indication.

## 8 Postmarket Experience

There is no postmarketing data for [REDACTED] (estradiol vaginal insert).

## 9 Appendices

### 9.1 Literature Review/References

For all summary documents (nonclinical and clinical), numerous literature references are included in the application. These literature references could be accessed through hyperlinks provided in the summary documents or from the list of references at the end of the application.

### 9.2 Labeling Recommendations

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This reviewer recommends that this application receive a Complete Response action due to the absence of long-term general and endometrial safety data and chronic use drug exposure data in the NDA application.

No labeling recommendations will be provided to the applicant.

### 9.3 Advisory Committee Meeting

No Advisory Committee was conducted for NDA 208564.

### 9.4 Table of Currently Available Treatments for a Non-Specific VVA Indication

Estrogen-Alone Products Approved for the Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

<b>Oral Estrogen-Alone Products</b>	<b>Available Dosage Strengths</b>
Cenestin® (synthetic conjugated estrogens, A)	0.3 mg once daily
Menest® (esterified estrogens)	0.3 mg, 0.625 mg, 1.25 mg, or 2.5 mg once daily
Ogen (estropipate)	0.625 mg, 1.25 mg, or 2.5 mg once daily
Premarin® (conjugated estrogens) Tablets	0.3 mg, 0.45 mg, 0.625 mg, 0.9 m, or 1.25 mg once daily
Various Generics (estradiol) Tablets	0.5 mg, 1.0 mg, 2.0 mg
<b>Transdermal Products</b>	<b>Available Dosage Strengths</b>
Alora® (estradiol matrix patch)	0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
Climara® (estradiol matrix patch)	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied once weekly
Estraderm® (estradiol reservoir patch)	0.05 mg or 0.1 mg; patch applied twice weekly
VivelleDot® (estradiol matrix patch)	0.0375 mg, 0.05 mg, 0.075 mg, or 0.1 mg; patch applied twice weekly
(b) (4)	(b) (4)
Various Generics (estradiol matrix patch)	0.05 mg or 0.1 mg; patch applied once or twice weekly
<b>Topical Products</b>	<b>Available Dosage Strengths</b>
EstroGel® 0.06% (estradiol gel)	1.25 grams containing 0.75 mg estradiol applied once daily
<b>Vaginal Cream</b>	<b>Available Dosage Strengths</b>
Estrace (estradiol) Vaginal Cream	2 to 4 grams (0.1 mg per gram) inserted intravaginal daily for 1 to 2 weeks, then 1 gram inserted intravaginal daily thereafter
Premarin® (conjugated estrogens) Vaginal Cream	0.5 to 2 grams (0.625 mg per gram) inserted intravaginal daily
<b>Vaginal Rings</b>	<b>Available Dosage Strengths</b>
Estring® (estradiol)	Release of 7.5 mcg estradiol; ring worn for 90 days
Femring® (estradiol acetate)	Release of 0.05 mg estradiol or 0.10 mg estradiol;

	ring worn for 90 days
<b>Vaginal Tablet</b>	<b>Available Dosage Strengths</b>
Vagifem® (estradiol hemihydrate)	10 mcg vaginal tablet inserted daily for 2 weeks, then inserted twice weekly

### Estrogen Plus Progestin Products Approved for the Treatment of Moderate to Severe Symptoms of Vulvar and Vaginal Atrophy due to Menopause

<b>Oral Estrogen Plus Progestin Products</b>	<b>Available Dosage Strengths</b>
Angeliq® (drospirenone [DRSP] plus estradiol estradiol [E2])	0.25 mg DRSP plus 0.5 mcg E2 taken daily or 0.5 mg DRSP plus 1 mg E2 taken daily
Prefest® (estradiol [E2] plus norgestimate)	1 mg E2 taken daily for 3 days, then 1 mg E2 plus 0.09 mg norgestimate taken daily for 3 days, repeated continuously
Premphase® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.625 mg CE taken daily for 14 days, then 0.625 mg CE plus 5.0 mg MPA taken daily on days 15-18
Prempro® (conjugated estrogens [CE] plus medroxyprogesterone acetate [MPA])	0.3 mg or 0.45 mg CE plus 1.5 mg MPA taken daily or 0.625 mg CE plus 2.5 mg or 5.0 mg MPA taken daily
<b>Transdermal Estrogen Plus Progestin Products</b>	<b>Available Dosage Strengths</b>
CombiPatch® (estradiol [E2] plus norethindrone Acetate [NETA])	Release of 0.05 mg E2 plus 0.14 mg NETA; patch applied twice weekly or 0.05 mg E2 plus 0.25 mg NETA; patch applied twice weekly

