

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210132Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum: October 15, 2018

Requesting Office or Division: Division of Bone, Reproductive and Urologic Products (DBRUP)

Application Type and Number: NDA 210132

Product Name and Strength: Bijuva (estradiol and progesterone) capsules
(b) (4)
1 mg estradiol/100 mg progesterone

Applicant/Sponsor Name: TherapeuticsMD, Inc.

FDA Received Date: October 5, 2018

OSE RCM #: 2018-22-1

DMEPA Safety Evaluator: Celeste Karpow, PharmD, MPH

DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the revised blister package labeling, professional sample blister label, and professional sample carton labeling for estradiol and progesterone capsules, NDA 210132 (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised blister package labeling and professional sample carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Karpow C. Label and Labeling Memorandum for Bijuva (estradiol and progesterone) capsules (NDA 210132). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 01. RCM No.: 2018-22.

A. APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 5, 2018

- Blister package labeling
- Professional sample blister labels
- Professional sample carton labeling
- Prescribing Information (Image not shown)

(b) (4)

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/s/

CELESTE A KARPOW
10/15/2018

LOLITA G WHITE
10/15/2018

**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: October 5, 2018

To: Hylton 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)

Sharon W. Williams MSN, BSN, RN
Senior Patient Labeling Team Reviewer, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Lynn Panholzer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): BIJUVA (estradiol and progesterone)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 210132

Applicant: TherapeuticsMD

1 INTRODUCTION

On January 31, 2018, TherapeuticsMD submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 210132 for BIJUVA (estradiol and progesterone) capsules, for oral use. The purpose of this submission is to propose (b)(4) BIJUVA (estradiol and progesterone) capsules, 1/100 (b)(4) (mg estradiol/mg progesterone), for the treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on February 14, 2018 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for BIJUVA (estradiol and progesterone) capsules, for oral use.

2 MATERIAL REVIEWED

- Draft BIJUVA (estradiol and progesterone) PPI received on January 31, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 25, 2018.
- Draft BIJUVA (estradiol and progesterone) Prescribing Information (PI) received on January 31, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 25, 2018.
- Approved ACTIVELLA (estradiol/norethindrone acetate) tablets, for oral use comparator labeling dated November 1, 2017.
- Approved PREMPRO (conjugated estrogens/medroxyprogesterone acetate tablets) comparator labeling dated November 1, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
10/05/2018

LYNN M PANHOLZER
10/05/2018

SHARON W WILLIAMS
10/05/2018

LASHAWN M GRIFFITHS
10/09/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 9, 2018

To: Kim Shiley, RN, Regulatory Project Manager
Division of Bone, Reproductive, and Urologic Products (DBRUP)

From: Lynn Panholzer, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for BIJUVA (estradiol and progesterone)
1 mg/100 mg capsules, for oral use (Bijuva)

NDA: 210132

In response to DBRUP's consult request dated February 14, 2018, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for BIJUVA.

PI and PPI: OPDP's comments on the proposed PI are based on the draft PI received by electronic mail from DBRUP on September 25, 2018, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the draft PPI, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labels: OPDP has reviewed the attached proposed carton and container labels submitted by the Applicant to the electronic document room on September 13, 2018 (proposed trade carton labels) and May 31, 2018 (professional sample carton and blister labels), and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lynn Panholzer at (301) 796-0616 or lynn.panholzer@fda.hhs.gov.

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/s/

LYNN M PANHOLZER
10/09/2018

Clinical Inspection Summary

Date	8/21/2018
From	Cheryl Grandinetti, Pharm.D. Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Kim Shiley, RPM Theresa van der Vlugt, M.D., Clinical Reviewer Shelley Slaughter, M.D., Ph.D. Clinical Team Leader Division of Bone, Reproductive, and Urologic Products
NDA #	210132
Applicant	TherapeuticsMD, Inc
Drug	Bijuva (estradiol/progesterone)
NME	No
Therapeutic Classification	Hormonal therapy
Proposed Indication	Treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus.
Consultation Request Date	February 7, 2018
Summary Goal Date	September 7, 2018
Action Goal Date	October 26, 2018
PDUFA Date	October 28, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Waldbaum, Redrick, and Hurtado were inspected in support of this NDA. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspections of Drs. Waldbaum, Redrick, and Hurtado was No Action Indicated (NAI).

