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APPLICATION NUMBER:

208564Orig1s000

NON-CLINICAL REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 208564

Supporting document/s: SDN 34, eCTD 034, 11-29-2017

Applicant's letter date: November 29, 2017

CDER stamp date: November 29, 2017

Product: TX-004HR, Estradiol vaginal (b) (4) capsules (vaginal inserts)
(Proposed trade name: IMVEXXY)

Indication: Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause

Applicant: TherapeuticsMD, Inc
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Review Division: Division of Bone, Reproductive and Urologic Products

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Supervisor/Team Leader: Mukesh Summan, PhD, DABT

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Project Manager: Kimberly Shiley

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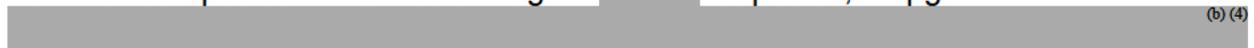
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1 Executive Summary

1.1 Introduction

TX-004HR is a vaginally administered solubilized 17 β -estradiol product indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause. TX-004HR is designed as a (b) (4) capsule (vaginal insert), without the need for an applicator. The active ingredient is (b) (4) 17 β -estradiol (as estradiol (b) (4)). The formulation (as compared to the approved tablets for the same indication – Vagifem®) has been designed to mitigate the common limitations found with other vaginal forms of estradiol, ease vaginal administration, provide improved convenience and acceptability, and provide low systemic estrogen levels compared to currently available estrogen tablets.

This submission constitutes an NDA Resubmission, responding to the FDA's Complete Response Letter (CRL) dated May 5, 2017, and post CRL communications. There is no new or updated nonclinical information included in this submission. The sponsor continues to seek approval via the 505(b)(2) pathway and intends to rely in part on published literature (estradiol) for the nonclinical toxicology, genotoxicity and carcinogenicity sections of this NDA, rather than the Agency's findings of safety and efficacy of an approved estradiol product. The submitted nonclinical literature will inform Sections 8 and 13 of the labeling.

1.2 Brief Discussion of Nonclinical Findings

The safety of estradiol is well-established and documented in the published literature following many years of clinical use. There are also a number of approved products that contain estradiol as the active pharmaceutical ingredient at the same or similar doses, and for the same or similar indication as TX-004HR (e.g. Vagifem, Femring, Estrace, Estring). As such, the sponsor has not conducted any nonclinical studies of their own for estradiol, and proposes to rely on relevant published literature to support the nonclinical safety of estradiol, and to inform nonclinical sections of labeling. 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.

Upon initial submission of this NDA (SDN1, 7-7-2016), the pharmacology/toxicology review team recommended approval of TX-004HR for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. This determination has not changed. We reference the previous NDA review submitted to DARRTS on 3-29-2017 for a full nonclinical review.

1.3 Recommendations

1.3.1 Approvability

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.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

See Section 11 below for a tabular listing of the sponsor-proposed labeling versus the Division's proposed changes. Main edits were to Section 8 to comply with PLLR. The nonclinical review team agrees with the PLLR edits made by the labeling review team and does not have any further edits in this regard. The only nonclinical team edit was a deletion of text within the pharmacologic class listed under Indications and Usage in Highlights.

2 Drug Information

2.1 Drug

CAS Registry Number: (b) (4) (b) (4)

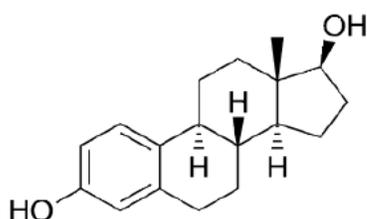
Generic Name: Estradiol, 17 β -estradiol, estradiol (b) (4)
17 β -estradiol (b) (4)

Code Name: TX-004HR; TX-12-004HR

Chemical Name: Estra-1,3,5(10)-triene-3, 17 β -diol

Molecular Formula/Molecular Weight: C₁₈H₂₄O₂, 1/2 H₂O; 272.39 g/mol
(b) (4)

Structure or Biochemical Description



Pharmacologic Class: Estrogen

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 114477: Estradiol and Progesterone Capsule; Therapeutics MD
(Treatment of vasomotor symptoms in postmenopausal women)

IND 116267: Estradiol Capsule; Therapeutics MD
(Treatment of moderate to severe vasomotor symptoms associated with the menopause)

NDA 20908: Vagifem® (estradiol vaginal tablet, 10 and 25 µg); Novo Nordisk

(b) (4)

2.3 Drug Formulation

Drug substance manufacturer: (b) (4)

Drug product manufacturers:

Catalent Pharma Solutions, LLC (registration batches and commercial drug product manufacture)

(b) (4)

Estradiol vaginal (b) (4) capsules, 4, 10, (b) (4) µg, are light pink, tear-shaped, soft gelatin capsules 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.

Table 1, Table 2, and Table 3 show the composition of the active ingredient per capsule, as well as the (b) (4) shell material. The (b) (4) shell material does not change between each capsule strength, only the fill material. The fill material changes are shown below in Tables 2 and 3.

The CMC review team has confirmed that the appropriate USP nomenclature for this product should be "Estradiol vaginal insert" instead of "(b) (4)". According to USP, the term "Vaginal Inserts", rather than "Vaginal Tablets", (b) (4) or "Vaginal Suppositories" is used in the title of this general type of vaginal preparation to decrease the potential for misadministration of these products. The term "Vaginal" is also preferred rather than "Intravaginal" as defining term for the administration route.

