CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210132Orig1s000

NON-CLINICAL REVIEW(S)

Memorandum

PHARMACOLOGY/TOXICOLOGY

LABELING REVIEW

Date:	September 13, 2018
IND or NDA #	NDA 210132
Sponsor:	TherapeuticsMD, Inc
Drug/Indication:	TX-001HR (17β-estradiol and micronized progesterone); Treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus
Reviewer:	Frederic Moulin, DVM, PhD

Background:

TherapeuticsMD is developing an oral fixed-dose combination product (development code name TX-001HR, proposed tradename BIJUVA®) consisting of a soft gel capsule containing solubilized 17β-estradiol and micronized progesterone. (b) (4)

TX-001HR is intended to treat moderate to severe vasomotor symptoms (VMS) due to menopause in women with a uterus, while protecting the endometrium from unopposed estradiol.

The application for BIJUVA® was opened in December 28, 2017 via the 505(b)(2) pathway and relies partially on the FDA's finding of safety for Prometrium® (NDA 019781) as the Listed Drug (LD) for progesterone. Published literature is provided to support the safety of estradiol and inform Sections 8 (Use in Specific Populations) and 13 (Nonclinical Toxicology) of the label. The nonclinical review of BIJUVA® was presented in a separate document dated September 10, 2018. This review is for labeling only.

Label

Sponsor Proposal	Final Label
HIGHLIGHTS OF PRESCRIBING INFORMATION **1. INDICATIONS AND USAGE** TRADENAME is a combination of (b) (4) and progesterone indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause (b) (4)	**HIGHLIGHTS OF PRESCRIBING INFORMATION** **INDICATIONS AND USAGE** BIJUVA is a combination of an estrogen and progesterone indicated in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause.
8. USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** **Risk Summary** (b) (4)	**8. USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** **Risk Summary** BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are not indicated for use in pregnancy. There are no data with the use of BIJUVA 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 (estrogen and progestins) before conception or during early pregnancy.
8.2 Lactation **Risk Summary** (b) (4)	**8.2 Lactation** **Risk Summary** BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, are 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.
(b) (4)	*See Note 2 regarding Section 8.3*

(b) (4)	
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment Fertility** Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors, and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen. Progesterone did not show evidence of genotoxicity in in vitro studies for point mutations or for chromosomal damage. In vivo studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg. Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would	**13 NONCLINICAL TOXICOLOGY** **13.1 Carcinogenesis, Mutagenesis, Impairment Fertility** <u>Nonclinical toxicity studies to determine the potential of BIJUVA (estradiol and progesterone) capsules, 1 mg/100 mg, to cause carcinogenicity or mutagenicity have not been performed. The effect of BIJUVA on fertility has not been evaluated in animals.</u> Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver. Progesterone has not been tested for carcinogenicity in animals by the oral route of administration. When implanted into female mice, progesterone produced mammary carcinomas, ovarian granulosa cell tumors, and endometrial stromal sarcomas. In dogs, long-term intramuscular injections produced nodular hyperplasia and benign and malignant mammary tumors. Subcutaneous or intramuscular injections of progesterone decreased the latency period and increased the incidence of mammary tumors in rats previously treated with a chemical carcinogen. Progesterone did not show evidence of genotoxicity in in vitro studies for point mutations

impair fertility until the cessation of treatment.	or for chromosomal damage. In vivo studies for chromosome damage have yielded positive results in mice at oral doses of 1000 mg/kg and 2000 mg/kg. Exogenously administered progesterone has been shown to inhibit ovulation in a number of species and it is expected that high doses given for an extended duration would impair fertility until the cessation of treatment.

Note 1: Suggested changes to the applicant's label are underlined.
Note 2: Section 8.3 was not considered relevant to the label of this product and deleted. The product is not indicated in males or females of reproductive potential.

