

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208564Orig1s000

OTHER REVIEW(S)

OSE DUE DATE: 02/28/2018

PDUFA GOAL DATE: 05/29/2018

(remove date statements above before entering in DARRTS)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 4, 2018
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products
Application Type and Number:	NDA 208564
Product Name and Strength:	Imvexxy ^a (estradiol vaginal insert) 4 mcg and 10 mcg
Product Type:	Single ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	TherapeuticsMD, Inc
Submission Date:	November 29, 2017
OSE RCM #:	2017-2558
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
DMEPA Team Leader:	Lolita White, PharmD

^a The proposed proprietary name, Imvexxy, is currently under review

1 REASON FOR REVIEW

As part of the approval process, the Division of Bone, Reproductive, and Urologic Products (DBRUP) requested we evaluate the proposed blister card insert labeling, blister carton labeling, professional sample blister carton, professional sample blister cards and Prescribing Information (PI) for Imvexxy (estradiol vaginal inserts), NDA 208564 for their vulnerability to medication errors. TherapeuticsMD, Inc submitted labels and labeling in their resubmission after Complete Response (CR).^b

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C N/A
ISMP Newsletters	D N/A
FDA Adverse Event Reporting System (FAERS)*	E N/A
Other	F N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed labels and labeling for risk of medication error.

Our review of the labels and labeling notes that the Sponsor refers to the dosage form “vaginal insert,” (b) (4) and (b) (4) inconsistently however the approved USP dosage form is vaginal insert. We defer to the Office of Pharmaceutical Quality (OPQ) to address this issue of wrong dosage form designation throughout the labels and labeling.

Our review of the graphics and administration instructions in the labeling notes the product is similar to most oral dosage forms (e.g. tablets, capsules) and is not co-packaged with an applicator. As such, we are concerned this product may be taken orally and contribute to wrong route medication errors. In a previous review,^c we considered the risk of the vaginal insert to be

^b Complete Response (CR) letter was issued on May 5, 2017.

^c Baugh, D. Review of Use Related Risk Analysis for Estradiol Vaginal Inserts. Silver Spring (MD), Food and Drug Administration, Center for Drug Evaluation Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US). 2017 Apr 27. RCM No.: 2017-783.

administered orally and determined that this product poses no greater risk than other estrogen products if ingested in excess. We also found the proposed labeling and graphics adequate to mitigate this risk of wrong route administration errors. We have no further concerns.

In addition, our review of the proposed Prescribing Information (PI), carton labeling, blister card insert labeling, and professional samples labeling identified the following areas that may contribute to medication errors:

Full Prescribing Information (PI)

- A. Section 2, Dosage and Administration, uses the phrase (b) (4) which is inconsistent with the Division of Medical Policy Program (DMPP) recommendations.
- B. The patient information section of the PI can be improved to clearly indicate how many days apart each dose should be administered during the maintenance phase. We are concerned this lack of specific dosing instructions may lead to administration on two consecutive days in the same week.
- C. The patient information section of the PI does not indicate what users should do if they miss a dose.

Blister Carton Labeling, Blister Card Insert Labeling, Professional Sample Carton Labeling, and Professional Sample Blister Labeling:

- D. The statement of strength per vaginal insert is not prominently displayed, which may lead to strength selection or dosing errors.
- E. The identified expiration date format can be improved to minimize confusion.
- F. As currently presented, the statements of strength are not adequately differentiated. We are concerned this inadequate differentiation may contribute to strength selection errors.
- G. The product code in the NDC number for the 4 mcg strength (b) (4) is sequential to the product code in the NDC number for 10 mcg strength (b) (4) and are not adequately differentiated.

Blister Carton Labeling (commercial configuration)

- H. As currently presented, the linear barcode on the Imvexxy (estradiol vaginal inserts) carton appears that it will be folded under and not immediately visible on the outside of the carton in accordance with 21CFR 201.25(c)(2) and section 201(k) of the FD&C Act (21 U.S.C. 321(k)).

Maintenance Blister Carton Labeling (commercial configuration and professional sample)

- I. The blister carton labeling can be improved to remind the user what days each dose will be administered during the maintenance phase.

Blister Card Insert Labeling (commercial configuration)

- J. The insertion instructions use terminology that may not be readily understood by users and contribute to administration medication errors.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 to help minimize the potential for medication errors to occur with the use of the product.