Table 1: Composition of Estradiol Vaginal (b) (4) Capsules, 4 µg

Ingredient	Quality Standard	Manufacturer	Function	mg/Capsule	% w/w ^a					
(b) (4) Fill Material										
Micronized estradiol (as estradiol hemihydrate)	(b) (4)					(b) (4)				
(b) (4) (medium chain triglycerides)										
(b) (4) (mixture of PEG (b) (4) stearate NF, ethylene glycol palmitostearate NF and PEG (b) (4) stearate NF)										
<i>Total Fill Material</i>										
Softgel Shell Material										
Gelatin, (b) (4)										
Hydrolyzed Gelatin										
(b) (4)										
(Sorbitol sorbitan solution)										
Glycerin										
(b) (4)										
(b) (4)										
(b) (4)										
(b) (4) (mixture of ethanol, ethyl acetate, propylene glycol, titanium dioxide, polyvinyl acetate phthalate, purified water, isopropyl alcohol, polyethylene glycol ammonium hydroxide)										
Ethanol										
(b) (4)										
<i>Total Shell Material</i>										
Total						(b) (4)				

Table 2: Composition of Estradiol Vaginal (b) (4) Capsules, 10 µg

Ingredient	Quality Standard	Manufacturer	Function	mg/Capsule	% w/w ^a
Softgel Fill Material					
Micronized estradiol, (as estradiol hemihydrate)					(b) (4)
(b) (4) (medium chain triglycerides)					
(b) (4) (mixture of PEG (b) (4) stearate NF, ethylene glycol palmitostearate NF and PEG (b) (4) stearate NF)					
<i>Total Fill Material</i>					



2.4 Comments on Novel Excipients

During development, (b) (4) (medium chain triglycerides) was noted as a novel excipient, as there were no listed intravaginal dosage routes in the FDA Inactive Ingredient Database. The sponsor conducted GLP study (b) (4)/1013/G/T077 (28-day repeat dose toxicity study of (b) (4) in rabbits) which detailed the use of intravaginal TX-004HR (10 µg) with the new excipient (b) (4). This study qualifies the vaginal use of this excipient.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is postmenopausal women, as the indication is for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

TX-004HR is a small, light pink, tear-shaped, immediate release, (b) (4) capsule (vaginal insert) containing 4 µg, 10 µg, (b) (4) µg of solubilized estradiol. TX-004HR is intended for intravaginal administration only. One (b) (4) capsule should be inserted vaginally once daily for 14 days, then twice weekly thereafter for maintenance (for example, Monday and Thursday). Therapy should be started at the lowest effective dose and the shortest duration consistent with treatment goals and risks. Dosage adjustment should be guided by the clinical response.

2.7 Regulatory Background

The IND for this product and indication (IND 118439) has been in-house since May 2013 (Primary nonclinical reviewer – Kimberly Hatfield, PhD). The 30-d safety review contained no nonclinical studies, as the sponsor stated that the nonclinical assessment would be based on previous findings of safety for the active moiety, estrogen. The sponsor also stated at the time that the clinical safety assessment would be based on comparison to the approved tablet product Vagifem®. The dose of TX-004HR used in the Phase 1 studies was a single 10 or 25 µg capsule and is equal to the approved dose for Vagifem® (estradiol vaginal tablet, 10 and 25 µg). Phase 2 clinical studies investigated TX-004HR 10 µg for 14 days. The Phase 3 clinical trial investigated TX-004HR at 4 µg, 10 µg and 25 µg doses for 12 weeks. The difference between TX-004HR and Vagifem® is the identity of the inactive ingredients, as TX-004HR is a capsule (vaginal insert) and Vagifem® is a tablet.

In written responses dated 7-18-2014, it was agreed that the TX-004HR formulation had been adequately assessed from a nonclinical perspective in order to proceed with the proposed Phase 3 trial as well as in support of the planned new drug application, pending review of the final report of the 28-day repeat dose toxicity study of (b) (4) in rabbits. It was also noted at that meeting that the sponsor (in their meeting package) intended to rely upon ‘existing preclinical and clinical data from Estrace, Estring and/or Femring NDAs and relevant published literature’.

At the pre-NDA meeting on December 17, 2015, the following were communicated:

- Study report (b) (4)/1013/G/T077 (28-day repeat dose toxicity study of (b) (4) in rabbits) adequately assesses the proposed formulation.
- The Division does not agree with a submission that only addresses “de minimis nonclinical requirements” or that the proposed NDA constitutes a 505(b)(1) application.
 - FDA provided two options for Pharmacology/Toxicology under a 505(b)(2) pathway:

- 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.
- Refer to a Listed Drug. Under this option, labeling language from the listed drug can be used for your product as long as you establish a bridge demonstrating that your product and the listed drug are sufficiently similar. No literature submissions would be necessary.

In response, TherapeuticsMD stated that they intend to submit a 505(b)(2) application.

TherapeuticsMD submitted the initial NDA on July 7, 2016. The review cycle ended with the sponsor receiving a Complete Response Letter on May 5, 2017. Following post-CR communications with the Division, the sponsor resubmitted this NDA on November 29, 2017.

3 Studies Submitted

3.1 Studies Reviewed

No new or updated nonclinical information was submitted.

3.3 Previous Reviews Referenced

IND 118439, SD#1 (non-eCTD), 5-10-2013 (Reviewed by Kimberly Hatfield, PhD)

IND 118439, SD#8 (eCTD # 006), 7-15-2014 (Reviewed by Kimberly Hatfield, PhD)

IND 118439, SD#25 (eCTD #0023), 5-13-2015 (Reviewed by Kimberly Hatfield, PhD)

NDA 208564, SD#1 (eCTD #001), 3-29-2017 (Reviewed by Kimberly Hatfield, PhD)

11 Integrated Summary and Safety Evaluation

TX-004HR is a vaginally administered solubilized 17 β -estradiol product proposed for the treatment of moderate to severe dyspareunia (painful sexual intercourse), a symptom of vulvar and vaginal atrophy due to menopause. TX-004HR is designed as a (b) (4) capsule vaginal insert, with the active ingredient being (b) (4) 17 β -estradiol (as estradiol (b) (4)). The new formulation (as compared to the approved tablets for the same indication – Vagifem®) has been designed to mitigate the common limitations found with other vaginal forms of estradiol, ease vaginal administration, provide improved convenience and acceptability, and provide low systemic estrogen levels compared to currently available estrogen tablets.