Outstanding Nonclinical Issue:

N/A

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/s/

FREDERIC J MOULIN
10/24/2018

KIMBERLY P HATFIELD
10/25/2018

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	210132
Supporting document/s:	SDN 1, eCTD 0001
Applicant's letter date:	12/28/2017
CDER stamp date:	12/28/2017
Product:	Estradiol and Progesterone Capsules: 1/100 (b) (4) (mg estradiol/mg progesterone) (Proposed trade name: BIJUVA)
Indication:	treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus.
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:	Frederic Moulin, DVM, PhD
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	Hylton Joffe, MD, MMSc
Project Manager:	Kimberly Shiley

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 210132 are owned by TherapeuticsMD or are data for which TherapeuticsMD has obtained a written right of reference.
Any information or data necessary for approval of NDA 210132 that TherapeuticsMD does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 210132.

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1 Executive Summary

1.1 Introduction

TherapeuticsMD is developing an oral fixed-dose combination product (estradiol and progesterone, development code name TX-001HR) consisting of a soft gel capsule containing solubilized 17β-estradiol and micronized progesterone. TX-001HR is intended to treat moderate to severe vasomotor symptoms (VMS) due to menopause in women with a uterus, while protecting the endometrium from unopposed estradiol.

(b) (4)

The development of TX-001HR aims to satisfy the current unmet medical need for a combination endogenous hormone therapy provided as continuous/combined dose regimens with improved bioavailability and without allergenic components (such as peanut oil).

The sponsor is seeking approval via the 505(b)(2) pathway, as agreed to with the Division at a previous pre-NDA meeting (minutes dated January 13, 2016), and intends to rely on the FDA's finding of safety for Prometrium® (NDA 019781) as the Listed Drug (LD) for progesterone. Published literature is provided to support the safety of estradiol, and inform Sections 8 (Use in Specific Populations) and 13 (Nonclinical Toxicology) of the label, as well as the nonclinical sections of the proposed 505(b)(2) NDA.

1.2 Brief Discussion of Nonclinical Findings

The safety assessment of this new capsule formulation of solubilized estradiol plus micronized progesterone (TX-001HR) is based on previous findings of safety for the progesterone Listed Drug (LD) Prometrium® and relevant published literature to support the safety of estradiol. The highest proposed clinical doses of estradiol and progesterone in TX-001HR are also equal to or less than the approved doses for marketed oral estradiol and Prometrium® (oral progesterone).

Estradiol is an endogenous sex hormone present in many approved drug products for diverse indications, including the treatment of moderate to severe vasomotor symptoms as a single daily dose of 1 or 2 mg (e.g. Estrace®, Climara®, EstroGel®, Vagifem®, Vivelle®). The safety of estradiol is well-established and documented in the published literature following many years of clinical use. For this reason, the sponsor has not conducted any nonclinical studies of their own for estradiol and relied on relevant published literature to support the nonclinical safety and to inform nonclinical sections of the label. The literature that the sponsor has submitted is adequate for this purpose without requiring reliance on previous findings of safety for a reference drug product.

The nonclinical evidence supporting the safety of progesterone in TX-001HR are based on the Agency's determination of safety for the Listed Drug, Prometrium® (NDA 19-781). Prometrium® is an approved drug product (progesterone; 100 mg and 200 mg oral capsules) that is indicated for use in the prevention of endometrial hyperplasia in nonhysterectomized postmenopausal women who are receiving conjugated estrogens tablets (single daily dose of 200 mg at bedtime for 12 days sequentially per 28-day cycle), as well as for use in secondary amenorrhea (single daily dose of 400 mg at bedtime for 10 days). The scientific bridge between TX-001HR and oral Prometrium® is provided by two comparative bioavailability (BA) studies (studies EPROG-1K-351-12 and EPROG-1K-352-12) and one bioequivalence (BE) study (EPROG-1K-459-12). In the pivotal comparative BE study, the Applicant demonstrated that the progesterone exposure of a 1 mg estradiol/100 mg progesterone capsule administered under fed conditions was less than or comparable to the reference drug (Prometrium®). Refer to the clinical pharmacology review submitted by Dr. Peng Zou for further elaboration on the scientific bridge.

1.3 Recommendations

1.3.1 Approvability

Nonclinical data support approval of TX-001HR for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause in women with a uterus.