II. BACKGROUND

Bijuva is a combination product of 17β-estradiol and progesterone in a softgel capsule form comprised of active ingredients that are chemically and biologically identical to endogenous estradiol and progesterone. The Applicant submitted this NDA as a 505(b)2 to support the use of Bijuva (estradiol and progesterone) softgel capsules for the treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus. The NDA identifies estradiol (DMF # (b) (4)) and progesterone (DMF # (b) (4)) as the reference listed drugs. An inspection was requested for the following protocol in support of this application:

TXC12-05, entitled "A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multi-Center Study to Evaluate the Safety and Efficacy of Estradiol in Combination with

Progesterone in Postmenopausal Women with an Intact Uterus: Estradiol to Reduce the Frequency and Severity of Vasomotor Symptoms and Progesterone to Manage the Incidence of Endometrial Hyperplasia.”

This was a randomized, double-blind, placebo-controlled, parallel group study in postmenopausal subjects with an intact uterus. The study involved a screening period of approximately 60 days before randomization, approximately 12 months (13 cycles) of treatment, and a 15-day follow-up period. During the screening period, subjects who experienced a minimum daily frequency of ≥ 7 (or ≥ 50 per week) moderate to severe hot flushes participated in a vasomotor symptoms (VMS) sub-study during the first 12 weeks of treatment. The sub-study subjects were stratified by treatment arm within the sites, and only sub-study subjects had possibility of being randomized to placebo. Following the screening period, sub-study subjects were randomized in a 1:1 ratio to one of the following 5 treatment arms.

- Treatment 1: Combined Estradiol 1 mg / Progesterone 100 mg formulation
- Treatment 2: Combined Estradiol 0.5 mg / Progesterone 100 mg formulation
- Treatment 3: Combined Estradiol 0.5 mg / Progesterone 50 mg formulation
- Treatment 4: Combined Estradiol 0.25mg / Progesterone 50 mg formulation
- Treatment 5: Placebo

All other subjects who qualified for the study (that is subjects who did not qualify for the VMS sub-study) were stratified by treatment arm within sites to one of the first four active treatment arms as listed above and received blinded study medication for 12 months.

This study took place in 117 sites in the United States, beginning August 5, 2013 and ending October 28, 2016. A total of 1845 subjects were randomized into the trial (1079 to the Non-Sub-study and 766 to the VMS Sub-study).

The primary objective of the study was to determine whether the estradiol and progesterone combination in Bijuva, given in a continuous fashion to postmenopausal subjects with an intact uterus was effective at:

- Reducing the frequency and severity of moderate to severe vasomotor symptoms associated with menopause when compared with placebo treatment at weeks 4 and 12
- Achieving a $\leq 1\%$ incidence rate of endometrial hyperplasia following 12 months of therapy

The primary efficacy endpoints (VMS sub-study) were the following:

- Mean change in frequency of moderate to severe vasomotor symptoms from baseline to week 4 in an active treatment group compared with placebo
- Mean change in frequency of moderate to severe VMS from baseline to week 12 in an active treatment group compared with placebo
- Mean change in severity of moderate to severe VMS at baseline to mild, moderate to

severe vasomotor symptoms at week 4 in an active treatment group compared with placebo

- Mean change in severity of moderate to severe VMS at baseline to mild, moderate to severe vasomotor symptoms at week 12 in an active treatment group compared with placebo

The primary safety endpoint was the incidence rate of endometrial hyperplasia at 12 months based on an a priori plan in which a consensus among two out of three pathologists is the final endometrial pathology diagnosis.

