CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218718Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 6, 2024
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 218718
Product Name, Dosage Form, and Strength:	Femlyv (norethindrone acetate and ethinyl estradiol) orally disintegrating tablets, 1 mg/20 mcg
Applicant Name:	Millicent Puerto Rico LLC
FDA Received Date:	June 3, 2024
TTT ID #:	2023-6589-2
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Millicent Puerto Rico LLC submitted revised carton labeling (cartons and pouches) received on June 3, 2024 for Femlyv. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised carton labeling for Femlyv (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and memorandum.[a,b]

2 CONCLUSION

Millicent Puerto Rico LLC implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kalonia, J. Label and Labeling Review for Femlyv (NDA 218718). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAR 14. TTT ID: 2023-6589.

[b] Kalonia, J. Label and Labeling Review for Femlyv (NDA 218718). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAY 22. TTT ID: 2023-6589-1.

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/s/

JUSTINE H KALONIA
06/06/2024 03:18:03 PM

STEPHANIE L DEGRAW
06/06/2024 08:33:16 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 22, 2024
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 218718
Product Name, Dosage Form, and Strength:	Femlyv (norethindrone acetate and ethinyl estradiol) orally disintegrating tablets, 1 mg/20 mcg
Applicant Name:	Millicent Puerto Rico LLC
FDA Received Date:	May 7, 2024
TTT ID #:	2023-6589-1
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Millicent Puerto Rico LLC submitted revised container labels and carton labeling received on May 7, 2024 for Femlyv. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container labels and carton labeling for Femlyv (Appendix A) to determine if they are 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 container label and carton labeling are unacceptable from a medication error perspective. As presented, it is unclear what the expiration date format will be, so we are unable to evaluate this from a medication error perspective. Additionally, we acknowledge they have implemented the change from (b) (4) to "ODT", but the carton and container do not specify that ODT is an abbreviation for "orally disintegrating tablet". Further, the Applicant's response stated that they implemented the recommendation to replace (b) (4) with "See Prescribing Information" on the carton labeling, but that does not appear to have been implemented on the carton labeling received. Thus, we provide our recommendations for the Applicant below.

3 RECOMMENDATIONS FOR MILLICENT PUERTO RICO LLC

A. General Comments (Container Labels & Carton Labeling)
    1. We acknowledge that you indicate where you intend to place the expiration date, however, you have not provided the intended format of the expiration date. Thus, we are unable to assess the proposed expiration date format from a medication safety perspective. Provide the format of the expiration date you intend to use on the container labels and carton labeling.

B. Carton Labeling (Cartons and Pouches)
    1. We acknowledge that you revised (b) (4) to "ODT" on the carton labeling. However, the carton does not specify that ODT is the abbreviation for "orally disintegrating tablet". First use of abbreviations should be defined to prevent confusion. To improve clarity, we recommend revising the statements (b) (4) (b) (4) that appear on the principal display panels to read "This package contains X blister card(s) of 28 orally disintegrating tablets (ODTs)". The "ODT" and "ODTs" abbreviations may continue to be used on the side panels.
    2. Your response stated that you implemented the recommendation to revise the Dosage statement on the carton labeling such that the 2nd sentence should now read "See Prescribing Information." However, the 2nd sentence of the Dosage statement on the carton labeling received in the submission still reads (b) (4)

[a] Kalonia, J. Label and Labeling Review for Femlyv (NDA 218718). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAR 14. TTT ID: 2023-6589.

(b) (4) Therefore, this revision does not appear to have been implemented. We again recommend revising the 2nd sentence to read "See Prescribing Information."

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/s/

JUSTINE H KALONIA
05/22/2024 11:13:49 AM

STEPHANIE L DEGRAW
05/22/2024 02:43:47 PM

M E M O R A N D U M

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

DATE: 5/8/2024

TO: Division of Urology, Obstetrics, and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 218718

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in December 2023. The inspection was conducted under the following submission: NDA Non-Responsive.