1.3.2 Additional Non-Clinical Recommendations

No additional nonclinical studies are recommended.

1.3.3 Labeling

Product labeling will be completed under a separate review.

2 Drug Information

2.1 Drug

2.1.1 Estradiol (b) (4)

CAS Registry Number: (b) (4)

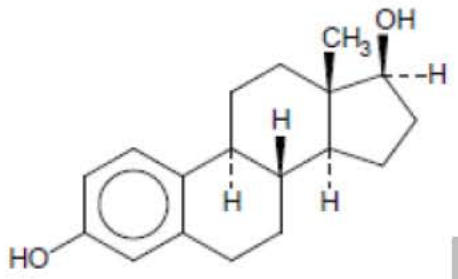
Generic Name: Estradiol (b) (4)

Code Name: TX-001HR

Chemical Name: Estra-1,3,5(10)-triene-3, 17β-diol, (b) (4)

Molecular Formula/Molecular Weight: (b) (4)

Structure or Biochemical Description: Estradiol has five asymmetric carbon centers in the steroid skeleton. The conformation of the product in TX-001HR corresponds to the conformation of the naturally occurring hormone molecule.



(b) (4)

Pharmacologic Class: Estrogen

2.1.2 Progesterone

CAS Registry Number: 57-83-0

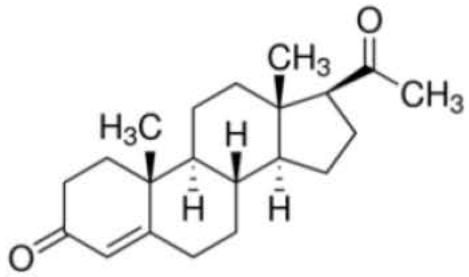
Generic Name: Progesterone

Code Name: TX-001HR

Chemical Name: Pregn-4-ene-3,20-dione, 17 alpha-hydroxy-6 alpha-methylpregn-4-ene-3, 2-dione.

Molecular Formula/Molecular Weight: $C_{21}H_{30}O_2$; 314.47 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Progestin

2.2 Relevant INDs, NDAs, BLAs and DMFs

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

(b) (4)

NDA 019781 (Virtus Pharms): Prometrium (progesterone oral capsule); indicated for 1) use in the prevention of endometrial hyperplasia in nonhysterectomized

postmenopausal women who are receiving conjugated estrogens tablets, and 2) secondary amenorrhea.

DMF # (b) (4) Estradiol/estradiol (b) (4) USP (Letter of authorization provided)

DMF # (b) (4) Micronized Progesterone USP (Letter of authorization provided)

2.3 Drug Formulation

TX-001HR consists of (b) (4) estradiol (b) (4) and micronized progesterone in a proprietary (b) (4) oral softgel capsule. The two drug substances are chemically and biologically identical to the endogenous 17β-estradiol and progesterone. The estradiol (b) (4) USP is sourced from (b) (4) and the progesterone USP is sourced from (b) (4)). Both active pharmaceutical ingredient (API) manufacturers have provided Letters of Authorization to reference their respective Drug Master File (DMF).
The drug product was originally manufactured by (b) (4) (clinical and registration batch), and subsequently by Catalent Pharma Solutions, LLC (registration batches) which is the proposed commercial manufacturer.

The softgel capsules are oval, opaque, light pink on one side and dark pink on the other side, filled with a (b) (4) containing the drug substances. (b) (4)

Table 1: Composition of (b) (4) TX-001HR Capsules

Component	Standard	Manufacturer	Function	Quantity/capsule (mg) (b) (4) 1/100 (1C1)
Estradiol (b) (4)	USP	(b) (4)		1.0
Progesterone (micronized)	USP			100.0
Medium chain mono/diglycerides (b) (4)	NF			(b) (4)
Lauroyl polyoxyl-32 glycerides (b) (4)	NF			

[redacted]

Gelatin, [redacted]	NF	[redacted]	[redacted]
Hydrolyzed gelatin	NF	[redacted]	[redacted]
Glycerin	USP	[redacted]	[redacted]
[redacted] **FD&C Red #40**	In house	[redacted]	[redacted]
[redacted] **Titanium Dioxide**	In house	[redacted]	[redacted]
Purified water	USP	[redacted]	[redacted]

2.4 Comments on Novel Excipients

There is no novel excipient in TX-001HR. The amount of each excipient for the [redacted] estradiol/progesterone strength capsule (1 mg/100 mg) is presented in Table 3, along with the corresponding oral potency listed in the FDA Inactive Ingredients Database (IID). All excipients are below IID limits.