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the proposed blister card insert labeling, blister carton labeling, professional sample blister carton, professional sample blisters and Prescribing Information (PI) labeling where important product identifier information should be added or information should be revised to support the safe use of this product. See our recommendations in Section 4.1 for the Division and in Section 4.2 for TherapeuticsMD, Inc below.

4.1 RECOMMENDATIONS FOR THE DIVISION

- A. The administration frequency [REDACTED] (b) (4) is used in section 2, Dosage and Administration of the PI and throughout the labeling. We recommend you consider revising [REDACTED] (b) (4) to “two times every week,” throughout the labeling which is preferred term for this administration frequency and is consistent with the Division of Medical Policy Program (DMPP) recommendations.
- B. Section 2.1 Treatment of Moderate to Severe Dyspareunia, a Symptom of Vulvar and Vaginal Atrophy, Due to Menopause of the full PI can be improved to clearly communicate that the insert should not be inserted on consecutive days during the maintenance phase. We are concerned the lack of dosing instructions may lead to inconsistent administration or administration on two consecutive days in the same week. Consider adding the phrase “every three to four days” prior to the cited example in the PI of “(for example, Monday and Thursday).”
- C. The patient information section of the PI does not indicate what users should do if they miss a dose. Without instructions that address missed doses, we are concerned for risk of overdose or dose omission medication errors. Consider adding a statement to the Patient Information to address what users should do if they miss a dose.

4.2 RECOMMENDATIONS FOR THERAPEUTICSMD, INC

Prior to approval of this NDA, we recommend implementation of the following:

Blister Carton Labeling, Blister Card Insert Labeling, Professional Sample Carton Labeling, and Professional Sample Blister Labeling:

- A. The statement of strength (i.e., 4 mcg, 10 mcg) per vaginal insert is not prominently displayed and may lead to strength selection or dosing errors. Revise the statement of strength on the principal display panel (PDP) and professional sample blister cards to read “xx mcg per insert” to mitigate the risk of strength selection or dosing errors.
- B. The expiration date format you propose (b) (4) can be improved. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format like either
DDMMYYYY (e.g., 31JAN2013)
MMYYYY (e.g., JAN2013)
YYYY-MM-DD (e.g., 2013-JAN-31)
YYYY-MM-DD (e.g., 2013-01-31)
- C. The statements of strength appear similar and can be improved to better differentiate the two strengths and prevent strength selection errors. For example, we note the statement of strength for the 4 mcg and 10 mcg strengths is small and both strengths are presented in the same color font. We recommend you consider further differentiation of the two strengths in accordance with 21 CFR 201.15(a)(6), taking into account all pertinent factors including typography, layout, contrast, boxing, bolding, and other printing features. Furthermore, we recommend that the colors used to denote the statement of strength do not overlap with the carton trade dress.
- D. The product code in the NDC number for the 4 mcg strength (b) (4) is sequential to the product code in the NDC number for 10 mcg strength (b) (4). The similarity of the product code numbers has led to wrong drug, strength selection, and dispensing errors. The middle digits of the NDC number are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, the assignment of sequential numbers for the middle digits is not an effective differentiating feature. Revise the product code in the NDC numbers to ensure that the middle digits are not sequential numbers between the different strengths. If the middle digits cannot be revised, increase the prominence of the middle digits by increasing their size in comparison to the remaining digits in the NDC number and/or put them in bold type. For example: XXXX-**XXX**-XX.

Blister Carton labeling (commercial configuration)

- E. As currently presented, the linear barcode on the Imvexxy (estradiol vaginal inserts) commercial carton labeling appears that it will be folded under and not immediately visible on the outside of the carton. The drug barcode is often used as an additional verification before dispensing in the outpatient setting and before drug administration in the inpatient setting; therefore, it is an important safety feature that should be visible on the label whenever possible according to 21CFR 201.25(c)(2) and section 201(k) of the FD&C Act (21 U.S.C. 321(k)). We recommend that the linear and 2D barcodes on the carton labeling are visible on the outside of the cartons with adequate whitespace and presented in close proximity to each other to minimize confusion users may experience with multiple barcodes.

Maintenance Blister Carton Labeling (commercial configuration and professional sample)

- F. The carton labeling can be improved to remind the user what days each dose will be administered during the maintenance phase. We are concerned this lack of specific biweekly dosing instructions may lead to inconsistent administration or administration on two consecutive days in the same week. To mitigate this risk, we recommend you consider adding a statement to the carton labeling to instruct users to identify and write down their twice weekly administration days. Consider a phrase similar to, "Write down the days you will insert Imvexxy vaginal inserts: _____ and _____."