Rationale for Site Selection

The clinical sites were chosen for inspection because of their relatively large enrollment, treatment effect, and protocol deviations.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects Enrolled	Inspection Dates	Classification
Site #105 Arthur Waldbaum, M.D. 3773 Cherry Creek Drive North, Suite 685 Denver, CO 80209	TXC12-05 Subjects: 66	26-30 March 2018	NAI
Site #127 Scott Redrick, M.D. 6122 West Corporate Oaks Drive Crystal River, FL 34429	TXC12-05 Subjects: 47	20-23 March 2018	NAI
Site #142 Sandra Hurtado, M.D. 7400 Fannin, Suite 1280 Houston, TX 77054	TXC12-05 Subjects: 58	24-26 April 2018	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable

1. Arthur Waldbaum, M.D.

At this site for Protocol TXC12-05, 150 subjects were screened, 66 were randomized, 13 subject discontinued, and 53 subjects completed the study. The EIR did not include information on all subject who were discontinued from the study. Per the sponsor data listings, reasons for study discontinuation included loss to follow-up (5 subjects), protocol deviations (3 subjects) withdrawal of consent (2 subjects), adverse events (2 subjects), and lack of efficacy (1 subject).

Records reviewed during the inspection included study and subject source records (including source records for the primary efficacy and safety endpoints), communications with the IRB, contract research organization (CRO) and sponsor, drug accountability, informed consents, subject study visits, randomization, and adverse events.

An audit of the study records for all randomized subjects was conducted. Site personnel entered data into an electronic data capture system. A flash drive containing the eCRF information was sent to the site at the end of the study and was available at the time of inspection for verification of data listings against source data. No deficiencies or significant errors were noted. There was no evidence of under-reporting of adverse events and the primary efficacy endpoint data were verifiable.

The following major protocol deviations were noted during the inspection.

Subject Number	Protocol Deviation	OSI Reviewer's Comment	Reported to FDA
(b) (6)	Selection criteria not met	The protocol excludes subjects with a history of thyroid disease. The subject was diagnosed with hyperthyroidism in 1969; had surgery and was cured. The subject was enrolled in (b) (6) and completed the study on (b) (6). In (b) (6), sponsor was notified of protocol deviation and subject was permitted to continue	Yes
(b) (6)	Selection criteria not met	The protocol excludes subjects with a history of liver disease. This subject has a history of hepatitis C in 2005 but was cured that same year. All labs were normal prior to entry so subject was enrolled and randomized in (b) (6). In (b) (6), sponsor advised that the subject be withdrawn because she did not meet eligibility criteria.	Yes

The sponsor reported a protocol deviation for Subject # (b) (6) for taking citalopram, a prohibited medication, during the study. While this was reported as a protocol deviation, on further review during inspection, it was noted that this patient had been on a stable dose of

citalopram for depression since 2007. The protocol prohibits use of SSRIs for hot flushes within 28 days prior to screening and throughout the study. However, SSRIs are acceptable as long as the SSRIs are used for treatment of conditions other than hot flushes and the subject has been on a stable dose for greater than or equal to 6 months.

No under-reporting of adverse events and no protocol deviations other than those listed in the line listings were observed.

Reviewer’s comments: The major protocol deviations noted above likely do not have an impact on the efficacy or safety results of the study. The reported protocol deviation involving the use of a prohibited medication was in fact not a deviation because the protocol permitted the use of an SSRI for conditions other than hot flushes. The two protocol deviations involved inclusion/exclusion criteria in the study, with one subject later being withdrawn by the sponsor and the other being allowed to continue.

2. Scott Redrick, M.D.

At this site for Protocol TXC12-05, 70 subjects were screened, 47 were randomized, 17 subject discontinued, and 30 subjects completed the study. Records reviewed during the inspection included study and subject source records, including IRB documentation and source records for the primary efficacy and safety endpoints, drug accountability, informed consents, subject study visits, randomization, and adverse events. An in-depth audit of the study records for 24 of the 47 randomized subjects was conducted. No under-reporting of adverse events and no protocol deviations other than those listed in the line listings were observed. The source documentation from the site matched with the line listings that the sponsor provided to the FDA for the efficacy, safety and protocol deviations.