Table 3: Comparison of Drug Product Excipient Quantities and FDA IID Potencies

Component	Maximum Quantity per Capsule (mg)	FDA IID Oral Potency (mg)
Medium chain mono/di-glycerides, NF [redacted]	[redacted]	[redacted]
Lauroyl polyoxyl-32 glycerides, NF [redacted]	[redacted]	[redacted]
Gelatin NF	[redacted]	[redacted]
Hydrolyzed gelatin NF	[redacted]	[redacted]
Glycerin USP	[redacted]	[redacted]
[redacted] **(FD&C Red 40** [redacted]**)**	[redacted]	[redacted]
[redacted] **(Titanium dioxide** [redacted]	[redacted]	[redacted]
Purified water, USP	[redacted]	[redacted]

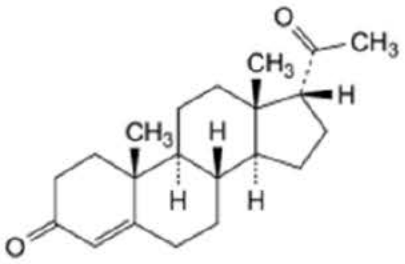
2.5 Comments on Impurities/Degradants of Concern

2.5.1 Progesterone Impurity Substance M

The specifications for impurities in the progesterone drug substance are based on the European Pharmacopoeia (EP) monograph, as well as the [redacted] DMF Technical Package acceptance criteria. [redacted] has included potential impurities, their acceptance limits and

quantitation methods in their DMF, and TherapeuticsMD transferred these methods to its manufacturing process. Among the (b) (4) specification for impurities in progesterone USP, a process impurity referred as EP Impurity M ((17α)-pregn-4-ene-3,20-dione; 17-Isoprogesterone; CAS# 2000-66-0) has an acceptance limit of no-more-than (NMT) (b) (4)%.

Figure 1: Progesterone Impurity M

EP Impurity M *Potential Process Impurity.*	(17α)-pregn-4-ene-3,20-dione.	

EP Impurity M was observed above the ICH identification limit of 0.2% on accelerated stability conditions for Phase 3 clinical batches manufactured at (b) (4) During the evaluation of clinical stability data, EP impurity M was identified in both room temperature and accelerated stability conditions samples. This impurity/degradant was present between (b) (4) to (b) (4)% in the drug product at release, with the proportion increasing under accelerated stability conditions. For (b) (4) lot number PN0082-25, this impurity/degradant was at (b) (4)% in the 6-month accelerated stability conditions samples, and the retest values ranged from (b) (4) to (b) (4)%.

EP Impurity M is chemically (17α)-isoprogesterone, a stereoisomer of progesterone with no reported toxicity in the literature. Since EP Impurity M was present in the clinical batches manufactured by (b) (4) at up to (b) (4)%, 23 months after manufacturing, it is "qualified" for safety at up to (b) (4)% through its administration in the phase 3 trial without adverse effect. EP impurity M was not predicted to react with DNA by two separate QSAR models (Leadscope and Derek Nexus) and is considered of no mutagenic concern following ICH M7(R1) guidance. ICH M7(R1) does not recommend further genotoxicity testing.
The request by TherapeuticsMD to increase the acceptance limits from (b) (4)% to (b) (4)% is within the guidance of "allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristic". In addition, there are no significant toxicities associated with this impurity. The no-more-than (NMT) (b) (4)% limit for EP Impurity M does not create a safety risk for patients and is therefore acceptable.