This submission constitutes an NDA Resubmission, responding to the FDA's Complete Response Letter (CRL) dated May 5, 2017, and post CRL communications. There is no

new or updated nonclinical information included in this submission. The sponsor continues to seek approval via the 505(b)(2) pathway and intends to rely in part on published literature (estradiol) for the nonclinical toxicology, genotoxicity and carcinogenicity sections of this NDA, rather than the Agency's findings of safety and efficacy of an approved estradiol product. The submitted nonclinical literature will inform Sections 8 and 13 of the labeling.

The safety of estradiol has already been established and is well-documented in the published literature and through many years of clinical use. Estradiol, at the same or similar dose, is also approved for use in other products, also for the same or similar indication of symptoms of vulvar and vaginal atrophy due to menopause (e.g. Vagifem, Femring, Estrace, Estring). The sponsor does not intend to rely on previous findings of safety of an approved product, and has submitted relevant published literature in order to support the nonclinical safety of estradiol in TX-004HR, and to inform nonclinical sections of labeling. The data provided from this literature are adequate to support the nonclinical safety of estradiol without relying on previous findings of safety for an approved product. This information was reviewed during the first review cycle under the initial submission of NDA 208564 (7-7-2016), and was found to support approval of this product.

Nonclinical issues regarding labeling:

The nonclinical team reviewed the pharmacologic class in Highlights, Section 8.1-8.3 and Section 13. The Labeling Review Team made initial changes to Section 8 to conform to PLLR, which are noted via underline and strikethrough in the table below. Other than the proposed deletion under Indications and Usage in Highlights, the nonclinical team did not have any additional edits to the label.

(b) (4)

(b) (4)



Overall Conclusions: Pharmacology/Toxicology recommends approval for TX-004HR for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause.

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/s/

KIMBERLY P HATFIELD
04/17/2018

MUKESH SUMMAN
04/17/2018
I concur

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 208564

Supporting document/s: SDN 1, eCTD 001, 7-7-2016
SDN 5, eCTD 005, 10-11-2016

Applicant's letter date: July 7, 2016

CDER stamp date: July 7, 2016

Product: TX-004HR, Estradiol vaginal (b) (4) capsules
(Proposed trade name: still under discussion)
(Originally proposed trade name: YUVVEXY)

Indication: Treatment of moderate to severe dyspareunia, a
symptom of vulvar and vaginal atrophy, due to
menopause

Applicant: TherapeuticsMD, Inc
6800 Broken Sound Parkway NW, 3rd floor
Boca Raton, FL 33487 USA

Review Division: Division of Bone, Reproductive and Urologic Products

Reviewer: Kimberly Hatfield, PhD

Supervisor/Team Leader: Mukesh Summan, PhD, DABT

Division Director: Hylton Joffe, MD, MMSc

Project Manager: Kimberly Shiley

Disclaimer

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1 Executive Summary

1.1 Introduction

TX-004HR is a vaginally administered solubilized 17β -estradiol product for the treatment of moderate to severe dyspareunia (painful sexual intercourse), a symptom of vulvar and vaginal atrophy due to menopause. TX-004HR is designed as a (b) (4) capsule vaginal insert. The active ingredient is (b) (4) 17β -estradiol (as estradiol (b) (4)). The new formulation (as compared to the approved tablets for the same indication – Vagifem®) has been designed to mitigate the common limitations found with other vaginal forms of estradiol, ease vaginal administration, provide improved safety of insertion, minimize vaginal discharge following administration and provide a more effective dosage form with improved efficacy, safety and patient compliance.

The sponsor is seeking approval via the 505(b)(2) pathway and intends to rely on published literature (estradiol) for the nonclinical toxicology, genotoxicity and carcinogenicity sections of this NDA, rather than the Agency's findings of safety and efficacy of an approved estradiol product. The submitted nonclinical literature will inform Sections 8 and 13 of the labeling.

1.2 Brief Discussion of Nonclinical Findings

The safety of estradiol is well-established and documented in the published literature following many years of clinical use. There are also a number of approved products that contain estradiol as the active pharmaceutical ingredient at the same or similar doses, and for the same or similar indication as TX-004HR (e.g. Vagifem, Femring, Estrace, Estring). As such, the sponsor has not conducted any nonclinical studies of their own for estradiol, and proposes to rely on relevant published literature to support the nonclinical safety of estradiol, and to inform nonclinical sections of labeling. 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.

The only nonclinical study conducted by the sponsor was a 28-day repeat dose toxicity study in rabbits to evaluate the safety of the novel excipient (b) (4). While (b) (4) has been used in other approved products, there were no listed intravaginal dosage routes in the FDA Inactive Ingredient Database, and the amount proposed in the TX-004HR soft gel capsule was much higher than the maximum potency amounts listed for topical cream/gel administration, or even oral gel administration. The results of the completed study showed that test article (10 μ g estradiol) containing (b) (4) was not a vaginal irritant compared to control, and that the amount of (b) (4) 2 present in the formulation is acceptable for use in the drug product. This study also bridges to literature data that documents the safety of estradiol via other routes of administration, and supports the vaginal use of this product.

1.3 Recommendations

1.3.1 Approvability

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.

1.3.2 Additional Non Clinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

Labeling for this product will be conducted under separate review.

