# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 218718Orig1s000

# NON-CLINICAL REVIEW(S)

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

# PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

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| Application number: | 218718 |
| Supporting document/s: | SN 0001 |
| Applicant's letter date: | September 27, 2023 |
| CDER stamp date: | September 27, 2023 |
| Product: | FEMLYV (norethindrone acetate 1 mg/ethinyl estradiol 0.02 mg) oral disintegrating tablets |
| Indication: | Combination Hormonal Contraceptive |
| Applicant: | Millicent Pharma |
| Clinical Review Division: | Division of Urology, Obstetrics, and Gynecology (DUOG) |
| Pharm/Tox Division: | Division of Pharm/Tox for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine/Specialty Medicine (DPT-RPURM/SM) |
| Reviewer: | Edna Albuquerque, PhD |
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*Template Version: September 1, 2010*

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# 1 Executive Summary

## 1.1 Introduction

The Applicant, Millicent Pharma, is using the 505(b)(2) regulatory path to develop a new pharmaceutical formulation (orally disintegrating tablets) of norethindrone acetate (1 mg) and ethinyl estradiol (0.02 mg) for pregnancy prevention in women of reproductive age. The proposed tradename of their drug product is FEMLYV.

Combination hormonal contraceptives (CHC) such as FEMLYV lower the risk of becoming pregnant primarily by preventing ovulation through their actions on the hypothalamic-pituitary-ovarian axis, as indicated by changes in luteinizing hormone (LH) and follicle stimulating hormone (FSH) plasma levels over the course of the menstrual cycle.

As part of their drug development program, the Applicant conducted clinical pharmacological studies to establish the bioequivalence between their drug product and the listed drug (LD) Minastrin 24 Fe Chewable Tablets, which was approved under NDA 203667 on May 08, 2013. The LD is no longer marketed in the United States.

The LD product was available in 28-blister packages with 24 white “active” tablets and 4 brown non-hormonal placebo tablets. In the LD product, each active tablet contained norethindrone acetate (1 mg) and ethinyl estradiol (0.02 mg), and each placebo tablet contained 75 mg ferrous fumarate, which did not serve any therapeutic purpose.

The Applicant’s drug product, FEMLYV, will be available in 28-blister packages of 24 green active tablets, each containing the same active pharmaceutical ingredients at the same strengths as those in the active LD tablets, and 4 white non-hormonal placebo tablets. None of the FEMLYV tablets contains ferrous fumarate.

## 1.2 Brief Discussion of Nonclinical Findings

The Applicant did not conduct nonclinical studies with FEMLYV, and no nonclinical studies were required to support their NDA application. Instead, the Applicant conducted clinical pharmacological studies to establish an adequate scientific bridge between their product and the LD such that they could rely on findings of safety and effectiveness described in the FDA-approved labeling of the LD.

The scientific bridge between FEMLYV and the LD, Minastrin 24 Fe, was established by three single-dose clinical pharmacology studies comparing the bioavailability of FEMLYV and the LD under different conditions:

1. Clinical BA Study MP0008-0001.2-PR: This study was conducted in healthy premenopausal female volunteers to compare the bioavailability of norethindrone acetate and ethinyl estradiol from a FEMLYV tablet: (a) allowed to disintegrate in the mouth without water, and (b) swallowed whole with water, relative to that from a Minastrin chewable tablet that was chewed, swallowed, and followed with water.

2. Clinical BA Study MP0008-0002.1-PR: This study was conducted in healthy premenopausal female volunteers to evaluate the effect of a high-fat/high-calorie meal consumed 30 minutes prior to an oral dose of FEMLYV on norethindrone acetate and ethinyl estradiol absorption, compared to administration of FEMLYV after an overnight fast.
3. Clinical Study MP0008-003.4-PR: This study was designed to investigate the potential for oral irritation to develop after taking a FEMLYV active orally disintegrating tablet daily for 24 days (tablet disintegration in the mouth, swallowed with saliva).
4. Clinical BA Study MP0008-0004.0-PR: This study was conducted in healthy premenopausal female volunteers to compare the bioavailability of norethindrone acetate and ethinyl estradiol from an oral FEMLYV tablet (allowed to disintegrate in the mouth prior to swallowing, then followed with water), either after an overnight fast or after a high-fat/high-calorie meal, relative to that from a Minastrin tablet (chewed prior to swallowing with water) after an overnight fast.

Based on internal discussions, the Clinical Pharmacology team indicated that results of the study MP0008-004.0-PR listed above demonstrated comparable bioavailability between the Applicant's drug product, FEMLYV, and the LD, Minastrin 24 Fe. These findings successfully bridged the two products. The Biopharmaceutical Team reported that an in-vitro assessment conducted by the Applicant indicated that the FEMLYV tablet dissolution was adequate, and the Clinical Team reported that no safety signals, including local toxicity due to the disintegration of the oral FEMLYV tablets in the mouth, emerged in the clinical studies.