## 9.5 Individual Studies Not Reviewed for Efficacy

### 9.5.1 Phase 2 Trial TXV13-01

#### 9.5.1.1 Objectives

**Primary:**

The primary objectives of Trial TXV13-01 with 10 mcg TX-004HR (estradiol vaginal insert) (hereafter referred to as 10 mcg estradiol vaginal insert) was to:

- Evaluate the efficacy of 10 mcg estradiol vaginal insert in reducing severity of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause after 14 days of treatment, and to estimate the effect size and variability of vulvar and vaginal atrophy endpoints.
- Investigate the safety of 10 mcg estradiol vaginal insert in treating moderate to severe symptoms of vaginal atrophy associated with menopause.
- Investigate the systemic exposure to estradiol from single and multiple doses of 10 mcg estradiol vaginal insert.

**Secondary:**

The secondary objective of Trial TXV13-01 was to use the results to design a phase 3 trial with TherapeuticsMD estradiol vaginal insert formulation.

### 9.5.1.2 Enrollment Criteria

#### **Inclusion Criteria:**

To participate in the trial, a woman **MUST** have met the following criteria:

- 6 Female between 40 and 75 of age at time of randomization who is will to participate in the trial as documented by signing the Informed Consent Form.
- 7 Be postmenopausal defined as:
  - At least 12 months of spontaneous amenorrhea, or
  - 12 month post bilateral oophorectomy, with or without hysterectomy
- 8 Met all evaluation requirements:
  - $\leq 5\%$  superficial cells on a vaginal smear cytology
  - Vaginal pH  $> 5.0$
  - Estradiol level  $\leq 50$  pg/mL
  - At least one self-assessed moderate to severe symptom of VVA identified by the woman as being most bothersome to her:
    - Vaginal dryness
    - Vaginal pain associated with sexual activity
    - Vaginal and/or vulvar irritation/itching
    - Dysuria
    - Vaginal bleeding associated with sexual activity (absence vs, presence)
- 9 Have a Body Mass Index (BMI) less than or equal to  $34 \text{ kg.m}^2$ .
- 10 Be willing to abstain from using products (other than trial medication) that contain estrogen throughout trial participation.
- 11 Be judged by the investigator/subinvestigator as being in generally good health based on medical evaluation performed within 28 days prior to initial dose of trial medication.
- 12 Be willing to abstain from sexual activity and use of vaginal douching within 24 hours prior to screening and Visit 3 vaginal pH measurements.

#### **Exclusion Criteria:**

To participate in the trial, a woman must **NOT**:

1. Be hospitalized, have a contraindication to blood collection, estrogen therapy, or use 15 or more cigarettes per day.
2. Have a history of any of the following: deep vein thrombosis, thromboembolic disorder, coronary artery or cerebrovascular disease, liver or kidney dysfunction or disorder, gallbladder dysfunction or disorder, diabetes, thyroid disease or other endocrinological disease, estrogen-dependent neoplasia, atypical ductal hyperplasia of the breast, undiagnosed vaginal bleeding, vaginal infection requiring treatment, endometrial hyperplasia or uterine/endometrial, breast or ovarian cancer, other malignancy within the last 5 years, drug and/or alcohol abuse within 1 year of start of trial.
3. Have used estrogen alone or estrogen plus progestin within any of the time periods recommended in the Agency's 2003 clinical evaluation Guidance for

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Industry or any over-the-counter product that would be expected to interact with estradiol.

4. Have participated in a clinical trial with 30 days prior to screening.

### **Allowed and excluded Medications:**

Medications necessary for the woman's well-being were allowed during the trial with the following exceptions: estrogen hormone therapy, progestogen medication, vaginal lubricants and moisturizers within 14 days prior to screening, sexual activity and vaginal douching within 24 hours prior to scheduled vaginal pH measurements.