Blister Card Insert Labeling

- G. The insertion instructions advise the user to place the vaginal insert in the (b) (4) _____ We are concerned that this terminology may not be readily understood by users and contribute to administration medication errors. Therefore, we recommend that this language be revised to, _____ (b) (4) _____

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Imvexxy (estradiol vaginal inserts) that TherapeuticsMD, Inc submitted on November 29, 2017.

Table 2. Relevant Product Information for Imvexxy (estradiol) vaginal inserts	
Initial Approval Date	N/A
Active Ingredient	Estradiol
Indication	Treatment of moderate to severe dyspareunia due to menopause
Route of Administration	Vaginal
Dosage Form	Insert
Strength	4 mcg, 10 mcg
Dose and Frequency	One vaginal insert once daily for two weeks, then twice weekly thereafter
How Supplied	Imvexxy vaginal inserts are provided in opaque push-through blisters. One carton contains either 18 vaginal inserts (starter pack) or 8 vaginal inserts (maintenance pack).
Storage	20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).
Container Closure	Blister pack – Polybar – Aclar film with foil push through

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 2, 2018, we searched the L: drive and AIMS for previous DMEPA reviews using the terms, “Estradiol Vaginal” and “208564.”

B.2 Results

Our search identified two previous reviews.^{de} On April 5, 2017 DMEPA completed a label and labeling review for Estradiol Vaginal Inserts^d (OSE RCM #2016-1911). The review identified areas of the proposed label and labeling that could be revised for clarity.

RCM #	Type of Review	Summary of Recommendations	Comment
2016-1911	Labeling Review	Revise the dosage form from (b) (4) to read “vaginal insert” on all labels and labeling to reflect the acceptable dosage form for this estradiol product.	Our recommendations to revise the terminology to “vaginal insert” were not implemented consistently throughout all labels and labeling.
2016-1911	Labeling Review	There is insufficient differentiation between the strengths. We recommend avoiding the use of colors that overlap with or are similar to the trade dress as a designation of strength to decrease the risk of dispensing errors.	Although the trade dress carton label, and colors have been revised, there is still insufficient differentiation between strengths.
2016-1911	Labeling Review	We recommend you increase the prominence of the established name.	Our recommendations were implemented.
2016-1911	Labeling Review	We recommend you relocate the statement of strength to immediately follow the dosage form.	Our recommendations were implemented.

^d Baugh, D. Label, Labeling, and Packaging Review for Estradiol Vaginal Inserts. Silver Spring (MD), Food and Drug Administration, Center for Drug Evaluation Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US). 2017 Apr 05. RCM No.: 2016-1911.

^e Baugh, D. Review of Use Related Risk Analysis for Estradiol Vaginal Inserts. Silver Spring (MD), Food and Drug Administration, Center for Drug Evaluation Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US). 2017 Apr 27. RCM No.: 2017-783.

2016-1911	Labeling Review	We recommend you include drug-identifying information on the blister label and use a format similar to one of the following: MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g., JAN012019) for the expiration date.	Our recommendations were implemented.
-----------	-----------------	---	---------------------------------------

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following Imvexy (estradiol vaginal inserts) labels and labeling submitted by TherapeuticsMD, Inc on November 29, 2017.

- Starter blister carton labeling
- Starter blister card insert labeling
- Maintenance blister carton labeling
- Maintenance blister card insert labeling
- Professional sample carton labeling
- Professional sample blister card labeling
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images

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

^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

CELESTE A KARPOW
04/05/2018

LOLITA G WHITE
04/06/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 11, 2017

To: Hylton V Joffe, MD
Director
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Twanda Scales, RN, BSN, MSN/Ed.
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name (established name): YUVVEXY (estradiol)

Dosage Form and Route: vaginal (b) (4) capsules

Application Type/Number: NDA 208564

Applicant: TherapeuticsMD, Inc.

1 INTRODUCTION

On July 7, 2016 TherapeuticsMD, Inc. submitted for the Agency's review an Original New Drug Application (NDA) 208564 for estradiol vaginal (b) (4) capsules, 4 mcg, 10 mcg and (b) (4). The proposed tradename, YUVVEXY, was conditionally accepted by the Agency on February 10, 2016. YUVVEXY (estradiol) is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

On August 22, 2016 the Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for YUVVEXY (estradiol) vaginal (b) (4) capsules.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for YUVVEXY (estradiol) vaginal (b) (4) capsules.