2 Drug Information

2.1 Drug

CAS Registry Number: (b) (4) (b) (4)

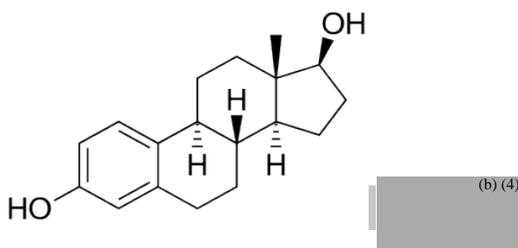
Generic Name: Estradiol, 17 β -estradiol, estradiol (b) (4)
17 β -estradiol (b) (4)

Code Name: TX-004HR; TX-12-004HR

Chemical Name: Estra-1,3,5(10)-triene-3, 17 β -diol

Molecular Formula/Molecular Weight: C₁₈H₂₄O₂, 1/2 H₂O; 272.39 g/mol
(b) (4)

Structure or Biochemical Description



Pharmacologic Class: Estrogen

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 114477: Estradiol and Progesterone Capsule; Therapeutics MD
(Treatment of vasomotor symptoms in postmenopausal women)

[REDACTED] (b) (4)

NDA 20908: Vagifem® (estradiol vaginal tablet, 10 and 25 µg); Novo Nordisk

[REDACTED] (b) (4)

2.3 Drug Formulation

Drug substance manufacturer: [REDACTED] (b) (4)

Drug product manufacturers:

Catalent Pharma Solutions, LLC (registration batches and commercial drug product manufacture)

[REDACTED] (b) (4)

Estradiol vaginal [REDACTED] (b) (4) capsules, 4, 10, [REDACTED] (b) (4) µg, are light pink, tear-shaped, soft gelatin capsules with a cloudy fill appearance and printed with the strength identifiers “04,” “10,” [REDACTED] (b) (4)” respectively, in white ink on one side of the capsule. Each capsule is formulated as a 300 mg fill and then encapsulated.

Table 1, Table 2, and Table 3 show the composition of the active ingredient per capsule, as well as the [REDACTED] (b) (4) shell material. The [REDACTED] (b) (4) shell material does not change between each capsule strength, only the fill material. The fill material changes are shown in Tables 2 and 3.

Table 1: Composition of Estradiol Vaginal (b) (4) Capsules, 4 µg

Ingredient	Quality Standard	Manufacturer	Function	mg/Capsule	% w/w ^a						
(b) (4) Fill Material											
(b) (4) estradiol (as (b) (4)	(b) (4)					(b) (4)					
(b) (4) (medium chain triglycerides)											
(b) (4) (mixture of PEG (b) (4) stearate NF, ethylene glycol palmitostearate NF and PEG (b) (4) stearate NF)											
<i>Total Fill Material</i>											
Softgel Shell Material											
Gelatin, (b) (4)						(b) (4)					
Hydrolyzed Gelatin											
(b) (4) (Sorbitol sorbitan solution)											
Glycerin											
(b) (4)											
(b) (4)											
(b) (4) (mixture of ethanol, ethyl acetate, propylene glycol, titanium dioxide, polyvinyl acetate phthalate, purified water, isopropyl alcohol, polyethylene glycol ammonium hydroxide)											
Ethanol											
(b) (4)											
<i>Total Shell Material</i>											
Total											
(b) (4)											

Table 2: Composition of Estradiol Vaginal (b) (4) Capsules, 10 µg

Ingredient	Quality Standard	Manufacturer	Function	mg/Capsule	% w/w ^a
Softgel Fill Material					
(b) (4) estradiol, (as estradiol (b) (4))	USP	Gedeon Richter	Active	0.0103 ^b	0.002
(b) (4) (medium chain triglycerides)	NF	Cremer	Vehicle	269.99	48.3
(b) (4) (mixture of PEG (b) (4) stearate NF, ethylene glycol palmitostearate NF and PEG (b) (4) stearate NF)	Pharmaceutical grade	Gattefosse	Thickening agent	30.00	5.4
<i>Total Fill Material</i>				<i>300.00</i>	<i>53.7</i>



2.4 Comments on Novel Excipients

During development, (b) (4) (medium chain triglycerides) was noted as a novel excipient, as there were no listed intravaginal dosage routes in the FDA Inactive Ingredient Database. The amount of (b) (4) in the (b) (4) capsule was much higher than the maximum potency amounts listed for topical cream/gel administration, or even oral gel administration. In order to qualify the excipient and evaluate local tolerance to this product, a nonclinical vaginal irritation study was requested. The sponsor conducted GLP study (b) (4)/1013/G/T077 (28-day repeat dose toxicity study of (b) (4) in rabbits) which detailed the use of intravaginal TX-004HR (10 µg) with the new excipient (b) (4). See Section 10 Special Toxicology Studies for a review. This study qualifies the vaginal use of this excipient.

The manufacturer for (b) (4) also describes this excipient as (b) (4)



(b) (4)
As such, the amount of (b) (4) is acceptable for use in this product.

(b) (4) is not listed in the Inactive Ingredient Database, however (b) (4)
As gelatin products however, there is little concern.

All other excipients are at acceptable levels.

2.5 Comments on Impurities/Degradants of Concern

There are no impurities or degradants of concern.

The manufacturer has characterized the impurities of estradiol (b) (4) and provided details in their (b) (4) Estradiol (b) (4) USP (b) (4) is routinely monitored for related substances, known impurities, other impurities and residual solvents. Specifications are in place for impurities in the drug substance, and are based on (b) (4) acceptance criteria.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is postmenopausal women, as the indication is for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

TX-004HR is a small, light pink, tear-shaped, immediate release, (b) (4) capsule containing 4 µg, 10 µg, or 25 µg of solubilized estradiol. TX-004HR is intended for intravaginal administration only. One (b) (4) capsule should be inserted vaginally once daily for 14 days, then twice weekly thereafter for maintenance (for example, Monday and Thursday). Therapy should be started at the lowest effective dose and the shortest duration consistent with treatment goals and risks. Dosage adjustment should be guided by the clinical response.

