U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Rare Diseases, Pediatrics, and Reproductive Medicine
Division of Urology, Obstetrics, and Gynecology
Primary Clinical Review Addendum

Application Number:	**NDA 209405**
Sponsor:	**Exeltis USA, Inc.**
Drug:	**EV402 - Levonorgestrel 0.1 mg/Ethinyl Estradiol 0.02 mg (LNG/EE) Tablets**
Proposed Indication:	**Prevention of pregnancy**
Date Review Completed:	**March 30, 2020**
Reviewer:	**Anandi D. Kotak, MD, MPH, DUOG**
Team Leader:	**Gerald Willett, MD, DUOG**
Materials Reviewed:	**Full Prescribing Information (FPI)** **Patient Prescribing Information (PPI)** **Instructions for Use (IFU)** **Chemistry, Manufacturing, and Controls (CMC)/Office of Pharmaceutical Quality (OPQ) Draft Review**

Executive Summary:

This memorandum summarizes changes to the dosage form designation and labeling of EV402 that occurred subsequent to the primary clinical review completed on February 26, 2020. (b) (4) ." Changes to the Full Prescribing Information (FPI), Patient Prescribing Information (PPI), and Instructions For Use (IFU) occurred as a result of removing the term (b) (4) In addition, substantive changes occurred to Highlights, Sections 2, 4, 7, 8, and 17 that were unrelated to the (b) (4) . These changes to do not affect the approvability of EV402. Lastly, the Sponsor's proposed proprietary name was denied. Therefore, the non-proprietary name Levonorgestrel/Ethinyl Estradiol Tablets is used throughout labeling. EV402 meets the regulatory requirements for efficacy and safety as a tablet that may be chewed or swallowed and is recommended for approval.

Background:

The Sponsor initially submitted NDA 209405 via the 505(b)(2) regulatory pathway on January 7, 2019 for the indication of prevention of pregnancy. The Sponsor also sought (b) (4) The initial submission resulted in a refusal to file action due to incomplete data sets. The resubmission was received on May 30, 2019. The Office of Clinical Pharmacology completed its review and recommended approval

on the basis of bioequivalence demonstrated in study EXS-P3-239. The clinical review division completed its review and recommended approval based on the overall safety of EV402 in oral irritation studies.

Summary of Change in Dosage Form Designation:

(b) (4)

OPQ concluded that the product is recommended for approval, (b) (4) EV402 may also be swallowed whole. Therefore, the product will be approved as "levonorgestrel and ethinyl estradiol tablet."

Summary of Labeling Changes:

Given the determination that EV402 (b) (4), substantive changes were made to the full prescribing information (FPI) to remove the (b) (4), as well as to Highlights of Prescribing Information and Section 2: Dosage and Administration. In addition, the proposed proprietary name was denied by the Division of Medication Error Prevention and Analysis (DMEPA). Therefore, the non-proprietary name "Levonorgestrel/Ethinyl Estradiol Tablets" was substituted throughout the Substantially Complete Prescribing Information (SCPI), which includes the FPI, PPI, and IFU.

Additional substantive changes were made to Highlights and Sections (b) (4) 8, 17, and PPI to remove (b) (4). This change reflects the Agency's decision to make product labels current. Additional edits for clarity were made to Table 2: Instructions for Missed LNG/EE Tablets. The Sponsor accepted all changes and submitted the Full PI, PPI, and IFU for approval on March 30, 2020.

Important changes were made to the following sections:

1. **<u>Product Title:</u>**
   The product title now reads:

   "**LEVONORGESTREL AND ETHINYL ESTRADIOL tablets, for oral use."**

[1] Seggel M. NDA 209405 LNG+EE Tablets OPQ IQA working draft 03.27.2020.

2. **Highlights and Section 2 - Dosage and Administration:**
The Highlights of Prescribing Information and Section 2: Dosage and Administration information now reads:

> Take LNG/EE Tablets in one of two ways: (1) swallow whole on an empty stomach or (2) chew and then immediately swallow with a full glass of 240 mL water on an empty stomach (2.1).

In addition, Table 2 Instructions for Missed LNG/EE Tablets instructions on 2 consecutive missed tablets was modified for clarity:

• If two white active tablets are missed in Week 1 or Week 2	Take two active tablets as soon as possible. Then, take two active tablets the next day. This means taking 4 tablets in 2 days. Continue taking one tablet a day until the pack is finished. Additional nonhormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.

3. **Highlights and Sections (b) (4) 8, and 17: (b) (4) (b) (4)**
The Agency has determined that (b) (4) hormonal contraceptive use. However, there is no need or benefit to using hormonal contraception during pregnancy. Therefore, hormonal contraception should be discontinued during pregnancy. (b) (4) . Language in Sections 8 (Use in Specific Populations) and 17 (Patient Counseling Information) are as follows:

- **8.1 Pregnancy**
Risk Summary

> There is no use for contraception in pregnancy; therefore, LNG/EE Tablets should be discontinued during pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to CHCs before conception or during early pregnancy.
>
> In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically

recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

- **17 Patient Counseling Information**
  Use During Pregnancy

  Advise women that there is no reason to use LNG/EE Tablets during pregnancy. Instruct the woman to stop LNG/EE Tablets if pregnancy is confirmed during treatment *[see Use in Specific Populations (8.1)].*

4. **Section 12.3 – Pharmacokinetics:**
   The Office of Clinical Pharmacology recommended deletion of the paragraph indicating the effect of food to avoid prescribers' confusion.

5. **Section 17 - Patient Counseling:**
   When counseling a patient, the prescriber should inform the patient that bleeding irregularities may occur after initiating use. The patient should seek medical advice if bleeding irregularities persist. The statement reads:

   Bleeding Irregularities
   Advise women that irregular bleeding and/or spotting may occur. Bleeding irregularities typically resolve after the first few months of use. Advise women to consult their healthcare provider if bleeding irregularities persist for more than three to four months *[see Warnings and Precautions (5.8)]*.

Conclusion:

The CMC determination that EV402 does not [redacted] (b) (4) tablet has not ultimately affected the approvability of the application. All labeling changes are accepted by the Sponsor. Therefore, EV402 is recommended for approval for prevention of pregnancy in females of reproductive potential.

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/s/

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