The establishment of the adequate scientific bridge enabled the Applicant to rely on previous findings of safety and effectiveness and nonclinical aspects (including mechanism of action) described in the FDA-approved labeling of Minastrin 24 Fe Chewable Tablets.

## 1.3 Recommendations

### 1.3.1 Approvability

The nonclinical team recommends approval of the application.

### 1.3.2 Additional Non-Clinical Recommendations

No additional nonclinical studies are recommended.

### 1.3.3 Labeling

The Division completed the review of the Applicant's product labeling, and the Applicant accepted all the Division's proposed changes and comments to the prescribing information and updated the document to eliminate formatting deficiencies [Applicant's Letter, April 30, 2024].

Text segments edited in nonclinically related sections are listed below.

- In Section 8.1 (Pregnancy), (b) (4) was replaced with "Discontinue FEMLYV if pregnancy occurs, because there is no reason to use hormonal contraceptives during pregnancy." This was based on recommendations from the Contraceptive labeling guidance of 2018.
- (b) (4) However, during final revisions of the text, the Nonclinical team noticed interchangeable use of COC and CHC in different sections of the label. Following discussions with the Clinical Team, it was recommended that, for consistency, the Applicant replaces "combined hormonal contraceptive" and "CHC" with "combined oral contraceptive" and "COC," respectively, throughout the label.
- In Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility), (b) (4) (b) (4) was replaced with "See Warnings and Precautions (5.4, 5.5)." This was based on updated subheadings in Section 5.

# 2 Drug Information

## 2.1 Drug

CAS Registry Number (Optional)

- Ethinyl estradiol: 57-63-6
- Norethindrone Acetate: 51-98-9

Generic Name

- Ethinyl estradiol
- Norethindrone Acetate

Code Name

- MP0008 (ethinyl estradiol plus norethindrone acetate)

Chemical Name

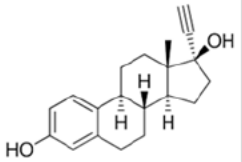
- Ethinyl estradiol: (8R,9S,13S,14S,17R)-17-ethynyl-13-methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthrene-3,17-diol
- Norethindrone Acetate: [(8R,9S,10R,13S,14S,17R)-17-ethynyl-13-methyl-3-oxo-1,2,6,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-17-yl] acetate

Molecular Formula/Molecular Weight

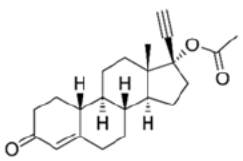
- Ethinyl estradiol: $C_{20}H_{24}O_2$ / 296.4 g/mol
- Norethindrone Acetate: $C_{22}H_{28}O_3$ / 340.5 g/mol

Structure or Biochemical Description

Ethinyl estradiol




Norethindrone Acetate



Pharmacologic Class

- Ethinyl estradiol: Estrogen
- Norethindrone Acetate: Progestin

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

**Table 1. List of Relevant INDs, NDAs, and DMFs.**

| NDAs and IND | | DMFs |
|---|---|---|
| NDA 203667 | Minastrin 24 Fe | (b) (4) |
| NDA 21871 | Loestrin 24 Fe | |
| NDA 22501 | Lo Loestrin Fe | |
| NDA 17876 | Loestrin 21 1/20 | |
| NDA 17875 | Loestrin® 21 1.5/30 | |
| IND 73510 | Lo Loestrin | |
| IND 151441 [a] | MP0008 | |

[a]IND 151441 is the IND associated with this NDA. During its development, the to-be-marketed product FEMLYV was referred to by the code MP0008. IND reviews were conducted by Dr. Pratisha Tamrakar (see Table 4).

## 2.3 Drug Formulation

FEMLYV is an immediate release, fixed-dose combination, orally disintegrating tablet containing norethindrone acetate (1.00 mg) and ethinyl estradiol (0.020 mg). Table 2 lists the components of the product formulation.

**Table 2. Formulation of FEMLYV Active Tablets with the Inactive Ingredient Report (IIR) Maximum Daily Exposures (MDEs) for the Excipients in Previously Approved Products [Data from DocuBridge Section 3.2.P.1 (Active Tablets) and DocuBridge Section 3.2.P.1 (Placebo Tablets)].**

| Name of Ingredient | Function | Amount (mg/tablet) | IIR MDEs | IIR Application[a] |
|---|---|---|---|---|
| Ethinyl Estradiol[b] | Active Ingredient | 0.02 | - | - |
| Norethindrone acetate[b,c] | Active Ingredient | 1.00 | - | - |
| Microcrystalline Cellulose | (b) (4) | (b) (4) | 5,117 mg | (b) (4) |
| Croscarmellose Sodium | | | 736 mg | |
| Mannitol | | | 7621 mg | |
| Starch (b) (4) Pregelatinized | | | (b) (4) mg | |
| Magnesium Stearate | | | 980 mg | |
| Sucralose | | | 60 mg | |
| Spearmint | Flavor | (b) (4) | NA[g] | |
| Vitamin E (DL-α-Tocopherol)[b] | | (b) (4) | 246 mg | |
| Mint Green Lake Blend[b] | | | (b) (4) | |
| (b) (4) | | | | |
| | | | - | - |
| | | | - | - |
| Approximate total tablet weight (mg) | | 70.0 | - | - |