2.5.2 (b) (4)

(b) (4) is used as (b) (4) in (b) (4) of the synthesis process employed by (b) (4) to manufacture the estradiol API. TherapeuticsMD proposes to fix the acceptance limits in the final drug product to NMT (b) (4) parts per million (ppm). However, (b) (4) is not a (b) (4) included in the guidelines for (b) (4) and its permitted daily exposure limits have not been specified in guidance.

The central nervous system is a primary target for (b) (4) toxicity in humans and animals. Acute exposure to high concentration of (b) (4) vapors can lead to central nervous system depression, loss of consciousness, and even death. Prolonged exposures produce neurobehavioral and vision changes with inhaled concentrations as low as (b) (4) ppm. In addition to the central nervous system, nonclinical studies have identified the kidney, liver, reproductive system, and developing fetus as targets of (b) (4) toxicity. The liver and kidney toxicities are believed to be mediated by metabolites, while the parent compound is considered the active neurotoxicant. Neurobehavioral changes occur at lower concentrations than any other effects.

Because of its neurological toxicity and non-genotoxic mouse carcinogenicity, (b) (4) should be considered a (b) (4) per (b) (4) guidance. IARC has classified (b) (4) as a (b) (4) carcinogen (probably carcinogenic to humans) (IARC 2013).

Most of the evidences supporting the neurological and neurobehavioral effects of low exposures to (b) (4) comes from inhalation exposure. However, pharmacokinetics studies in animals have found similar blood concentrations after inhalation and oral administration, and the toxicity is expected to be similar.

The Agency for Toxic Substances and Disease Registry (ATSDR) indicates that the "Minimal Risk Levels (MRL) for chronic (≥ 365 days) oral exposure to (b) (4) is (b) (4) mg/kg/day. An MRL is an "estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure". For a female patient of 60 kg, the permissible daily exposure (PDE) would be (b) (4) x 60 = (b) (4) mg/day. The PDE can be used with the known maximum daily dose of the drug substance to determine the concentration of (b) (4) allowed in the drug product. Such limits are considered acceptable if the (b) (4) has been reduced to the practical minimum.

The PDE is (b) (4) mg/day and the maximum daily dose of estradiol in TX-001HR is 1 mg per day. Hence the maximum permissible concentration of (b) (4) in the estradiol component of TX-001HR is greater than the proposed specification of NMT (b) (4) The proposed specification is therefore an acceptable limit for (b) (4) in TX-001HR as per (b) (4)

Also, according to ICH M7(R1), a Threshold of Toxicological Concern (TTC)-based acceptable intake of a mutagenic impurity of 1.5 µg per person per day is associated with a negligible risk (theoretical excess cancer risk of <1 in 100,000 over a lifetime of exposure). The TTC is used for most pharmaceuticals as a default to derive acceptable limits to control mutagenic impurities present in pharmaceuticals when no definitive carcinogenicity data are available (Classes 2 and 3). Because (b) (4) is classified as a (b) (4) carcinogen, the TTC does apply to it. A daily intake of 1 mg estradiol from TX-001HR containing (b) (4) ppm ((b) (4) ng/mg) would result in a daily intake of (b) (4) ng of (b) (4) which is well below the TTC of 1.5 µg per day. The proposed specification of NMT (b) (4) ppm is also an acceptable limit for (b) (4) in TX-001HR as per ICH M7(R1).

There are no other impurities or degradants of concern in TX-001HR.

2.6 Proposed Clinical Population and Dosing Regimen

TX-001HR is intended to provide an oral continuous combined hormonal therapy regimen for menopausal women with an intact uterus who suffer from VMS associated with estrogen deficiency. TX-001HR provides postmenopausal women with a combination of natural estradiol and natural progesterone in a single capsule free of peanut oil and thus can be used in women who are unable to tolerate currently approved therapy due to peanut allergies.

(b) (4) TX-001HR 1 mg /100 mg (b) (4) demonstrated a clinically meaningful and statistically significant difference versus placebo in the reduction of the frequency and severity of moderate to severe VMS at Weeks 4 and 12 in the 12-week efficacy study (Study TXC12-05). The onset of action for frequency was observed at Week 3 for the 1 mg /100 mg dose group (b) (4)

2.7 Regulatory Background

The IND for this product and indication (IND 114477) has been in-house since August 2012 (Primary nonclinical reviewer – Kimberly Hatfield, PhD).