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please let us know if you have any questions.

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

/s/

TWANDA D SCALES
04/11/2017

MARCIA B WILLIAMS
04/11/2017

LABEL, LABELING, AND PACKAGING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: April 5, 2017
Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products
Application Type and Number: NDA 208564
Product Name and Strength: Estradiol Vaginal Inserts
4 mcg, 10 mcg, (b) (4)
Product Type: Single Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: TherapeuticsMD, Inc.
Submission Date: October 11, 2016
OSE RCM #: 2016-1911
DMEPA Primary Reviewer: Denise V. Baugh, PharmD, BCPS
DMEPA Team Leader: Lolita White, PharmD

1 REASON FOR REVIEW

As part of the approval process, the Division of Bone, Reproductive, and Urologic Products (DBRUP) requested we evaluate the proposed blister label, carton labeling, and Prescribing Information (PI) for Estradiol vaginal inserts, NDA 208564 for their vulnerability to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed Prescribing Information (PI), blister label, and carton labeling identified the following areas that may contribute to medication errors:

- a. The carton labeling trade dress contains colors that overlap with colors used for expressions of strength and also the individual strengths can be better differentiated. We are concerned the overlap of colors decreases the differentiation between the strengths and may contribute to strength selection errors.
- b. The carton labeling and container label and the PI uses the dosage form designation (b) (4) This is not an acceptable dosage form for this product.
- c. The established name on the carton labeling lacks prominence commensurate with the proprietary name. We are concerned the lack of prominence may contribute to product selection error.
- d. The strength statement on the carton labeling is located away from the established name and dosage form. This presentation may contribute to strength selection errors.

- e. There is lack of drug-identifying information on the blister label. Specifically, the blister label lacks important product information (e.g. proprietary and established name; product strength; lot or control number; expiration date [per USP]; and the name of the manufacturer, packer, or distributor) in accordance with 21 CFR 201.10(i) and 21 CFR 201.17 .

4 CONCLUSION & RECOMMENDATIONS

We identified areas of the container label and carton labeling which can be revised for clarity and to support the safe use of this product. See our recommendations in Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

The PI labeling describes the dosage form as (b) (4). This is not the approved dosage form for the product which may lead to confusion. Revise the dosage form from (b) (4) to read “vaginal insert” on all labels and labeling to reflect the acceptable dosage form for this estradiol product.

4.2 RECOMMENDATIONS FOR THERAPEUTICSMD, INC

Prior to approval of this NDA, we recommend implementation of the following:

1. Carton Labeling

- a. There is insufficient differentiation between the strengths. This is because the colors used with the proprietary name and the logo ((b) (4)) are the primary colors used on the principal display panel and side panels. For example, the (b) (4) color used for the proprietary name is the same color used for the 4 mcg carton labeling. This use of color dilutes the impact of color differentiation and increases the risk for strength selection errors. The colors chosen should be unique to that strength and avoid overlap or similarity with the trade dress. Specifically, due to the prominence of pink, purple, and green throughout the trade dress, we recommend avoiding the use of these colors as a designation of strength to decrease the risk of dispensing errors.
- b. The dosage form is described as (b) (4). This is not the approved dosage form for the product. We recommend you revise the dosage form from (b) (4) to read “vaginal insert” on all label and labeling to reflect the acceptable dosage form for this product.
- c. The established name lacks prominence commensurate with the proprietary name. We recommend you increase the prominence of the established name taking into account all pertinent factors including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
- d. The statement of strength is located away from the dosage form. We are concerned this important product strength information may be overlooked and lead to medication dispensing errors. We recommend you relocate the

statement of strength to immediately follow the dosage form so it allows the reader immediate access to this information.

2. Blister label

- a. There is lack of drug-identifying information on the blister label in accordance with 21 CFR 201.10(i)(1) and per 21 CFR 201.17 . Specifically, the blister label lacks important product information (e.g. proprietary and established name; product strength; lot or control number; expiration date [per USP]; and the name of the manufacturer, packer, or distributor). Furthermore, to help minimize confusion with the expiration date presentation, we recommend that you use a format similar to one of the following: MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g., JAN012019)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for ‘Estradiol Vaginal Inserts’ that was submitted by Therapeutics MD, Inc. on October 11, 2016.

