CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209405Orig1s000

NON-CLINICAL REVIEW(S)

PHARMACOLOGY/TOXICOLOGY Review

Date:	03/31/20
IND or NDA #	NDA 209405
Sponsor:	Exeltis USA Inc.
Drug/Indication:	Levonorgestrel/ethinyl estradiol (LNG/EE) (b) (4) tablets/Prevention of Pregnancy
Reviewer:	Miyun Tsai-Turton, PhD, MS

Background:

Drug Product

EV402 [levonorgestrel / ethinyl estradiol (LNG/EE) (b) (4) tablets] is a progestin/estrogen (b) (4) combined oral contraceptive containing 21 active white tablets of 0.10 mg levonorgestrel and 0.02 mg ethinyl estradiol and 7 inactive peach tablets (28 daily tablet regimen). The intended administration is (b) (4) one tablet daily for oral administration. EV402, like other combination oral contraceptives (COC), contains estrogen and progestin and acts by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increases the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

Label Guidance for COC

Below texts were extracted from the Labeling for Combined Hormonal Contraceptives Guidance for Industry *DRAFT GUIDANCE*

8.1 Pregnancy

Risk Summary

[This section should summarize the human, animal, and pharmacologic data and identify the source of the data. If the product contains a new progestin or estrogen, applicants should provide a risk statement(s) that describes, for the drug, the risk of adverse developmental outcomes based on all relevant human data, animal data, and the drug's pharmacology. If there are no human data, then a statement that there are no human data must be made in the Risk Summary (21 CFR 201.57(c)(9)(i)(B)) and the human data section should not be included. If embryo/fetal studies were conducted, then a sentence summarizing those studies should be included here with details under "Animal Data." If no studies were done, then a statement should be made in the Risk summary and the animal data section should not be included.

If the product contains a well-characterized progestin and estrogen, the class language provided below should be used.]

[NAME] is contraindicated in pregnancy because there is no reason to use CHCs in pregnancy. Discontinue [NAME] if pregnancy occurs. 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 animal reproduction studies in **[species]**, **[results should be summarized]**. **[OR]** Animal studies to evaluate embryo/fetal toxicity were not conducted.

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.

Data

Human Data

[Applicants should describe the data regarding adverse developmental outcomes, adverse reactions, and other adverse effects, including information about the data source, number of subjects, study duration, exposure time, and limitations of the data.]

Animal Data

[Embryo/fetal (Segment II and III) studies should be reported here. If no studies were done, this heading should not be included.]

8.2 Lactation

Risk Summary

Contraceptive hormones and/or metabolites are present in human milk. **[The concentration in human milk and the actual or estimated infant dose, if available, should be described, as well as the effects on the breast-fed infant.]** CHCs can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. *[See also Dosage and Administration (2.2).]* The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breast-fed child from (name of drug) or from the underlying maternal condition.

Data

[If available, specific pharmacologic data should be added here concerning the percentage of the product that is present in the breast milk of postpartum females.]

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[If applicable, nonclinical data should be summarized if human data are not available.]

13.2 Animal Toxicology and/or Pharmacology

[If applicable, nonclinical data should be summarized if human data are not available. Embryo/fetal (Segment II and III) studies should be summarized in subsection 8.1]

Label:

Exeltis Proposed	DBRUP PT proposed	FINAL LABEL
HIGHLIGHTS **INDICATIONS AND USAGE** (b) (4) indicated for use by females of reproductive potential to prevent pregnancy. (1)	**HIGHLIGHTS** **INDICATIONS AND USAGE** (b) (4) indicated for use by females of reproductive potential to prevent pregnancy. (1)	**HIGHLIGHTS** **INDICATIONS AND USAGE** Levonorgestrel and Ethinyl Estradiol Tablets (LNG/EE Tablets) is a combination of levonorgestrel, a progestin, and ethinyl estradiol, an estrogen, indicated for use by females of reproductive potential to prevent pregnancy. (1)
1 INDICATIONS AND USAGE Tradename is indicated for use by females of reproductive potential to prevent pregnancy.	No changes proposed.	**1 INDICATIONS AND USAGE** Levonorgestrel and Ethinyl Estradiol Tablets (LNG/EE Tablets) is indicated for use by females of reproductive potential to prevent pregnancy.
8 Use in Specific Populations **8.1 Pregnancy** Risk Summary (b) (4) 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. (b) (4) 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.	**8 Use in Specific Populations** **8.1 Pregnancy** Risk Summary (b) (4) 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. (b) (4) 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.	**8 Use in Specific Populations** **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.

