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APPLICATION NUMBER:

209405Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	March 27, 2020
From	Gerald Willett, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	209405
Applicant	Exeltis USA, Inc.
Date of Submission	May 30, 2019 (resubmission)
PDUFA Goal Date	March 30, 2020
Product Name	EV402 (no approved tradename at this time)
Established or Proper Name	Levonorgestrel/ethinyl estradiol
Dosage Forms	Tablets
Applicant Proposed Indication(s)/Population(s)	Prevention of pregnancy
Applicant Proposed Dosing Regimen(s)	Levonorgestrel 0.10mg/ethinyl estradiol 0.02mg tablet once daily by mouth for 21 days followed by one inactive tablet daily for 7 days
Recommendation on Regulatory Action	Approval
Recommended Population	Females of childbearing potential

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Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

As Cross-Discipline Team Leader, I recommend the approval of EV402 for use by females of reproductive potential to prevent pregnancy.

EV402 is a combination hormonal contraceptive (CHC) that contains levonorgestrel (LNG) 0.1 mg and ethinyl estradiol (EE) 0.02 mg. Since initially marketed in the early 1970s, the safety and efficacy of the LNG/EE CHC combination has been well characterized over nearly 50 years. EV402 was developed as a contraceptive product that could be chewed. Approval of EV402 was sought through the 505(b)(2) pathway using Alesse® as the listed product and its generic as the current reference standard.

The Clinical Pharmacology team determined that the Applicant had demonstrated bioequivalence of EV402 compared to the reference standard in the pivotal relative bioavailablity Study EXS-P3-239. This determination bridges the Agency's findings of efficacy and safety of the reference standard to of EV402.

The primary medical officer reviewed the safety data from three clinical pharmacology studies and two oral irritation studies and found EV402 to be well tolerated. There were no deaths or serious adverse events. There were no new safety signals identified in the five studies. Advese oral findings in the 80 subjects in the two oral irritation studies were rare and were mild in severity.

In summary, I concur with the review disciplines in recomemending the approval of NDA 209405.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Condition	Unintended pregnancy has important personal, societal and health consequences for women and their families	Development of oral hormonal contraceptive products that may be chewed adds a dosage administration option for women seeking to avoid unintended pregnancy.
Current Treatment Options	(see Background section for other oral contraceptives that may be chewed)	The Divisions has previously approved two products that may be chewed or swallowed and one that must be chewed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	EV402 was found to be bioequivalent to a generic for Alesse the originator product.	Bioequivalence to the generic for Alesse supports clinical benefit for the product in regard to pregnancy prevention.
Risk and Risk Management	No new safety findings have been identified in the development of EV402.	Safety information for the product's label will include the originator product (Alesse) and where appropriate class labeling from the Division's contraceptive labeling guidance document.

1. Background

EV402 is a combination hormonal contraceptive (CHC) tablet that has been evaluated by the Applicant as a product that may be chewed. Administration by chewing may be beneficial to those patients who have trouble swallowing tablets. EV402 contains levonorgestrel (LNG) 0.1 mg and ethinyl estradiol (EE) 0.02 mg. The combination of LNG/EE as a CHC has been marketed in the U.S. since the early 1970s. Therefore the safety and efficacy of the components of this product are well known. EV402 will be the first LNG/EE product submitted for approval that will have labeling that allows either chewing or swallowing (whole tablet) in the dosing instructions.

The Applicant seeks approval via the 505(b)(2) pathway using Alesse® (LNG 0.10 mg / EE 0.02 mg, NDA 20-683 approved on April 1997) as the listed drug for reliance on the FDA's labeled safety and efficacy. Since Alesse is no longer marketed in the U.S., the Applicant used Lutera® (ANDA 76-625 by Mayne Pharma, Inc.), the current reference standard as the reference product in the relative bioavailibilty/bioequivalence studies.

This application is a resubmission. The Applicant's initial NDA submission received January 7, 2019, lacked analysis datasets that led to a refusal to file letter on March 8, 2019.

CDTL Comment:
Based on the adequacy of the datasets in NDA resubmission (received on May 30, 2019), we deemed the application to be fileable.

2. Product Quality

The chemistry review team identified an issue which had important labeling implications. This finding was conveyed to the Applicant in an Advice Letter dated March 6, 2020. Key information from this letter is provided verbatim below:

> "We have determined that the nomenclature for your proposed drug product, [redacted] (b) (4)," should be revised to "levonorgestrel and ethinyl estradiol tablets." [redacted] (b) (4) Revise the labels and labeling of your proposed drug product accordingly. The established name of your product should be revised from, [redacted] (b) (4) to "levonorgestrel and ethinyl estradiol tablets." The Product Title is "Tradename (levonorgestrel and ethinyl estradiol) tablets, for oral [redacted] (b) (4) The Dosage and Administration section should be revised to include the options for chewing and swallowing or swallowing whole. For example, "Tablets may be chewed and swallowed or swallowed whole."

CDTL Comment:
The Applicant has complied with this labeling change. The Chemistry team found no deficiencies in their application parameters and recommended approval of the product.

3. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology team (Miyun Tsai-Turton, Ph.D., M.S. and Kimberly Hatfield, Ph.D.) found that the application did not raise any toxicological concerns.