Table 2. Relevant Product Information for Estradiol Vaginal Inserts	
Initial Approval Date	N/A
Active Ingredient	estradiol
Indication	Treatment of moderate to severe dyspareunia due to menopause
Route of Administration	vaginal
Dosage Form	insert
Strength	4 mcg, 10 mcg, (b) (4)
Dose and Frequency	One vaginal insert once daily for 2 weeks, then twice weekly thereafter
How Supplied	One carton contains either 18 vaginal inserts or 8 vaginal inserts
Storage	20°C to 25°C (68°F to 77°F), excursions permitted to (15°C to 30°C) 59°F to 86°F; USP Controlled Room Temperature

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On April 3, 2017, we searched the L: drive and AIMS using the terms, “Estradiol Vaginal” and “208564” to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous reviews relevant to this review.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors, Failure Mode and Effects Analysis,^a and post-market medication error data, we reviewed the following ‘Estradiol vaginal inserts’ labels and labeling submitted by TherapeuticsMD, Inc on October 11, 2016.

- Blister Label
- Carton labeling
- Professional Sample Blister cards
- Professional Sample Carton Labeling
- Prescribing Information (PI)-no image

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

^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

DENISE V BAUGH
04/05/2017

LOLITA G WHITE
04/05/2017

Clinical Inspection Summary

Date	March 22 2017
From	Roy Blay, Ph.D., Reviewer, GCPAB\OSI Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI Susan D. Thompson, M.D., Team Leader, GCPAB\OSI for Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
To	DBRUP\Team Leader\Shelley Slaughter DBRUP\Medical Officer\Theresa van der Vlugt DBRUP\Project Manager\Kim Shiley
NDA/BLA #	NDA 208564
Applicant	TherapeuticsMD, Inc.
Drug	Yuvvexy (estradiol vaginal insert)
NME (Yes/No)	No
Therapeutic Classification	Standard Review
Proposed Indication(s)	Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.
Consultation Request Date	August 25, 2016
Summary Goal Date	April 2, 2017
Action Goal Date	May 5, 2017
PDUFA Date	May 7, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Koltun, Magloire, Portman, and Kroll were inspected in support of this NDA. The final classification of all of these inspections was No Action Indicated (NAI).

Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

2. BACKGROUND

The Applicant submitted this BLA to support the use of Yuvvexy in the treatment of moderate to severe dyspareunia, a symptom of vulvo-vaginal atrophy (VVA) due to menopause.

Protocol TXV14-01, entitled "A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Trial to Evaluate the Safety & Efficacy of TX-004HR in Postmenopausal Women with Moderate to Severe Symptoms of Vulvar & Vaginal Atrophy" was inspected in support of this application.

Protocol TXV14-01 was conducted at 89 sites (randomizing at least one subject) across the U.S. and Canada with a projected enrollment of 700 subjects.

According to the sponsor, the results of this study demonstrated that Yuvvexy at all three doses exhibited consistent efficacy for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy (VVA) due to menopause.

Protocol TXV14-01

The primary objective of this study was to assess the safety and efficacy of 3 doses of TX-004HR (4 µg, 10 µg, and 25 µg) 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) defined as the most bothersome symptom (MBS) associated with VVA.

This was a randomized, double blind, placebo controlled study comparing TX-004HR (4 µg, 10 µg, and 25 µg) with placebo in the treatment of moderate to severe dyspareunia, a symptom of VVA due to menopause. Subjects who met entry criteria were randomized in a 1:1:1:1 ratio to TX-004HR 4 µg, TX-004HR 10 µg, TX-004HR 25 µg, or matching placebo. The study period was 12 weeks with a 15 day follow-up period.

The four co-primary efficacy endpoints included the change from Baseline to Week 12 in the following:

- the percentage of vaginal superficial cells (by vaginal cytologic smear) compared to placebo
- the percentage of vaginal parabasal cells (by vaginal cytologic smear) compared to placebo
- vaginal pH as compared to placebo
- the severity of the MBS of dyspareunia associated with VVA as compared to placebo

Dr. Koltun's site was selected for inspection because two of the eight subjects in the 10 mcg estradiol vaginal insert treatment group (mITT population) enrolled at the site had major protocol deviations. Subject 019 used boron (trace mineral) for the entire trial duration. Boron is reported to help arthritis and osteoporosis, and help to reduce postmenopausal symptoms. Subject 008 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. These protocol deviations were reported in the line listings.

Dr. Portman’s site was selected for inspection because the site was critical to the efficacy evaluation of the lowest dose (4 mcg); i.e., it had a relatively large treatment effect compared to the higher two doses. If this site were removed from the efficacy analysis, the low dose treatment (4 mcg) would demonstrate no statistically significant improvement in treating the most bothersome symptom of moderate to severe dyspareunia, a symptom of VVA due to menopause.