(b) (4)	(b) (4)	
8.2 Lactation Risk Summary Contraceptive hormones and/or metabolites are present in human milk CHCs can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. [See also Dosage and Administration (2.2).] The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breast-fed child from (name of drug) or from the underlying maternal condition. Data Small amounts of oral-contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk (b) (4)	No changes proposed.	**8.2 Lactation** Risk Summary Contraceptive hormones and/or metabolites are present in human milk. CHCs can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding *[see Dosage and Administration (2.2)].* The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for LNG/EE Tablets and any potential adverse effects on the breast-fed child from LNG/EE Tablets or from the underlying maternal condition. Data Small amounts of oral-contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk.
12.1 Mechanism of Action	**12.1 Mechanism of Action**	**12.1 Mechanism of Action**

CHCs (b) (4) primarily by suppressing ovulation.	CHCs (b) (4) lower the risk of becoming pregnant[4] primarily by suppressing ovulation.	CHCs lower the risk of becoming pregnant primarily by suppressing ovulation.
13 Nonclinical Toxicology **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** [*see Warnings and Precautions (5.10)* (b) (4) **5.10 Cervical Cancer** Some studies suggest that CHCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. There is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.	**13 Nonclinical Toxicology** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** [*see Warnings and Precautions (5.10)* (b) (4)	**13 Nonclinical Toxicology** **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** [*see Warnings and Precautions (5.10)*

(b) (4)

[4] See Balcoltra and Annovera label

(b) (4)

Conclusion(s):

See above for the final nonclinical-related labeling. This NDA is approved on 03/30/20.

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/

MIYUN M TSAI-TURTON
03/31/2020 09:49:16 AM

KIMBERLY P HATFIELD
03/31/2020 12:26:49 PM

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	209405
Supporting document/s:	SN 0005, eCTD 0006
Applicant's letter date:	05/30/19
CDER stamp date:	05/30/19
Product:	Levonorgestrel/ethinyl estradiol (LNG/EE) (b) (4) tablets
Indication:	Prevention of pregnancy
Applicant:	Exeltis USA Inc.
Review Division:	Division of Bone, Reproductive & Urologic Products (DBRUP)
Reviewer:	Miyun Tsai-Turton, PhD, MS
Supervisor/Team Leader:	Kimberly Hatfield, PhD
Division Director:	Hylton V. Joffe, MD, M.M.Sc
Project Manager:	Jennifer Dao

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209405 are owned by Exeltis USA Inc. or are data for which Exeltis USA Inc. has obtained a written right of reference.
Any information or data necessary for approval of NDA 209405 that Exeltis USA Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 209405.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

EV402 [levonorgestrel / ethinyl estradiol (LNG/EE) (b) (4) tablets] is a progestin/estrogen (b) (4) combined oral contraceptive containing 21 active white tablets of 0.10 mg levonorgestrel and 0.02 mg ethinyl estradiol and 7 inactive peach tablets (28 daily tablet regimen). The intended administration is (b) (4) one tablet daily for oral administration. EV402, like other combination oral contraceptives (COC), contains estrogen and progestin and acts by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduces the likelihood of implantation).

The Applicant, Exeltis, is seeking a 505(b)(2) regulatory pathway with reference to the approved product Alesse® 28 Tablets (approved under NDA 020683 in April 1997). Alesse is a combined oral contraceptive (non-chewable) containing 21 pink active tablets each containing 0.10 mg of LNG, a totally synthetic progestogen, and 0.02 mg of EE. The inactive ingredients present are cellulose, hypromellose, iron oxide, lactose, magnesium stearate, polacrilin potassium, polyethylene glycol, titanium dioxide, and montanic ester wax. (b) (4)

Alesse has since been discontinued and is no longer marketed, but not for reasons of safety or efficacy. Therefore, in this NDA submission, the Applicant conducted comparative bioavailability trials comparing EV402 to the Listed Drug (Lutera®). Lutera® (EE and LNG) is the approved generic version (ANDA 76625, Mayne Pharma, Inc.) of the brand-name oral contraceptive, Alesse®. The composition of the active ingredients in EV402 is also the same as the Lutera® reference product (DMF no. (b) (4) for EE and DMF no. (b) (4) for LNG). In addition to three comparative bioavailability studies (EHE-P4-469, EXS-P3-821, and EXS-P3-239) assessing the pharmacokinetic (PK) evaluation of EV402 relative to the reference standard product, Lutera®, two safety studies (EHE-P4-471 and EXS-P1-531) were conducted to assess the oral safety and tolerability of chewable EV402.

1.2 Brief Discussion of Nonclinical Findings

Since this is a 505(b)(2) NDA, the Applicant relies on published literature and the FDA's previous findings of safety for Alesse®, which is the oral tablet formulation of 20 µg EE and 100 µg LNG.

Based on the published literature, the acute toxicity of the ethinyl estradiol/levonorgestrel (EE/LNG) combination is low, since doses much higher than those normally used in humans are required to produce significant changes in

preclinical species. Repeated administration of high doses of exogenous progestins to rats, dogs and rhesus monkeys results in the extension of the pharmacologic activity. No toxicity was observed in any preclinical species from 26 weeks through 10 years of dosing. EE/LNG is not teratogenic nor mutagenic. Carcinogenic potential has not been detected after administering doses higher than that normally given to humans over prolonged periods of time. In addition, the safe use of EE in combination with LNG is well established in the clinical literature. Long-term exposure to the proposed clinical doses has no toxicological consequence with respect to either organ toxicity or reproductive toxicity. Neither EE nor LNG, either alone or in combination, is directly genotoxic; sex steroid hormones are considered epigenetic carcinogens, but these effects appear to be species and sex-specific. Even though there are conflicting reports regarding the carcinogenicity of long-term use of EE and LNG, clinical experience thus far does not suggest increased incidence of breast cancer with low-dose EE use.