3. Sandra Hurtado, M.D.

At this site for Protocol TXC12-05, 131 subjects were screened, 58 were randomized, 13 subject discontinued, and 45 subjects completed the study. Records reviewed during the inspection included study and subject source records, including IRB documentation and source records for the primary efficacy and safety endpoints, drug accountability, informed consents, subject study visits, randomization, adverse events, protocol deviations, and concomitant medications. An audit of the study records for 74 of 131 subjects that were screened was conducted. This included all records for 37 of the 45 subjects who completed the study. There was 1 case where source data listings did not match those provided to the FDA (see table below for Subject # (b) (6)) and another case where the source data could not be verified (Subject # (b) (6)).

Patient Number/Treatment Group	Date	Data Listings Submitted to FDA (Daily Hot Flush Diary)	Source Documents, Hot Flush Diaries retained at the site
(b) (6) /Combined Estradiol 0.5 mg / Progesterone 50 mg	(b) (6) (Week -3)	Mild: 0 Moderate: 0 Severe: 3	Mild: 0 Moderate: 0 Severe: 2

Other than these discrepancies, the source documentation from the site matched with the line listings provided by the sponsor to the FDA for the efficacy, safety and protocol deviations. No under-reporting of adverse events and no protocol deviations other than those listed in the line listings were observed.

Reviewer's comments: The data discrepancies observed during the inspection involved the primary efficacy endpoint. The data discrepancy for Subject # [REDACTED]^{(b) (6)} occurred during the screening period (Week -3), so it likely does not have an impact on the efficacy or safety results of the study. However, for Subject # [REDACTED]^{(b) (6)}, we recommend that the data for this subject not be used in the efficacy analysis because the source data could not be verified against the data listings provided by the sponsor. This subject inconsistently used both tally marks and numbers to document the number of hot flushes experienced, and there was no documented follow-up from the clinical investigation site or sponsor to verify the number of hot flushes experienced by this subject.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D. Team Leader,
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Kassa Ayalew, M.D., M.P.H Branch Chief
Good Clinical Practice Assessment Branch
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cc:

Central Doc. Rm. NDA 210132

DBRUP /Project Manager/Kim Shiley

DBRUP /Medical Officer/ Theresa van der Vlugt

DBRUP/ Clinical Team Leader/ Shelley Slaughter

DBRUP/Division Director/Joffe Hylton

OSI /Office Director/David Burrow

OSI/DCCE/Division Director/Ni Khin

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OSI/DCCE/Team Leader/Phillip Kronstein

OSI/DCCE/GCP Reviewer/Cheryl Grandinetti

OSI/DCCE/GCP Reviewer/Roy Blay

OSI/ GCP Program Analysts/Yolanda Patague

OSI/Database Project Manager/Dana Walters

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/s/

CHERYL A GRANDINETTI
08/22/2018

PHILLIP D KRONSTEIN
08/22/2018

KASSA AYALEW
08/23/2018

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:	August 1, 2018
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products
Application Type and Number:	NDA 210132
Product Name and Strength:	Bijuva (estradiol and progesterone) capsules  (b) (4) 1 mg estradiol/100 mg progesterone
Product Type:	Multi-ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	TherapeuticsMD Inc
FDA Received Date:	December 28, 2017
OSE RCM #:	2018-22
DMEPA Safety Evaluator:	Celeste Karpow, PharmD, MPH
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 blister package labeling, professional sample blister label, professional sample carton labeling and Prescribing Information (PI) for estradiol and progesterone capsules, NDA 210132 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.

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

Full Prescribing Information (PI)

1. The imprint code for the (b) (4) tablet strength is not specified in section 16.1, How Supplied of the Full Prescribing information.
2. The patient information section of the PI does not indicate what users should do if they miss a dose.