The following item was discussed with the site:

- Non-Responsive

After review of the inspection findings and the site's response, OSIS concluded that the discussion items did not impact the reliability of the data for the inspected study.

Site

Facility Type	Facility Name	Facility Address
Clinical	Celerion	22-24 Lisburn Road, Belfast, Northern Ireland, United Kingdom

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/s/

FOLAREMI ADEYEMO
05/08/2024 01:32:32 PM

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

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

Memorandum

Date: May 6, 2024

To: Kalesha Grayson, Regulatory Project Manager, Division of Urology, Obstetrics, and Gynecology (DUOG)

Ionna Comstock, Clinical Reviewer, DUOG

From: Elvy Varghese, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets)

NDA: 218718

Background:
In response DUOG's consult request dated November 15, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI) and carton and container labeling for the original NDA submission for FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets) [Femlyv].

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 26, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on May 1, 2024.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on April 26, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at Elvy.Varghese@fda.hhs.gov.

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/s/

ELVY M VARGHESE
05/06/2024 07:31:46 AM

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:	May 1, 2024
To:	Kalesha Grayson Regulatory Project Manager **Division of Urology, Obstetrics, and Gynecology (DUOG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Elvy Varghese, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets)
Dosage Form and Route:	for oral use
Application Type/Number:	NDA 218718
Applicant:	Millicent Puerto Rico, LLC

1 INTRODUCTION

On September 27, 2023, Millicent Puerto Rico, LLC submitted for the Agency's review New Drug Application (NDA) #218718 for FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets). The proposed indication is for use by females of reproductive age to prevent pregnancy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Urology, Obstetrics, and Gynecology (DUOG) on November 15, 2023, for DMPP to review the Applicant's proposed PPI, for FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets), for oral use.

2 MATERIAL REVIEWED

- Draft FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets) PPI received on September 27, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on April 16, 2024.
- Draft FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets) PPI received on September 27, 2023, revised by the Review Division throughout the review cycle, and received by OPDP on April 26, 2024
- Draft FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets) Prescribing Information (PI) received on September 27, 2023, revised by the Review Division throughout the review cycle, and received by DMPP on April 16, 2024.
- Draft FEMLYV (norethindrone acetate and ethinyl estradiol orally disintegrating tablets) PPI received on September 27, 2023, revised by the Review Division throughout the review cycle, and received by OPDP on April 26, 2024.
- Approved comparator labeling for Minastrin 24 Fe (norethindrone acetate and ethinyl estradiol tablets and ferrous fumarate tablets) dated June 26, 2023.

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%.

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 APHont 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/

MARY E CARROLL
05/01/2024 02:14:52 PM

ELVY M VARGHESE
05/01/2024 02:18:09 PM

MARCIA B WILLIAMS
05/01/2024 02:44:15 PM

LASHAWN M GRIFFITHS
05/01/2024 03:15:22 PM

LABEL AND LABELING OR LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 14, 2024
Requesting Office or Division:	Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number:	NDA 218718
Product Name, Dosage Form, and Strength:	Femlyv (norethindrone acetate and ethinyl estradiol) orally disintegrating tablets, 1 mg/20 mcg
Product Type:	Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Millicent Puerto Rico LLC
FDA Received Date:	September 27, 2023
TTT ID #:	2023-6589
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Femlyv (norethindrone acetate and ethinyl estradiol) orally disintegrating tablets, the Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the proposed Femlyv Prescribing Information (PI), Patient Information (i.e., the proposed "Guide for using Femlyv"), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS 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 – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Information Request about Blister (b) (4)	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed Prescribing Information (PI), Patient Information (i.e., the proposed "Guide for using Femlyv"), container (blister card) label, and carton (pouch and carton) labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in **Section 4** for the Division and in **Section 5** for Millicent Puerto Rico LLC.