### 9.5.1.3 Trial Design and Conduct

Trial TXV13-01 entitled: "A Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of TX-004HR in Postmenopausal Women with Symptoms of Vulvar and Vaginal Atrophy" was a phase 2, randomized, double-blind, placebo-controlled, single center (Dr. John Hill, Avail Clinical Research LLC, DeLand, FL 32750) trial assessing the efficacy and safety of 10 mcg estradiol vaginal insert in treating moderate to severe symptoms of VVA associated with menopause after 14 days of treatment. The first trial participant was enrolled on July 31, 2013. The last trial participant completed the trial on September 5, 2013. Clinic visits occurred at Screening (up to -28 days), Day 1 (Randomization/Baseline), Day 8, and Day 15 (End-of-Trial).

This trial enrolled 50 postmenopausal women (24 to the 10 mcg estradiol vaginal insert treatment group and 26 to the placebo vaginal insert treatment group), 40 to 75 years of age, who met the trial entry criteria for VVA at Baseline. Efficacy measures included change from Baseline (Screening) to Day 15 in:

- the percentage of vaginal superficial cells compared to placebo,
- the percentage of vaginal parabasal cells compared to placebo,
- vaginal pH compared to placebo,
- severity of the most bothersome VVA symptom identified by the subject at Baseline (vaginal dryness; dyspareunia; vaginal and/or vulvar irritation or itching; dysuria) compared to placebo,
- vaginal bleeding associated with sexual activity compared to placebo (presence or absence), and
- investigator's assessment of the vaginal mucosa compared to placebo.

### 9.5.1.4 Assessment of Efficacy

#### **Primary Efficacy Endpoints:**

Trial TXV13-01 endpoints Include:

- Change from Baseline (Screening) to Day 15 in the maturation index (superficial and parabasal vaginal cells) of the vaginal smear
- Change from Baseline (Screening) to Day 15 in vaginal pH

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- Change from Baseline (Randomization) to Day 15 in severity of the most bothersome VVA symptom (vaginal dryness, vaginal pain associated with sexual activity, vaginal and/or vulvar irritation and itching, dysuria)
- Change from baseline (Randomization) to Day 15 in vaginal bleeding associated with sexual activity
- Change from Baseline (Randomization) to Day 15 in the investigator's assessment of the vaginal mucosa.

### 9.5.1.5 Assessment of Safety

Throughout the clinical trial vital signs, physical examination, pelvic (including vaginal cytology and vaginal pH, Pap smear if one was not conducted within last 12 months) and breast examination, mammogram (if one was not performed within previous 9 months with negative/normal results), and clinical laboratory tests (blood chemistry, hematology, estradiol hormone levels, urinalysis) were performed. The investigator rated the vaginal mucosal appearance at Day 1 and Day 15 (vaginal secretions, vaginal color, vaginal epithelial integrity, and vaginal epithelial surface thickness). Adverse events (AEs) were recorded for safety evaluation according to acceptable criteria and then coded into system organ class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

In this clinical trial, an assessment of insert disintegration state in the vagina (presence or absence) was performed on Day 1 (6 hours after dosing) and on Day 15 (last clinic visit) by the investigator.

### 9.5.1.6 Statistical Methodology

ANOVA was used to evaluate differences between trial participants receiving 10 mcg estradiol vaginal insert and placebo vaginal inserts for all efficacy endpoints, except for vaginal bleeding associated with sexual activity. The change from Baseline was correlated with the Baseline value ( $p < 0.05$ ), so Baseline was included as a covariate for all vaginal atrophy symptoms, except the severity of the most bothersome symptom. The 90% confidence intervals on the differences between the 10 mcg estradiol vaginal insert and placebo vaginal insert endpoint means were determined to evaluate the effect size. The change from Baseline in vaginal bleeding with sexual activity was evaluated in terms of treatment success or failure using Fisher's exact test. No adjustments were made for multiplicity of endpoints.

No formal statistical evaluations of safety data were conducted. The frequency and severity of all AEs were summarized descriptively by treatment group.

For the purpose of monitoring estradiol concentrations during the trial, blood samples were collected at 0, 1.0, 3.0, and 6.0 hours relative to dosing on Day 1, on Day 8

(before the morning dose), and on Day 15 more than 24 hours after final drug product administration.