Blister Package Labeling (commercial configuration) and Professional Sample Carton Labeling

3. The statement of strength per capsule is not prominently displayed, (b) (4)
4. The statement of strength on the principal display panel (PDP) and professional sample blister cards can be improved (b) (4).
5. The identified expiration date format can be improved to minimize confusion. (b) (4)
6. (b) (4)

Blister Package Labeling (commercial configuration)

7. The panel which contains the drug product lacks product identifier information (e.g. proprietary name, established name, NDC number, strength, expiration date, and lot number.)

Blister Package Labeling (commercial configuration)

8. The linear barcode is absent on the blister package labeling.

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 Prescribing Information (PI) labeling, blister package labeling, blister carton labeling, professional sample blister carton, and professional sample blisters 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.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Section 16.1, How Supplied of the Full Prescribing information states, “Each capsule is imprinted in white ink indicating the dosage strength ((b) (4) 1C1).” However, the imprint code for the (b) (4) tablet strength is not specified in this section. We recommend adding the imprint code (b) (4) to the How Supplied section in the PI labeling to facilitate product identification (b) (4)
2. 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

We recommend the following be implemented prior to approval of this NDA:

B. Blister Package Labeling (commercial configuration) and Professional Sample Carton Labeling

1. As currently presented, the strength per capsule is not prominently displayed and may lead to (b) (4) errors. Revise the statement of strength on the principle display panel (PDP) and professional sample to read “xx mg/xx mg per capsule” (b) (4)
2. To decrease clutter and emphasize the statement of strength, consider revising the statement of strength on the principal display panel (PDP) and professional sample blister cards (b) (4)
For example:

(b) (4)

“Bijuva
(estradiol/progesterone capsule)
1 mg/100 mg per capsule”

3. The expiration date format you propose (MMMDYYYY) 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)
MMMYYYY (e.g., JAN2013)
YYYY-MMM-DD (e.g., 2013-JAN-31)
YYYY-MM-DD (e.g., 2013-01-31)

4. (b) (4)

- C. Blister Package Labeling (commercial configuration)
 - 5. The panel that contains the drug product lacks important product identifier information. We recommend you include the proprietary name, established name, NDC number, strength, expiration date, and lot number on the panel that contains the product to prevent wrong drug errors.

- D. Blister Package Labeling (commercial configuration)
 - 6. As currently presented, the carton labeling lacks a linear barcode. The linear barcode is often used for 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 are visible on the outside of the carton labeling. Both the linear and 2D barcodes should be surrounded by sufficient white space to allow scanners to read the barcodes properly in accordance with 21 CFR 201.25(c)(1)(i). In addition, both the linear and 2D barcodes should be presented in close proximity to each other to minimize confusion users may experience with multiple barcodes.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for estradiol and progesterone softgel capsules received on December 28, 2017 from TherapeuticsMD Inc.

Table 2. Relevant Product Information for estradiol and progesterone softgel capsules	
Initial Approval Date	N/A
Active Ingredient	estradiol and progesterone
Indication	treatment of moderate to severe vasomotor symptoms associated with menopause in women with a uterus.
Route of Administration	oral
Dosage Form	capsule, liquid-filled
Strength	(b) (4) 1 mg estradiol/100 mg progesterone
Dose and Frequency	Take one capsule orally each evening with food.
How Supplied	(b) (4) estradiol and progesterone softgel capsule is provided in a blister package of (b) (4) capsules.
Storage	Store at 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 – (b) (4) (b) (4) push through paperbacked aluminum foil lidding

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 7, 2018, we searched DMEPA's previous reviews using the terms, "estradiol progesterone" and "210132." Our search did not identify any relevant previous reviews.

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,^a along with postmarket medication error data, we reviewed the following estradiol and progesterone capsule labels and labeling submitted by TherapeuticsMD Inc.

- Blister package labeling received on May 31, 2018
- Professional sample blister labels received on May 31, 2018
- Professional sample carton labeling received on May 31, 2018
- Prescribing Information (Image not shown) received on December 28, 2017

G.2 Label and Labeling Images

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

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08/01/2018

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