A pre-IND meeting was held on 04/10/2012 regarding the development plan for 17β-estradiol and progesterone (b) (4) combination soft gel capsules to treat moderate to severe vasomotor symptoms (VMS) associated with menopause.

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 ingredients, estrogen and progesterone. The sponsor stated at the time that the clinical safety assessment would be based on comparison to two approved oral products Estrace® and Prometrium® and the Division agreed that previous findings of safety and efficacy for the listed drugs (LD), and published literature data could provide the nonclinical support for the proposed IND.

On February 4th, 2014, TherapeuticsMD requested a meeting to clarify the role of progesterone for the efficacy endpoint of vasomotor symptoms. After receipt of the Agency's preliminary comments, the applicant needed no further discussion and the meeting was canceled.

On August 28, 2017, TherapeuticsMD requested a Type B preNDA meeting to discuss information required for submission of NDA 210132. The Division confirmed that relying on published literature for estradiol and FDA's finding of safety for the LD Prometrium® for progesterone, as the complete support for Sections 8 and 13 of the label and the non-clinical sections of the proposed 505(b)(2) NDA appeared acceptable. The Division reminded the Applicant that its proposed labeling had to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and that nonclinical information from the published literature for estradiol and the labeling for Prometrium® would be necessary. After receipt of the preliminary comments, TherapeuticsMD determined that further discussion was not needed, and the meeting was canceled.

3 Studies Submitted

3.1 Studies Reviewed

No new or updated nonclinical information was submitted.

3.2 Previous Reviews Referenced

IND 114477, SD# 4 (non-eCTD), 09/27/2012 (Reviewed by Kimberly Hatfield, PhD)
NDA 210132, SD# 1 (eCTD #001), 02/23/2018 (Filing review; Reviewed by Frederic Moulin, DVM, PhD)

11 Integrated Summary and Safety Evaluation

The safety assessment of this new capsule formulation of solubilized estradiol plus micronized progesterone is based on previous findings of safety for oral progesterone (Prometrium®) and the review of relevant published literature for estradiol.
Oral estradiol is an approved drug product that is used for several indications, including treatment of moderate to severe vasomotor symptoms associated with the menopause. Treatment with estradiol for vasomotor effects should be at the lowest dose and regimen that will control symptoms, and for the shortest duration consistent with treatment goals and risks. The usual initial dose range of estradiol for this indication is 1 to 2 mg daily, which is equal to or more than the proposed clinical dose of estradiol to be used in TX-001HR (b) (4) 1 mg). The sponsor does not intend to rely on previous findings of safety of an approved product for estradiol and has submitted relevant published literature in order to support the nonclinical safety of estradiol in TX-001HR, 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.

Prometrium® (100 mg and 200 mg capsules) is an approved oral progesterone drug product that is indicated for use in the prevention of endometrial hyperplasia in non-hysterectomized postmenopausal women who are receiving conjugated estrogens tablets, and for use in secondary amenorrhea. The applicant has demonstrated that the systemic exposure of patients to progesterone when administered as one capsule of TX-001HR was equal to or lower than the systemic exposure provided by equivalent doses of Prometrium. As a result, it is appropriate for the applicant to rely on the Agency's previous findings of nonclinical safety for Prometrium to support approval of the current product.

As an added safety measure, TX-001HR eliminates the use of the peanut oil excipient found in both branded and generic formulations of micronized progesterone, reducing the risk of unanticipated allergic reactions in patients prescribed this product.

Overall Conclusions: Pharmacology/Toxicology recommends approval of TX-001HR for the treatment of moderate to severe vasomotor symptoms (VMS) due to menopause in women with a uterus.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

FREDERIC J MOULIN
09/10/2018

KIMBERLY P HATFIELD
09/10/2018
I concur with the review and recommendations of Dr. Moulin.