**Clinical Reviewer's Comments:**

Per the application, erratic patterns and fluctuations in estradiol concentrations for numerous trial participants were reported. In addition, results from reanalysis of specimens produced vastly different results from the original analysis (> 30%) confirming the "lack of validity of the bioanalytical method used." In addition, approximately 40% of the samples failed to meet assay acceptance criteria during the reanalysis. The applicant considers the estradiol concentrations values obtained during this trial "invalid" and therefore, no pharmacokinetic or statistical analysis for estradiol concentrations was conducted.

9.5.1.7 Results

***Demographics:***

Fifty (50) women were enrolled in Trial TXV13-01. The mean age was 62.3 years with a range of 46 to 75 years old. The mean weight (kg) was 71.2 with a range of 44.5 to 100, and a mean BMI (kg.m<sup>2</sup>) of 26.8 with a range of 19 to 33. Approximately ninety-one percent (91.7%) of trial participants were White, 3 (6.3%) were Black, and 1 (2.1%) was Asian.

**Clinical Reviewer's Comments:**

The baseline characteristics of the postmenopausal women enrolled in this clinical trial in the two treatment groups (10 mcg estradiol vaginal insert and placebo vaginal insert) were similar. See Table 6 in the Clinical Trial Report for details.

***Disposition of Participating Women:***

Forty-eight (48) of the 50 women enrolled completed the trial. Two (2) enrolled women in the placebo treatment group (trial participant Number (b) (6) and trial participant Number (b) (6)) discontinued trial drug on Day 7 and Day 8, respectively.

***Primary Efficacy Analyses:***

Per the application, two-week treatment with 10 mcg estradiol vaginal insert led to a statistically significant greater mean increase in vaginal superficial epithelial cells than did placebo (35% compared to 9%, respectively; p=0.0002), a statistically significant greater mean decrease in vaginal parabasal epithelial cells than did placebo (54% compared to 5%, respectively; p<0.0001), and a statistically significant reduction in vaginal pH than did placebo (0.97 units compared to 0.34 units, respectively; p=0.0002). However, the decrease in severity of the most bothersome symptom self-identified at Baseline was essentially the same for both 10 mcg estradiol vaginal insert and placebo vaginal insert (-1.043 compared to -1.042, respectively; p=0.9951). These results are shown in the following composite Table 38.

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Table 38: Primary Efficacy Analysis Results of Change from Baseline\* Least-squares Mean in Vaginal Superficial Cells, Vaginal Parabasal Cells, Vaginal pH, and Most Bothersome Vaginal Symptom in Trial TXV13-01

Endpoint	Estradiol Vaginal Insert 10 mcg (N=24)	Placebo Vaginal Insert (N=24)	Difference Between Treatment Means	90% CI for Difference	P-value
Superficial Cells	35.2	8.8	26.5	(15.4, 37.6) <sup>a</sup>	0.0002 <sup>b</sup>
Parabasal Cells	-54.4	-4.8	-49.6	(-60.4, -38.8) <sup>c</sup>	<0.0001 <sup>d</sup>
Vaginal pH	-0.97	-0.34	-0.64	(-0.90, -0.37) <sup>a</sup>	0.0002 <sup>b</sup>
Most Bothersome Symptom	-1.043	-1.042	-0.002	(-0.497, 0.493) <sup>c</sup>	0.9951 <sup>d</sup>

Source: Adapted from NDA 208564, Clinical Trial Report for Trial TXV13-01, Table 7 on page 51 of 84, Table 8 on page 51 of 84, Table 10 on page 52 of 84, and Table 11 on page 53 of 84.

\*Baseline for superficial, and parabasal cells and vaginal pH was Screening and for Most Bothersome Symptom was Randomization.

<sup>a</sup> Confidence interval for 10 mcg estradiol vaginal insert – placebo vaginal insert from ANCOVA with treatment as a fixed effect and baseline as a covariate.

<sup>b</sup> Change from baseline P-value for treatment comparison from ANCOVA with treatment as a fixed effect and baseline as a covariate

<sup>c</sup> Confidence interval for 10 mcg estradiol vaginal insert – placebo vaginal insert from ANCOVA with treatment as a fixed effect.