4 RECOMMEDATIONS FOR DIVISION OF UROLOGY, OBSTETRICS, AND GYNECOLOGY (DUOG)

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information and Patient Information – General Issues			

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	The method of administration can be improved for clarity. (b) (4) [redacted]	We note that the listed drug for FEMLYV (i.e., Minastrin 24 Fe) is a tablet that may be "chewed and swallowed or swallowed whole". Not specifying what to do with the proposed ODT with regards to swallowing and the amount of water to follow it with may result in improper administration technique medication errors. Furthermore, the data presented by Clinical Pharmacology showed that taking this product without water results in higher exposure to the ethinyl estradiol component. Therefore, the labels and labeling should specify taking this product with the recommended 8 ounces (240 mL) of water in order to achieve a bioequivalent level of drug to the listed drug.	We recommend the Applicant add information on whether the ODT can or cannot be swallowed whole to the labeling. Additionally, we recommend revising the "follow with water" statements within the HPI (DOSAGE AND ADMINISTRATION), FPI (Section 2), and Patient Information ("How do I take FEMLYV?") to specify the specific amount of water recommended following each dose is 8 ounces (240 mL). Furthermore, we recommend including similar language in Section 17 (PATIENT COUNSELING INFORMATION). We also recommend this important information appear on the container label and carton labeling (see Table 3).
2.	The PI refers to the dosage form as "tablet(s)" in some places.	The correct dosage form is orally disintegrating tablet (ODT). Referring to this product as "tablet(s)" may result in confusion leading to incorrect method of	Consider revising all instances of "tablet(s)" alone to "orally disintegrating tablet(s)" or "ODT(s)", the abbreviation for the dosage form of this product, if appropriate.

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		administration errors (e.g., swallowing the tablet whole instead of allowing it to dissolve on the tongue).	Alternatively, in some instances it may be appropriate to refer to the product by the tradename, "FEMLYV".
3.	The incorrect dosage form "pill" is used throughout the PI and Patient Information labeling to describe solid-oral dosage forms of oral contraceptives, including the proposed product. This is inconsistent with USP definitions because the proposed product is an ODT dosage form, and the other marketed oral contraceptives are available as capsules, tablets, or chewable tablets. In the PI, we note the term "pill" is used in the phrases "another pill", "progestin only pill", and "post-pill amenorrhea".	Per USP Chapter <1151>, "Pills" are an official dosage form defined as *"drug substance-containing small, spherical, solid bodies intended for oral administration. The pill dosage form has been largely replaced by compressed tablets and by capsules. Unlike tablets, pills are usually prepared by a wet massing, piping, and molding technique. This term is frequently incorrectly used as a general term to describe solid oral dosage forms, such as tablets and capsules."*	We recommend revising the dosage form throughout the labeling to accurately describe the correct dosage forms of the proposed product and the other marketed oral contraceptives. For the proposed product, for example, "FEMLYV is a birth control pill" could be revised to read "FEMLYV is an orally disintegrating tablet used for birth control". For the other products, "birth control pills", "another pill", "Progestin-only pill", and "post-pill amenorrhea" could be revised to read "oral birth control products", "another oral contraceptive", "progestin-only oral contraceptive", and "post-treatment amenorrhea".
Highlights of Prescribing Information			
1.	In the DOSAGE AND ADMINISTRATION section of the HPI, the 2nd bullet point starts with the same language in the preceding bullet point ((b) (4)).	Duplicate language may result in overlooking the remainder of the information in the 1st or 2nd bullet points. Also, since both bullet points describe how to take the product, these can be combined for word economy.	We recommend removing the duplicate (b) (4) phrase from the 2nd bullet point, and combining the rest of the sentence (b) (4)) with the 1st bullet point, such that it reads:

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			• "Place one tablet on the tongue and allow to disintegrate, and then follow with 8 ounces (240 mL) of water at the same time every day for 28 days."
Full Prescribing Information – Section 2 Dosage and Administration			
1.	We note that Section 2.1 (b) (4) of the FPI has the following redundant sentences: (b) (4)	These sentences can be improved for conciseness.	We recommend revising these sentences to read: (b) (4) (b) (4) place one tablet on the tongue, allow to disintegrate, and then follow with 8 ounces (240 mL) of water at the same time every day."
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	We note that the storage statement includes symbols (hyphens) in the temperature range.	Symbols may be misinterpreted, and are error-prone.	To increase clarity, we recommend revising the storage statement by replacing hyphens with the intended meaning "to", such that the storage information reads: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to (b) (4) °C (59°F to (b) (4) °F)."
Patient Information (Patient Labeling: Guide for Using FEMLYV)			
1.	The title of the Patient Information is presented as "Guide for Using FEMLYV".	We recognize the Applicant modeled this labeling after the listed drug, however, for new NDA products we recommend the labeling be consistent with current content and format	We recommend revising the title of the Patient Information from "Guide for Using FEMLYV" to "Patient Information for FEMLYV". We defer to DMPP/PLT to make additional

Table 2. Identified Issues and Recommendations for Division of Urology, Obstetrics, and Gynecology (DUOG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		recommendations for patient labeling.	recommendations regarding the content and format of the Patient Information labeling.

5 RECOMMENDATIONS FOR MILLICENT PUERTO RICO LLC

Table 3. Identified Issues and Recommendations for Millicent Puerto Rico LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label, Pouch Labeling, and Carton Labeling			
1.	The placeholders for the lot number and expiration date are missing. We note you have designated a spot for the serialization information "GTIN, Lot, EXP, Etc." on only the proposed "sample carton" labeling; however, the container label, pouch labeling (trade and sample), and trade carton labeling do not designate a placeholder for the serialization information.	The lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). The label of an official drug product shall bear an expiration date per USP General Chapter <7>.	Add the placeholders for the lot number in accordance 21 CFR 201.10(i)(1). Add the placeholder for the expiration date in accordance with USP General Chapter <7>. We recommend you ensure that there are no other numbers located in close proximity to the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If

Table 3. Identified Issues and Recommendations for Millicent Puerto Rico LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date.
2.	The method of administration can be improved for clarity. We note that (b) (4) the PI specified that FEMLYV was administered as follows (b) (4) However, this instruction to follow with water is unusual for the administration of oral contraceptives and orally disintegrating tablets (ODTs). Therefore, it is important to include this information on the labels and labeling.	Not specifying what to do with your proposed ODT with regards to administration (i.e., allowing to disintegrate on the tongue, swallowing, and the amount of water to follow it with) may result in improper administration technique medication errors. Furthermore, the data presented in your submission showed that taking this product without water results in higher exposure to the ethinyl estradiol component. Therefore, to ensure patients achieve a bioequivalent level of drug to the listed drug, the labels and labeling should specify to take this product with 8 ounces (240 mL) of water.	We recommend you add to the container labels (if room allows), pouch labeling, and carton labeling this important information about how to administer the ODT (i.e., allow to disintegrate on the tongue, swallow, then follow with 8 ounces (240 mL) of water). For example, add a statement like "Allow ODT to disintegrate on the tongue before swallowing. MUST BE TAKEN WITH WATER; follow each dose with 8 ounces (240 mL) of water".
3.	As presented on the proposed labels and	This can be revised for clarity.	Ensure that each active ingredient appears on one line, replacing the forward slash