[a]IIR Application refers to the application from which the IIR MDE is derived, as listed in the IIR database consulted on May 15, 2024. [b]Not present in placebo tablets. (b) (4)

The final active drug product is a round, [redacted] green, oral disintegrating tablet with [redacted] debossed on one side of the tablet surface & '312' debossed on the other side of the tablet surface. Each tablet will weigh 70 mg.

The primary packaging is an [redacted] blister, with [redacted] pouch as the secondary packaging. The Applicant provided letters of authorization for the DMFs.

## 2.4 Comments on Novel Excipients

There are no novel excipients in the formulation, and all excipients are at concentrations that result in maximal daily exposures (MDEs) below those in previously FDA-approved drug products for oral use, as per the FDA Inactive Ingredient Report (IIR) database (Table 2).

The Applicant developed in-house quality control specifications for two excipients that do not meet USP/NF requirements: Spearmint (flavor) and Mint Green Lake Blend [redacted]

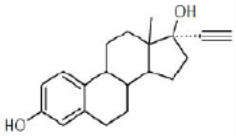
## 2.5 Comments on Impurities/Degradants of Concern

Norethindrone acetate-related substances
The norethindrone acetate-related substances are [redacted]. In line with the [redacted] the norethindrone acetate-related substances are controlled at NMT [redacted]%.

Ethinyl estradiol-related substances
The ethinyl estradiol-related substances include [redacted] In the to-be-marketed product, all ethinyl estradiol-related substance are controlled at NMT 1.0% [Drug Product Impurities - Justification of Specifications [DocuBridge Section 3.2.P.5.6]. This limit aligns with the recommendations in the ICHQ3B(R3) Guidance: Impurities in New Drug Products.

Early in the development of the Applicant's product, the ethinyl estradiol-related substances shown in Table 3 [redacted] were controlled at NMT [redacted]%. Because this limit exceeded the qualification threshold in the ICH Q3B(R3) Guidance, the Applicant provided an independent toxicology assessment of the potential health risk arising from the presence of these impurities at up to [redacted]% of the ethinyl estradiol dose (20 µg/day) resulting in daily exposures to [redacted] µg/day of each impurity. The Risk Assessment used to qualify these impurities is summarized below.

**Table 3. Ethinyl Estradiol-Related Impurities that, in the Early Phases of the Drug Development Program, Exceeded the ICH Q3B Guidance Qualification Levels [Excerpted from the Applicant's Package].**

| Chemical | Ethinyl estradiol | (b) (4) |
|---|---|---|
| Structure |  | |

*Risk Assessment for the Ethinyl Estradiol-Related Impurities* (b) (4)

(b) (4)

(b) (4)

Considering the outcomes of the risk assessment, controlling the impurities (b) (4) (b) (4) at NMT (b) (4) % was not expected to pose a health risk to patients receiving daily treatment with ethinyl estradiol-containing product for half of a lifetime (35 years) over and above any risk which may be posed by ethinyl estradiol itself.

## 2.6 Proposed Clinical Population and Dosing Regimen

FEMLYV is indicated for use by women of reproductive potential to prevent pregnancy. The proposed dose regimen is 1 active tablet for 24 consecutive days followed by 1 placebo (inactive) tablet for 4 consecutive days.

## 2.7 Regulatory Background

On July 24, 2020, Millicent Pharma submitted a pre-IND meeting package to seek initial FDA guidance on the suitability and sufficiency of their proposed plan for the development of their drug product, FEMLYV, an estrogen/progestin combination

containing norethindrone acetate (1 mg) and ethinyl estradiol (0.02 mg) as oral disintegrating tablets (ODT) for the prevention of pregnancy in women.

On August 27, 2020, FDA issued a Written Response Only addressing the various Nonclinical, Clinical, and Chemistry, Manufacturing, and Control (CMC) questions posed by the Applicant in their pre-IND meeting package.