2.7 Regulatory Background

The IND for this product and indication (IND 118439) has been in-house since May 2013 (Primary nonclinical reviewer – Kimberly Hatfield, PhD). The 30-d safety review contained no nonclinical studies, as the sponsor stated that the nonclinical assessment would be based on previous findings of safety for the active moiety, estrogen. The sponsor also stated at the time that the clinical safety assessment would be based on comparison to the approved tablet product Vagifem®. The dose of TX-004HR used in the Phase 1 studies was a single 10 or 25 µg capsule and is equal to the approved dose for Vagifem® (estradiol vaginal tablet, 10 and 25 µg). Phase 2 clinical studies investigated TX-004HR 10 µg for 14 days. The Phase 3 clinical trial investigated TX-

004HR at 4 µg, 10 µg and 25 µg doses for 12 weeks. The difference between TX-004HR and Vagifem® is the identity of the inactive ingredients, as TX-004HR is a capsule and Vagifem® is a tablet.

In written responses dated 7-18-2014, it was agreed that the TX-004HR formulation had been adequately assessed from a nonclinical perspective in order to proceed with the proposed Phase 3 trial as well as in support of the planned new drug application, pending review of the final report of the 28-day repeat dose toxicity study of (b) (4) in rabbits. It was also noted at that meeting that the sponsor (in their meeting package) intended to rely upon 'existing preclinical and clinical data from Estrace, Estring and/or Femring NDAs and relevant published literature'.

At the pre-NDA meeting on December 17, 2015, the following were communicated:

- Study report (b) (4)/1013/G/T077 (28-day repeat dose toxicity study of (b) (4) in rabbits) adequately assesses the proposed formulation.
- The Division does not agree with a submission that only addresses "de minimis nonclinical requirements" or that the proposed NDA constitutes a 505(b)(1) application.
 - FDA provided two options for Pharmacology/Toxicology under a 505(b)(2) pathway:
 - 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.
 - Refer to a Listed Drug. Under this option, labeling language from the listed drug can be used for your product as long as you establish a bridge demonstrating that your product and the listed drug are sufficiently similar. No literature submissions would be necessary.

In response, TherapeuticsMD stated that they intend to submit a 505(b)(2) application.

3 Studies Submitted

3.1 Studies Reviewed

Study # (b) (4)/1013/G/T077: 28 day repeated dose toxicity study of (b) (4) in New Zealand white female rabbits by vaginal route

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

IND 118439, SD#1 (non-eCTD), 5-10-2013 (Reviewed by Kimberly Hatfield, PhD)

IND 118439, SD#8 (eCTD # 006), 7-15-2014 (Reviewed by Kimberly Hatfield, PhD)

IND 118439, SD#25 (eCTD #0023), 5-13-2015 (Reviewed by Kimberly Hatfield, PhD)

4 Pharmacology

The Sponsor has not conducted any nonclinical pharmacology studies with TX-004HR, but has submitted relevant literature documenting the pharmacology of estradiol. A brief summary, as submitted by the sponsor, follows.

“17 β -estradiol is the primary female sex hormone and the most potent human estrogen (Kuhl 2005). The biological effect of estrogens including estradiol is based on interaction with estrogen receptors, ER α and ER β , which are ligand-activated transcription factors that alter the synthesis of messenger RNA from target genes (Goodman et al. 2001). Estradiol is highly efficacious and selective, with a relative binding affinity (RBA) of 100 for both ER α and ER β . Additional signaling mechanisms for estrogens include cell membrane receptors coupled with G-proteins which can activate intracellular signal cascades (Kuhl 2005).

The secondary pharmacological effects of estradiol and other estrogens are dose-related and are, at least in part, traditionally associated with unopposed estrogen treatment at large doses without a progestin component. Because TX-004HR is a low-dose, vaginally-administered, solubilized 17 β -estradiol product (4 to 25 μ g/day), no clinically meaningful secondary pharmacologic effects are anticipated.”

5 Pharmacokinetics/ADME/Toxicokinetics

The Sponsor has not conducted any nonclinical pharmacokinetic studies with TX-004HR. However, the PK of estradiol has been widely established with various routes of administration (oral, parenteral, transdermal, topical; see Goodman et al., 2001). A brief summary, as submitted by the sponsor, follows.

“Due to the lipophilic nature of estrogens including estradiol, absorption is generally good across dosing routes with the appropriate formulation. Preparations of low-dose estrogen products are available for topical administration to the vagina. These products, including TX-004HR, are intended to promote local effects only and low doses are utilized to limit the potential for systemic absorption. TX-004HR is a low-dose (4 to 25 μ g/day) vaginally-administered (b) (4) 17 β -estradiol product intended for a local treatment effect. No significant amount of systemic absorption, distribution, metabolism, or excretion is anticipated with TX-004HR.

Estradiol is extensively bound to plasma proteins in blood, including sex steroid-binding globulin (SSBG) and serum albumin (Goodman et al. 2001). Due to its size and lipophilic nature, estradiol readily distributes past the vascular space and into tissues. In general, estradiol undergoes rapid biotransformation with a half-life of minutes. Estradiol is metabolized by 17 β -hydroxysteroid dehydrogenase to estrone, which is in turn converted by 16 α -hydroxylation and 17-keto reduction to estriol, 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 gut.”