CDTL Comment:
Sections in the proposed labeling related to pregnancy (8.1) and lactation (8.2) are consistent with the Alesse label (Warning #7 and Precautions # 13). Consistent with the regulations under the Pregnancy and Lactation Labeling Rule, Category X listed in the Alesse label is no longer used. The CHC combination of LNG/EE

has no distinctive pharmacologic/toxicologic safety concerns that separates it from other CHCs.

4. Clinical Pharmacology

The clinical pharmacology review team (Jihong Shon, M.D., Ph.D. and Lu Yanhui, Ph.D.) found the application to be acceptable and recommended approval from a clinical pharmacology standpoint.

There were 3 clinical pharmacology studies:

EXS-P3-239
This was a single-dose crossover relative bioavailability study in the fasting state between the chewed EV402 product and the current reference standard, Lutera (ANDA 76-625) which was swallowed with water. This study was considered pivotal because one of the batches used (Formulation B, Batch F09251A) is identical to the to-be-marketed formulation.

The clinical pharmacology reviewers found that the pharmacokinetic comparison (Cmax and AUC) between chewed EV402 and swallowed Lutera was acceptable within the specified no-effect boundary of 80% to 125%.

Studies EHE-P4-469 & EXP-P3-821
These relative bioavailability studies were not considered pivotal by the clinical pharamacology reviewers because the formulations were different than that of the to-be-marketed product.

CDTL Comments:
In the pivotal Study EXS-P3-239, subjects were fasting and took the products with water. Similar instructions regarding fasting and water are appropriately incorporated in the product labeling. Although Studies EHE-P4-469 and EXP-P3-821did not have the to-be-marketed formulation they had findings consistent with EV402 pK differences when a high fat meal was studied and the product was used without water. A high fat meal blunted the Cmax for EE and LNG. Use without water resulted in a greater Cmax and AUC for EE.

5. Clinical Microbiology

The Chemistry review found that the manufacturing and controls were adequate to ensure the microbiological quality of a solid oral dosage form.

6. Clinical/Statistical- Efficacy

The primary clinical reviewer (Anandi Kotak, M.D., M.P.H.) provided study details on the BA/BE studies and concluded that bioequivalence between EV402 and the reference standard has been demonstrated to conclude that EV402 is effective as contraception in the intended population. In her review Dr. Kotak recommended approval of EV402 for the prevention of pregnancy.

7. Safety

The general safety of EV402 is supported by a demonstration of acceptable relative bioavailability (bioequivalence) to the reference standard. There were no new safety findings in the three clinical pharmacology and two oral irritation studies. There were no deaths or serious adverse events. One subject in a clinical pharmacology study discontinued for safety reasons unrelated to study drug.

An integrated table listing the frequency of adverse events in the five studies (total of 188 subjects) identified three preferred terms > 5.0%. These included headache 15.7%, nausea 8.6% and irregular menstruation 5.9%. These findings are consistent with the safety profile of other CHCs. Bleeding irregularities tend to be more common with the lower estrogen CHCs and this is a 0.02 mg EE product.

Adverse oral findings in the 80 subjects in the two oral irritation studies were rare and characterized as mild in severity. One subject had mild erythema and three subjects had what was described as small areas of apthous stomatitis (canker sores). Two of the cases of stomatitis occurred during treatment.

CDTL comment:
Apthous stomatitis is not completely understood, but is believed to involve a T cell-mediated immune response. Numerous contributing factors have been suggested including nutritional deficiencies, local trauma, stress, hormonal influences, allergies, and genetic predisposition. I did not see any narrative describing a past history for stomatitis in these subjects. I cannot rule out a possible relationship to EV402 but it seems unlikely. I did not see any reference to stomatitis in the other three labels for chewable contraceptives. Labeling regarding stomatitis is not warranted based on these limited findings.

8. Advisory Committee Meeting

An advisory committee meeting was not required for this application.

9. Pediatrics

Pediatric Research Equity Act (PREA) criteria do not apply to this application.

10. Other Relevant Regulatory Issues

There were no relevant regulatory issues regarding the following:

- Application Integrity Policy (AIP)
- Exclusivity or patent issues of concern
- Financial disclosures
- Other Good Clinical Practice (GCP) issues
- Office of Study Integrity and Surveillance (OSIS) audits

CDTL Comment:
There was a request for inspections of two sites in Canada (b) (4) ***but the Division of New Drug Bioequivalence Evaluation (DNDBE) within OSIS determined that on-site inspections were not warranted because both sites were recently inspected and that the final classifications of those inspections were No Action Indicated (NAI).***

11. Labeling

Key labeling issues include the following:

- Antradename was not available at the time of approval.
- CMC findings regarding the products evaluated (see CMC section) required that the Applicant provide dosing instructions in the label that allowed either chewing or swallowing the product whole. The formulation will be described as "tablet" (b) (4)
- Dosing instructions call for taking the product on an empty stomach and also call for a full glass of water following chewing the tablet.

- Certain sections of the label differed from the Alesse label (non-PLR) and reflected updates to be consistent with the Division's Draft Contraceptive Labeling Guidance. These updates included:
  - Removing the typical use-effectiveness table (derived from Trussell et al)
  - Incorporating changes to the cardiovascular warnings consistent with other CHC labels
  - Updating the adverse events section

Labeling agreement with the Applicant occurred on March 30, 2020.

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS) are not required for this application. Postmarketing Requirements (PMRs) and Commitments (PMCs) are not required.

13. Recommended Comments to the Applicant

Not applicable

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/

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