Table 3. Identified Issues and Recommendations for Millicent Puerto Rico LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	labeling, the established name reads: (b) (4) and (b) (4)		mark with the word "and". Additionally, to avoid users overlooking this unique dosage form, we recommend presenting the phrase "orally disintegrating tablets" together on one line below the active ingredients. Revise the established name and dosage form such that it reads: (norethindrone acetate and ethinyl estradiol orally disintegrating tablets).
Pouch Labeling and Carton Labeling			
1.	As currently presented, the proprietary name, established name, dosage form, and product strength do not have adequate legibility. The readability is compromised due to poor color contrast (b) (4) As a result, these statements lack conspicuousness, which is not in accordance with 21 CFR 201.15(a)(6). Additionally, the manufacturer information (e.g., manufacturer name and logo) competes in prominence with critical	The proprietary name, established name, dosage form, and product strength, along with the route of administration, and warnings or cautionary statements should be the most prominent information on the principal display panel (PDP). Inadequate legibility, readability, and color contrast of important information like the proprietary name, established name, dosage form, and product strength may lead to confusion during identification of the medical product, which can lead to medication errors.	We recommend improving the legibility of the proprietary name, established name, dosage form, and product strength by utilizing darker font color, heavier typeface, or other means to achieve this. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022). Additionally, ensure this information is more prominent than the manufacturer name and logo. Increase the conspicuousness of these statements in accordance with 21 CFR 201.15(a)(6) by improving the contrast between the font color and background color.

Table 3. Identified Issues and Recommendations for Millicent Puerto Rico LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	product information (e.g., proprietary name, established name, dosage form, strength) because of the poor color contrast of this critical information.	Lack of conspicuousness of critical product information may contribute to product selection medication errors. See 21 CFR 201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.	Consider all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement, NDC code, etc.).
2.	The terminology within the dosage statement of the pouch and carton labeling (b) (4) s inconsistent with the terminology in the Prescribing Information and is inconsistent between the pouch and carton labeling.	To ensure consistency with the terminology in the Prescribing Information and the Physician Labeling Rule (PLR) across all labeling, we recommend (b) (4) (b) (4) statements be revised to read as "Recommended Dosage" or just "Dosage".	We recommend revising the dosage statement on the carton labeling for consistency with the pouch labeling (i.e., remove the word (b) (4)). Also, replace the term (b) (4) with "Prescribing Information". In summary, we recommend revising the dosage statement on both the pouch and carton labeling to read, "Dosage: One tablet daily for 28 days as directed by the physician. See Prescribing Information."

Table 3. Identified Issues and Recommendations for Millicent Puerto Rico LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	We note that the pouch and carton labeling refers to the product as (b) (4) in some locations.	The correct dosage form is orally disintegrating tablets (ODT). Referring to this product as (b) (4) may result in confusion leading to incorrect method of administration errors (e.g., (b) (4)	Consider revising all instances of (b) (4) alone to "orally disintegrating tablets" or "ODT", the abbreviation for the dosage form of this product, if appropriate.
4.	We note that the principal display panel (PDP) and side panels of the pouch and carton labeling include the statement: (b) (4) We recognize that other oral contraceptives containing 24 active doses per blister include a similar statement on the labels and labeling.	This may result in confusion regarding the contents of each carton because each blister is a "28-day regimen" (i.e., each blister contains 28 ODTs, such that 24 are active and 4 are placebo). Additionally, we are concerned that this statement on the Trade carton labeling may be misleading because there are 24 active ODTs per blister card, and each Trade carton contains 3 blister cards (i.e., 72 active ODTs per carton).	We recommend revising (b) (4) on all pouch and carton labeling to read: "Each blister provides 24 days of active therapy". Further, we recommend removing or decreasing the prominence of the statement "Each blister provides 24 days of active therapy" on the PDP of the pouch and carton labeling, as well as the 2 side panels of the trade carton labeling. Additionally, we recommend either adding the statement "28-day regimen" or increasing the prominence of the quantity statement, and ensure that either statement appears more prominent than "each blister provides 24 days of active therapy" on the pouch and carton labeling.
Carton Labeling			

Table 3. Identified Issues and Recommendations for Millicent Puerto Rico LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The product identifier is missing.	In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.	We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers* (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Femlyv that Millicent Puerto Rico LLC submitted on September 27, 2023, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug (Minastrin 24 Fe) and Femlyv