On July 30, 2021, following guidance provided by the Agency, the Applicant opened an IND (IND 151441) for the conduct of clinical studies designed to compare the bioavailability of their drug product, then coded as MP0008, and their selected LD, Minastrin 24 Fe. The LD, Minastrin 24 Fe, contains the same APIs at the same strengths as those present in the Applicant's product. The Applicant intended to use the results of their clinical studies to establish an adequate scientific bridge that would enable reliance on findings of safety and effectiveness available in the FDA-approved labeling of the LD.

On September 27, 2023, the Applicant submitted an NDA to complete the development program for approval of their drug product.

The regulatory history related to the nonclinical discipline for IND 151441 and for this NDA is summarized in Table 4.

**Table 4. Nonclinical Reviews Completed During the Product Development.**

| IND 151441 | | | |
|---|---|---|---|
| SN | Submission/Interaction Type | Date Received | Nonclinical Review |
| 0001 | Pre-IND Meeting (Written Response Only) | 07/24/2020 | Nonclinical Review by Dr. Pratistha Tamrakar. DARRTS archival date: 08/31/2020 |
| 0002 | 30-Day Full Review | 07/30/2021 | Nonclinical Review by Dr. Pratistha Tamrakar. DARRTS archival date: 08/19/2021 |
| 0006 | Clinical Protocol Review | 01/07/2022 | Nonclinical Review by Dr. Pratistha Tamrakar. DARRTS archival date: 01/14/2022 |
| 0007, 0008 | Type C Meeting (Written Response Only – PK Data) | 05/25/2022 | Nonclinical Review by Dr. Pratistha Tamrakar. DARRTS archival date: 08/29/2022 |
| 0010 | Clinical Protocol Review | 09/14/2022 | Nonclinical Review by Dr. Pratistha Tamrakar. DARRTS archival date: 09/19/2022 |
| **NDA 218718** | | | |
| SN | Submission/Interaction Type | Date Received | Nonclinical Review |
| | Filing Review | 09/27/2023 | Nonclinical Review by Dr. Edna Albuquerque. DARRTS archival date: 11/08/2023 |

# 3 Studies Submitted

## 3.1 Studies Reviewed

No nonclinical study was conducted under this NDA or the accompanying IND (IND 151441).

## 3.2 Studies Not Reviewed

Not Applicable.

## 3.3 Previous Reviews Referenced

All nonclinical reviews completed during the regulatory history of the product are listed in Table 4 and were consulted in preparation of this NDA review.

# 4 Integrated Summary and Safety Evaluation

Millicent Pharma is using the 505(b)(2) regulatory path to develop FEMLYV, a new pharmaceutical formulation of orally disintegrating tablets containing norethindrone acetate (1 mg) and ethinyl estradiol (0.02 mg) for pregnancy prevention in women of reproductive potential. In their drug development program, the Applicant selected to conducted clinical studies that would establish an adequate scientific bridge between their drug product and the LD Minastrin 24 Fe to enable reliance on findings of safety and effectiveness described in the FDA-approved labeling of the LD.

FEMLYV (which was referred to as MP0008 during the drug development program) differs from the LD in its dosage form (Minastrin Fe 24 is a chewable tablet). In addition, the placebo tablets in FEMLYV, in contrast to those in Minastrin Fe 24, do not have ferrous fumarate as (b) (4) However, FEMLYV and the LD have the same APIs at the same strengths, making the LD an appropriate product to bridge the Applicant's product to. The recommended doses, clinical indication, and targeted clinical population are the same for both products.

The nonclinical pharmacological and toxicological profiles of norethindrone acetate and ethinyl estradiol are well established through the previous approval of other oral CHC products (e.g., Minastrin® 24 Fe, Nextstellis) containing the same or higher amounts of both APIs.

From the nonclinical perspective, the FEMLYV quality is acceptable. Its formulation has no new excipients, and the concentrations of all excipients in the formulation result in MDEs that are below those in previously approved oral drug products, as listed in the FDA IIR database. In addition, all impurities are properly qualified.

Based on internal discussions, the Clinical Pharmacology Team indicated that the Applicant successfully demonstrated comparable systemic exposures to the APIs following single oral doses of FEMLYV and Minastrin 24 Fe. These findings established an adequate scientific bridge between the Applicant's product and the LD. In addition, the Biopharmaceutical Team reported that an in-vitro assessment conducted by the

Applicant indicated that the FEMLYV tablet dissolution was adequate, and the Clinical Team reported that safety signals, including local toxicity due to the disintegration of the tablets in the mouth, were absent in the clinical studies.

Considering the absence of safety signals during the clinical studies and the successful establishment of a scientific bridge between FEMLY and the LD, no nonclinical studies were necessary to support the development of the Applicant's product. From the nonclinical perspective, this application is approvable.

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/s/

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EDNA D ALBUQUERQUE
05/31/2024 03:17:11 PM

KIMBERLY P HATFIELD
06/05/2024 09:45:39 AM
I agree with the reviews and recommendations of Dr. Albuquerque.