6 General Toxicology

The Sponsor has submitted relevant literature documenting the nonclinical safety of estradiol. These references also provide data to inform Sections 8 and 13 of patient labeling. Most literature references did not refer to a named product, but others referred to the use of named previously approved products (e.g. Vagifem, or an “Organon” product), so they cannot be used for support under 505(b)(2) regulations (Simunic et al., 2003; Nilsson and Heimer, 1992; MacKenzie, 1955). However, these 3 articles are not necessary for the approval of TX-004HR.

The sponsor has submitted two references to support the general toxicity of estradiol. The sponsor’s summary of Biegel et al., 1988a and 1988b is as follows:

“In a 90-day repeat study by Biegel et al. (Biegel et al. 1998a; Biegel et al. 1998b), male and female rats were administered estradiol in the diet for an average dose of 0. 0.003, 0.16, 0.61, or 3.7 mg/kg/day. Effects of estradiol in this study consisted of dose-dependent decreases in body weight and food consumption, minimal to mild non-regenerative anemia and lymphopenia, and changes in the weights of several organs, including liver, spleen, epididymides, accessory sex organs, and testes in males and spleen, uterus, and ovaries in females. Histopathology revealed diffuse hyperplasia of the pituitary gland, mammary gland hyperplasia in females, cystic ovarian follicles, hypertrophy of the endometrium and endometrial glands in the uterus, degeneration of the seminiferous epithelium, and atrophy of the testes and accessory sex glands.”

7 Genetic Toxicology

The sponsor has submitted a reference from Dhillon and Dhillon, 1995 to support the genotoxicity of estradiol. The sponsor’s summary of this study is as follows:

“In genotoxicity studies published by Dhillon and Dhillon (Dhillon and Dhillon 1995) estradiol was unable to induce any significant dose-related increase in the mean number of revertants/plate both with and without S9 mix. The actual number of revertants was not provided. A significant increase in the aberration

frequencies was observed in a dose- and time-dependent manner without metabolic activation. Six hours of treatment with estradiol in the presence of S9 mix induced a significant increase in aberration frequencies at the highest doses (10 and 100 µg/mL) as compared to the results obtained without metabolic activation. In human lymphocyte cultures, both chromatid and chromosomal type aberrations were observed. However, the frequency of chromatid-type aberrations was more than chromosomal type. The highest doses of the estradiol (1.0 and 10 mg/kg) caused a significant increase in the number of micronucleated polychromatic erythrocytes and sister chromatid exchanges as compared to the negative controls.”

8 Carcinogenicity

The sponsor has submitted four references to support the carcinogenicity of estradiol (Highman et al., 1980; Highman et al., 1978, Welsch et al., 1977; IARC, 1987). The sponsor’s summary of the data from these studies is as follows:

“These studies demonstrate that estradiol administration in mice can increase the incidences of mammary, pituitary, uterine, cervical, vaginal, testicular, lymphoid and bone tumors. In rats, there was an increased incidence of mammary and pituitary tumors.”

9 Reproductive and Developmental Toxicology

The sponsor has submitted two references to support the reproductive and developmental toxicity of estradiol. The sponsor’s summary of Leighton et al., 2000, and Schofield, 1962 is as follows:

“Leighton et al., 2000 describes a full battery of reproductive toxicity studies with 17β-estradiol in rats. This monograph also provides an extensive review on the pharmacology and toxicology of 17β-estradiol as well. Schofield, 1992 examines a rabbit embryofetal development study conducted with 17β-estradiol.

Estradiol administered in the feed to female Crl:CD BR rats at doses equal to 0, 0.003, 0.17, 0.69, or 4.1 mg/kg/day and to males at doses equal to 0, 0.003, 0.14, 0.53, or 3.2 mg/kg/day resulted in a decrease in the number of matings and no pregnancies at the two highest doses. For the three groups with pregnancies, there was no difference in gestation length, however, gestation body weight gain, food consumption, and mean number of implants were affected.

Mean number of live births was significantly decreased in the 0.17 mg/kg/day group compared to control. Parental administration of estradiol did not affect the anogenital distance in male or female pups. Onset of sexual maturity, as measured by prepubertal separation in males, was significantly delayed in the 0.17 mg/kg/day group. Onset of sexual maturity, as measured by vaginal opening in females, was decreased in both the 0.003 and 0.17 mg/kg/day dosed groups

(24/56 female pups were vaginally patent on the day of weaning). The F1 generation was not mated.

In white rabbits, intramuscular estradiol administration at 15 or 30 µg/animal for 3-6 consecutive days at different times during gestation resulted in 67 and 78% aborted or totally resorbed litters and 4% and 17% of litters with dead fetuses, respectively.”

10 Special Toxicology Studies

Study title: 28 day repeated dose toxicity study of (b) (4) in New Zealand white female rabbits by vaginal route

Study no.: (b) (4) /1013/G/T077
 Study report location: SD #8, eCTD# 006 Section 4.2.3.2, 7/15/14
 SD# 25, eCTD# 0023 Section 1.11.2, 5/13/15
 Conducting laboratory and location: (b) (4)
 Date of study initiation: January 16, 2014
 GLP compliance: Yes
 QA statement: Yes
 Drug, lot #, and % purity: (b) (4): Estradiol 10 µg vaginal capsule fill material with (b) (4) (See Table 4)
 Batch# 12-002-134
 Unique test item code: VPCD/TC/13/218

Key Study Findings

- Test article including (b) (4) was not a vaginal irritant at any dose, compared to saline controls.