Product Name	Minastrin 24 Fe[a]	Femlyv
Application Number	NDA 203667	NDA 218718
Initial Approval Date	May 8, 2013	N/A
Active Ingredient	norethindrone acetate and ethinyl estradiol	norethindrone acetate and ethinyl estradiol
Indication	For use by females of reproductive potential to prevent pregnancy.	For use by females of reproductive potential to prevent pregnancy.
Route of Administration	oral	oral
Dosage Form	tablets	orally disintegrating tablets (ODT)
Strength	1 mg norethindrone acetate and 20 mcg ethinyl estradiol	1 mg/20 mcg (1 mg norethindrone acetate and 20 mcg ethinyl estradiol)
Dose and Frequency	1 tablet daily chewed and swallowed or swallowed whole taken at the same time of day.	Place 1 tablet on the tongue and allow to disintegrate and then follow with water at the same time every day.
How Supplied	Each blister card contains 28 tablets in the following order: • 24 active tablets • 4 inactive tablets Each carton contains 5 blister cards.	Each blister card (dispenser) contains 28 ODTs in the following order: • 24 active ODTs • 4 inactive ODTs Each carton contains 3 blister cards.
Storage	Store at 20˚ to 25˚C (68˚ to 77˚ F); excursions permitted to 15˚ to 30˚C (59˚ to 86˚ F) [see USP Controlled Room Temperature].	Store at 20°C to 25 ˚ C (68°F to 77˚ F); excursions permitted to 15°C to (b) (4)˚C (59°F to (b) (4)˚ F).
Container Closure	Blister card	Blister card (dispenser)

[a] Minastrin 24 Fe [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. June 2023. [cited 2023 OCT 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/203667s012lbl.pdf.

APPENDIX E. INFORMATION REQUEST ABOUT BLISTER (b) (4)

On February 5, 2024, we issued an Information Request (IR) to inquire whether labeling is proposed for the "blister (b) (4) described in the Stability Summary and Conclusion received in the September 27, 2023 submission, and requested they submit any labeling, if any, proposed for the blister (b) (4) (along with photographic images of the blister, blister card, blister (b) (4) and pouch, if available) for our review.[b] On February 14, 2024, the Applicant responded that "there will be no printing or label language included on the (b) (4) (per the newly added blister (b) (4) description under Secondary Packaging in the revised Container Closure System document).[c]

[b] Borbor-Lebbie, Mammah. FDA Communication: NDA 218718 (Information Request email for Femlyv). Silver Spring (MD): FDA, CDER, OSE (US); 2024 FEB 05. NDA218718.

[c] Cover Letter – Response to Information Request – 14 Feb 2024 (Femlyv, NDA 218718). Caguas (Puerto Rico): Millicent Puerto Rico LLC; 2024 FEB 14. Available from: \\CDSESUB1\EVSPROD\nda218718\0005\m1\us\12-cover-letters\cover.pdf.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error experiences with similar products, we reviewed the following Femlyv labels and labeling submitted by Millicent Puerto Rico LLC received on September 27, 2023.

- Container label (Blister Card)
- Trade Carton labeling (Pouch and Carton)
- Professional Sample Carton Labeling (Pouch and Carton)
- Prescribing Information and Patient Information (Image not shown), available from \\CDSESUB1\EVSPROD\nda218718\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text.docx

F.2 Label and Labeling Images

Container label

- Blister Card:

(b) (4)

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

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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/

JUSTINE H KALONIA
03/14/2024 10:47:36 AM

STEPHANIE L DEGRAW
03/15/2024 09:10:24 AM

M E M O R A N D U M

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

DATE: 12/11/2023

TO: Division of Urology, Obstetrics, and Gynecology (DUOG)
Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine (ORPURM)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 218718

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Regulatory Assessment (RRA) for the site in NON-RESPONSIVE The RRA was conducted under the following submission: NDA NON-RESPONSIVE

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical		(b) (4)

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/

FOLAREMI ADEYEMO
12/11/2023 10:49:42 AM