Dr. Magloire’s site was selected for inspection because of four reported major protocol violations which involved not collecting Pap smears, per protocol procedure, at Week 12 on the following women:

- 1) Participating woman Number 484-011 in the 4 mcg estradiol vaginal insert treatment group,
- 2) Participating woman Number 484-120 in the 25 mcg estradiol vaginal insert treatment group,
- 3) Participating woman Number 484-005 in the placebo vaginal insert treatment group, and
- 4) Participating woman Number 484-071 in the placebo vaginal insert treatment group.

While not affecting efficacy endpoints, these four major protocol deviations demonstrate inconsistency in following established end-of-trial procedures. Dr. Kroll’s site was ranked as high in overall risk by the site selection tool.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
454 Koltun, William 9040 Friars Road, Suite 540 San Diego, CA 92108	TVX14-01/ 34	25-30 Jan 2017	NAI
435 Kroll, Robin 3216 NE 45th Place, Suite 100 Seattle, WA 98105	TVX14-01/ 18	29 Nov-6 Dec 2016	NAI
484 Magloire, Christ-Ann 1880 NE 163rd Street, Suite 102 North Miami Beach, FL 33162	TVX14-01/ 41	19-26 Jan 2017	NAI
400 Portman, David F. 99 North Brice Road, Suite 120 Columbus, OH 43213	TVX14-01/ 27	24-28 Oct 2016	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. William Koltun, M.D.

At this site for Protocol TVX14-01, 44 subjects were screened, 34 subjects were enrolled, and 33 subjects completed the study.

The consent forms for all screened subjects were reviewed. All subjects signed the consent forms prior to any study-related procedures. Data from subject source records were transcribed to electronic Case Report Forms (eCRFs). The study records of 18 subjects were reviewed comprehensively. Efficacy results were compared between source documents, eCRFs, and data listings. Other records reviewed included, but were not limited to, IRB correspondence, inclusion/exclusion criteria, adverse events, concomitant therapies, and test article accountability.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Robin Kroll, M.D.

At this site for Protocol TXV14-01, 43 subjects were screened, 25 failed screening, 18 subjects were randomized to the study, and one subject was terminated early.

The consent forms for all subjects, screened and enrolled, were reviewed. All subjects signed the consent forms prior to any study-related procedures. The source records for all enrolled and randomized subjects were reviewed. Records reviewed included, but were not limited to, source documents, Case Report Forms (CRFs), inclusion/exclusion criteria, randomization, adverse events, concomitant medications, subject diaries, monitoring correspondence, and drug accountability and storage.

A Form FDA 483 was not issued at the conclusion of the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Christ-Ann Magloire, M.D.

At this site for Protocol TVX14-01, 171 subjects were screened, 41 subjects were enrolled, and 38 subjects completed the study.

The consent forms for 24 of the 41 subjects were reviewed. These subjects signed the consent forms prior to any study-related procedures. The subject source records of 24 of the 41 enrolled subjects were compared with the data listings. Records reviewed included, but were not limited to, financial disclosures, IRB, sponsor, and monitor correspondence, inclusion/exclusion criteria, randomization, frequency of dosing, adverse events, dosing diaries, concomitant medications, protocol deviations, and test article storage and accountability.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. David F. Portman, M.D.

At this site for Protocol TXV14-01, 41 subjects were screened, 14 failed screening, 27 subjects were enrolled, 24 subjects completed the study, and 3 subjects were terminated early.

The consent forms for all subjects, screened and enrolled, were reviewed. All subjects signed the consent forms prior to any study-related procedures. The subject source records were compared with electronic Case Report Forms (eCRFs) and the data listings. Record review included, but was not limited to, IRB, sponsor, and monitor correspondence, financial disclosure forms, delegation logs, subject selection and enrollment, randomization, dates of study visits and subject evaluations including cytology analyses at Visit 1B, and test article accountability.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., Team Leader, for
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.\NDA 208564
DBRUP\Division Director\Hylton Joffe
DBRUP\Team Leader\Shelley Slaughter
DBRUP\Medical Officer\Theresa van der Vlugt
DBRUP\Project Manager\Kim Shiley
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Janice Pohlman
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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

/s/

ROY A BLAY
03/23/2017

JANICE K POHLMAN
03/23/2017

SUSAN D THOMPSON
03/23/2017