Methods

Doses: 0, 256, 512 and 1024 mg/rabbit ((b) (4))
 See Table 5 for dose range in mg/kg
 Frequency of dosing: Once daily for 28 consecutive days
 Route of administration: Intravaginal as a solution, not a capsule
 Dose volume: 0.3, 0.6 or 1.2 mL (see Table 6)
 Formulation/Vehicle: Vehicle = normal saline (Batch #305215068);
 Formulation: see Table 4
 *The test article is the actual product containing estradiol (10 µg) and Miglyol 812
 Species/Strain: New Zealand White Rabbit
 Number/Sex/Group: 24 total; 6 females per group

Age and weight: 5-7 months; 2.1-2.9 kg (sexually mature, nulliparous, non-pregnant)

Grading system: Erythema: 0=none; 1=very slight; 2= slight; 3= moderate to severe; 4=severe
 Edema and Discharge: 0=none; 1=very slight; 2=slight; 3=moderate; 4=severe.
 Microscopic findings (leukocyte infiltration, vascular congestion, edema): 0=absent; 1=minimal; 2=mild; 3=moderate; 4=marked.
 Irritation index: 0=none; 1-4=minimal; 5-8=mild; 9-11: moderate; 12-16=severe

Study design: Test item or vehicle was instilled into vaginal vault via gavage needle fitted with disposable syringe.
 Necropsy on Day 28. The entire vagina was collected for gross and histopathology.

Table 4: Test article - Estradiol 10 µg vaginal capsules containing (b) (4) (Study (b) (4)/1013/G/T077)

Ingredient	% W/W	Function
(b) (4) Estradiol, USP (as estradiol (b) (4))	0.003	Active
(b) (4) (Medium chain triglyceride)	89.997	(b) (4)
(b) (4) (Mixture of PEG (b) (4) Stearate, Ethylene Glycol Palmitostearate and PEG (b) (4) Stearate)	10.0	(b) (4)

Table 5: Dose information (Study (b) (4)/1013/G/T077)

Dose Group	Dose	Route	Dose Volume (mL/rabbit)	Dose (mg of Miglyol/rabbit)	No. of Rabbits/group	Animal Number	Body weight Range (Kg)	Dose range (mg/kg)
G-I (Control)	Vehicle (Normal saline)	Vaginal	1.2	0	6	T077/001 to T077/006	1.8489 - 2.9253	0
G-II (Low)	Test Item (Miglyol 812)		0.3	256	6	T077/007 to T077/012	2.1506 - 2.7543	92.95 - 119.04
G-III (Mid)			0.6	512	6	T077/013 to T077/018	2.1669 - 3.2297	158.53 - 236.28
G-IV (High)			1.2	1024	6	T077/019 to T077/024	2.1811 - 3.0120	339.97 - 469.49

Table 6: Study design (Study (b) (4) /1013/G/T077)

Dose Groups	Dose	Route	Dose Volume (mL/rabbit)	No. of Rabbits	Animal Number
G-I (Control)	Vehicle (Normal Saline)	Vaginal	1.2	6	T077/001 to T077/006
G-II (Low)	Test Item (Miglyol 812)		0.3	6	T077/007 to T077/012
G-III (Mid)			0.6	6	T077/013 to T077/018
G-IV (High)			1.2	6	T077/019 to T077/024

Observations and Results

Mortality: No animals died on study prior to necropsy.

Clinical observations: Erythema, edema and discharge were observed at very slight and slight severity at all doses, but with increased incidence at higher doses. White vaginal discharge was also noted in one mid-dose and one high dose rabbit at Day 14, but was not considered by the sponsor to be treatment-related. Hyperactivity was noted in 1 mid-dose female and 2 high dose females.

Observation	Incidence out of 6 animals per dose group			
	Vehicle	Low dose	Mid-dose	High dose
Erythema – very slight to slight	0	1	1	4
Edema - very slight to slight	0	1	2	3
Discharge - very slight to slight	0	1	2	1

Body weight: No treatment-related effects were noted.

Gross necropsy: Two high dose females had congested vaginal mucosa. This was confirmed microscopically as vascular congestion of moderate severity. However, microscopic vascular congestion was noted in all control and dose groups, so this was not treatment related. No other gross pathology was observed.

Histopathology: In the vagina, histopathology changes were not significantly different than control in regards to incidence and severity of findings (based on scoring of findings: epithelial changes, leukocyte infiltration, vascular congestion and edema). The group irritation score was considered to be in the 'minimal' range for all four groups. The irritation index via microscopy was considered ≤ 0 (dose group score minus the control group score) for each dose group, therefore the test item was

considered to be non-irritant. Evaluation of the irritation index during the experimental period also indicated that the test article was a non-irritant.

Group	Group Irritation Score	# with leukocyte infiltration (grade)	# with vascular congestion (grade)	# with edema (grade)
Control	3.00	5/6 (mild - moderate)	5/6 (minimal - mild)	1/6 (minimal)
Low dose	2.33	2/6 (minimal - mild)	6/6 (minimal - mild)	2/6 (minimal - mild)
Mid-dose	1.67	3/6 (minimal)	3/6 (minimal - mild)	2/6 (minimal - mild)
High dose	3.00	5/6 (minimal - mild)	5/6 (minimal - moderate)	2/6 (minimal)

Group irritation score is the sum of the severity scores for each category divided by the number of observations in the group.

	Control	Low Dose	Mid Dose	High Dose
Pre-dose Irritation index (during experimental period)	0.00	0.04	0.07	0.14
Post-dose Irritation index (during experimental period)	0.00	0.03	0.07	0.15
Irritation index (by microscopy)	0.00	-0.67	-1.33	0.00

- Irritation index during experimental period = (sum of daily vaginal observations divided by number of animals in the group) – control group average score
- Irritation index by microscopy = (sum of daily vaginal observations divided by number of animals in the group) – control group average score

Conclusion:

Overall, the test article containing (b) (4) is not a vaginal irritant compared to control. The amount of (b) (4) that is present in the formulation is acceptable for use in the drug product.