<sup>d</sup> Change from baseline P-value for treatment comparison from ANCOVA with treatment as a fixed effect. P-value <0.05 indicates a statistically significant difference.

**Clinical Reviewer’s Comments:**

As shown in the above table, the 10 mcg estradiol vaginal insert was statistically different compared with the placebo vaginal insert in the increase in superficial epithelial cells and the decrease in parabasal cells on a vaginal smear, and in the reduction of vaginal pH at Day 15. This is not unexpected for these objective evaluations at this dosage strength of estradiol. Table 38 shows, however, that at Day 15 the 10 mcg estradiol vaginal insert did not have an effect on the most bothersome vaginal atrophy symptom identified at Baseline (p=.9951). This too is not unexpected due to the small sample size (total of 50 participants) and the short duration of treatment (14 days). Trial TXV13-01 is not considered supportive of efficacy in this application, but is considered supportive of safety.

The change from Baseline to Day 15 for the investigator’s assessment of the vaginal mucosa is shown in Table 39.

Table 39: Primary Efficacy Analysis Results of Change from Baseline\* Least-squares Mean in Investigator’s Assessment of the Vaginal Mucosa

Endpoint	Estradiol Vaginal Insert 10 mcg (N=24)	Placebo Vaginal Insert (N=24)	Difference Between Treatment Means	90% CI for Difference	P-value <sup>a</sup>
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Vaginal color <sup>b</sup>	-0.199	-0.009	-0.91	(-0.434, 0.052)	0.1945
Vaginal epithelial integrity	-0.342	0.176	-0.518	(-0.726, -0.311) <sup>c</sup>	0.0001
Vaginal epithelial surface thickness	-0.034	-0.133	0.099	(-0.024, 0.221) <sup>c</sup>	0.1820
Vaginal secretions	-0.643	-0.274	-0.369	(-0.661, -0.076) <sup>c</sup>	0.0401

Source: Adapted from NDA 208564, Clinical Trial Report for Trial TXV13-01, Table 14 on page 56 of 84, Table 15 on page 56 of 84, Table 16 on page 57 of 84, and Table 18 on page 57 of 84.

\*Baseline as defined as Randomization.

<sup>a</sup> Change from baseline p-value for treatment comparison from ANCOVA with treatment as a fixed effect and baseline as a covariate. P=value < 0.05 indicates a statistically significant difference.

<sup>b</sup> Least-squares means and confidence interval for 10 mcg estradiol vaginal insert – placebo vaginal insert difference from ANCOVA with treatment as a fixed effect and baseline as a covariate.

<sup>c</sup> Confidence interval for 10 mcg estradiol vaginal insert – placebo vaginal insert from ANCOVA with treatment as a fixed effect and baseline as a covariate.

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

Although evaluated as a primary efficacy endpoints per protocol, the investigator assessment of signs of vaginal atrophy is not considered in the determination of the efficacy of a drug product to treat moderate to severe vaginal atrophy due to menopause.

One additional analysis reported the results of the investigator's assessment of insert disintegration on Day 1 (6 hours post-dose) and on Day 15. See Table 40.

Table 40: Summary Table of Insert Disintegration State in the Vagina on Day 1 and Day 15

	10 mcg Estradiol Vaginal Insert (n=24)		Placebo Vaginal Insert (N=26)	
	Day 1	Day 15	Day 1	Day 15
No evidence of insert present	23 (95.8%)	24 (100%)	26 (100%)	24 (92.3%)
Evidence of insert present	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Assessment not done	1 (4.2%)	0 (0%)	0 (0%)	2 (7.7%)

Source: Adapted for NDA 208564, Clinical Trial Report for Trial TXV13-01, Table 18 on page 58 of 84.

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

These results report no visual evidence of the insert (either whole or partial) at 6 hours post-dose in the majority of investigator evaluations on Day 1 and again on Day 15.

See Section 7 Safety of this review for a full discussion of the safety information generated in Trial TXV13-01.

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/s/  
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THERESA H VAN DER VLUGT  
04/28/2017

SHELLEY R SLAUGHTER  
04/28/2017  
I concur.