11 Integrated Summary and Safety Evaluation

TX-004HR is a vaginally administered solubilized 17 β -estradiol product proposed for the treatment of moderate to severe dyspareunia (painful sexual intercourse), a symptom of vulvar and vaginal atrophy due to menopause. TX-004HR is designed as a (b) (4) capsule vaginal insert, with the active ingredient being (b) (4) 17 β -estradiol (as estradiol (b) (4)). The new formulation (as compared to the approved tablets for the same indication – Vagifem®) has been designed to mitigate the common limitations found with other vaginal forms of estradiol, ease vaginal administration, provide

improved safety of insertion, minimize vaginal discharge following administration and provide a more effective dosage form with improved efficacy, safety and patient compliance.

The safety of estradiol has already been established and is well-documented in the published literature and through many years of clinical use. Estradiol, at the same or similar dose, is also approved for use in other products, also for the same or similar indication of symptoms of vulvar and vaginal atrophy due to menopause (e.g. Vagifem, Femring, Estrace, Estring). The sponsor does not intend to rely on previous findings of safety of an approved product, and has submitted relevant published literature in order to support the nonclinical safety of estradiol in TX-004HR, and to inform nonclinical sections of labeling. The data provided from this literature are adequate to support the nonclinical safety of estradiol without relying on previous findings of safety for an approved product.

During development, (b) (4) (medium chain triglycerides) was noted as a novel excipient in the new (b) (4) capsule formulation of TX-004HR. There were no listed intravaginal dosage routes in the FDA Inactive Ingredient Database for (b) (4) and the amount proposed in the (b) (4) capsule was much higher than the maximum potency amounts listed for topical cream/gel administration, or even oral gel administration. Upon Agency request, the sponsor conducted a nonclinical vaginal irritation study to evaluate (b) (4) in a 28-day repeat dose toxicity study of (b) (4) in rabbits. The results of this study showed that test article (estradiol) containing (b) (4) was not a vaginal irritant compared to control, and that the amount of (b) (4) present in the formulation is acceptable for use in the drug product. This study qualifies the vaginal use of this excipient and also bridges to published literature data that documents the safety of estradiol via other routes of administration, and thus supports the vaginal use of this product.

Nonclinical issues regarding labeling:

Labeling for this product will be conducted under separate review.

Overall Conclusions: Pharmacology/Toxicology recommends approval for TX-004HR for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause.

12 Appendix/Attachments

References (submitted by sponsor and used as basis for approval):

Biegel LB, Cook JC, Hurtt ME, O'Connor JC. Effects of 17 beta-estradiol on serum hormone concentrations and estrous cycle in female Crl:CD BR rats: effects on parental and first generation rats. *Toxicol Sci.* 1998a;44(2):143–54

Biegel LB, Flaws JA, Hirshfield AN, O'Connor JC, Elliott GS, Ladics GS, et al. 90-day feeding and one-generation reproduction study in Crl:CD BR rats with 17 beta-estradiol. *Toxicol Sci.* 1998b;44(2):116–42

Dhillon VS, Dhillon IK. Genotoxicity evaluation of estradiol. *Mutat Res Toxicol.* 1995;345(1-2):87–95

Goodman L, Hardman J, Limbird L, Gilman G. Estrogens and Progestins. In: Hardman JG, Limbird LE, Gilman AG, editors. *Goodman Gilman's Pharmacol Basis Ther.* 10th ed. New York: McGraw-Hill; 2001. p. 1597–634.

Highman B, Greenman DL, Norvell MJ, Farmer J, Shellenberger TE. Neoplastic and preneoplastic lesions induced in female C3H mice by diets containing diethylstilbestrol or 17 beta-estradiol. *J Environ Pathol Toxicol.* 1980;4(0146-4779 (Print)):81–95

Highman B, Norvell MJ, Shellenberger TE. Pathological changes in female C3H mice continuously fed diets containing diethylstilbestrol or 17beta-estradiol. *J Environ Pathol Toxicol.* 1978;1:1–30

IARC Monographs Supplement 7: Oestrogens , Progestins and Combinations. 1987

Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric.* 2005;8(sup1):3–63

Leighton J, Franceschi S, Boorman G, Gaylor D, MacLean J. Estradiol-17beta-, progesterone, and testosterone (WHO Food Additives Series 43) [Internet]. *Toxicol. Eval. Certain Vet. Drug Residues Food.* 2000 [cited 2016 Mar 16]. Available from: <http://www.inchem.org/documents/jecfa/jecmono/v43jec05.htm>

Schofield BM. The effect of injected oestrogen on pregnancy in the rabbit. *J Endocrin.* 1962;25:95–100

Welsch C, Adams C, Lambrecht L, Hassett C, Brooks C. 17beta-Oestradiol and enovid mammary tumorigenesis in C3H/HeJ female mice: counteraction by concurrent 2-bromo-a-ergocryptine. *Br J Cancer.* 1977;35:322–8

References (submitted by sponsor but not used as basis for approval):

Simunic V, Banovic I, Ciglar S, Jeren L, Pavicic Baldani D, Sprem M. Local estrogen treatment in patients with urogenital symptoms. *Int J Gynaecol Obstet*, 2003 Aug

Nilsson K, Heimer G. Low-dose oestradiol in the treatment of urogenital oestrogen deficiency--a pharmacokinetic and pharmacodynamic study. *Maturitas* [Internet]. 1992 Oct

MacKenzie I. The production of mammary cancer in rats using oestrogens. *Br J Cancer*. 1955;9(2):284-99

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/s/

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03/29/2017

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03/29/2017
Nonclinical supports AP