The Applicant has established a scientific bridge to the Listed Drug Alesse, using comparative bioavailability studies. The comparative BA studies (EHE-P4-469, EXS-P3-821, and EXS-P3-239) demonstrated that the PK of Alesse/Lutera and EV402 were the same. As such, they intend to rely on the Agency's previous findings of safety and efficacy for Alesse to support their 505(b)(2) submission for EV402. The sponsor has also conducted safety and oral tolerability trials (EHE-P4-471 and EXS-P1-531) for EV402 and submitted published literature for additional support of their 505(b)(2) application. All referenced literature was submitted in Module 4 of the NDA submission. No impurities of toxicological concern have been identified with EV402.

Taken together, the EV402, LNG/EE chewable tablets, application does not raise any toxicological concerns.

1.3 Recommendations

1.3.1 Approvability

Pharm/tox recommends approval.

1.3.2 Additional Nonclinical Recommendations

Not applicable.

1.3.3 Labeling

Below is the labeling proposed by the Applicant. Any edits to labeling will be provided in a separate review.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

(b) (4) 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. (b) (4)

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

(b) (4)

8.2 Lactation

Risk Summary

Contraceptive hormones and/or metabolites are present in human milk CHCs can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. [See also Dosage and Administration (2.2).] The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for (name of drug) and any potential adverse effects on the breast-fed child from (name of drug) or from the underlying maternal condition.

Data

Small amounts of oral-contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. (b) (4) .

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[*see Warnings and Precautions (5.10)* (b) (4)

5 Warning and Precautions

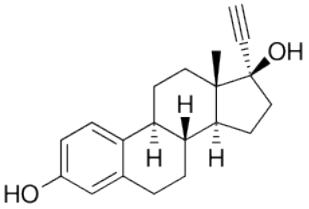
5.10 Cervical Cancer

Some studies suggest that CHCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. There is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

2 Drug Information

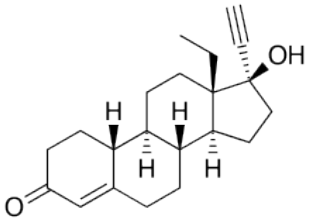
2.1 Drug

Ethinyl estradiol (synthetic estrogen)

- CAS Registry Number: 57-63-6
- Generic Name: ethinyl estradiol
- Code Name: EE, EE2
- Chemical Name: 17α-ethynylestradiol or as 17α-ethynylestra-1,3,5(10)-triene-3,17β-diol
- Molecular Formula/Molecular Weight: $C_{20}H_{24}O_2$ and 296.403 g/mol
- Structure or Biochemical Description: 

- Pharmacologic Class: estrogen

Levonorgestrel (synthetic progestogen)

- CAS Registry Number: 797-63-7
- Generic Name: levonorgestrel
- Code Name: LNG
- Chemical Name: (-)-13-Ethyl-17-hydroxy-18,19-dinor- 17α-pregn-4-en-20-yn-3-one
- Molecular Formula/Molecular Weight: $C_{21}H_{28}O_2$ and 312.446 g/mol
- Structure or Biochemical Description: 

- Pharmacologic Class: progestin

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 20683 (Alesse®, discontinued), ANDA 76-625 (Lutera®), DMFs (b) (4) and (b) (4) (active ingredients: ethinyl estradiol and levonorgestrel respectively)

2.3 Drug Formulation

The drug product is represented by 21 white colored active chewable tablets and 7 peach colored placebo chewable tablets.

Quantity, function and IIG limit for oral administration for Levonorgestrel / Ethinyl Estradiol 0.1 mg / 0.02 mg, chewable tablets.

Ingredient	Amount per tablet (mg)	Amount per tablet (% w/w)	Function	IIG Limit for Oral Route of Administration		
				CAS Number	UNII	Maximum Potency
Drug substances						
Levonorgestrel, USP	0.10	0.10	Active Ingredient		NA	NA
Ethinyl Estradiol, USP	0.02	0.02	Active Ingredient		NA	NA
Excipients						
Lactose Monohydrate, NF			(b) (4)	64044515	EWQ57Q8I5X	100 mg
Corn Starch, NF				9005258	O8232NY3SJ	170 mg
Pregelatinized Starch, NF						32 mg
Povidone (b) (4) NF				90003398	U725QWY32X	(b) (4)
Crospovidone, NF (b) (4)				9003398	2S7830E561	
(b) (4)					(b) (4)	
Magnesium Stearate, NF (b) (4)				557040	70097M6I30	50 mg
				--	--	--
				--	--	--
Total Weight	**100.00**	**100.00**				

* Not part of the finished product, removed during the manufacturing process.

Listed Drug: Alesse®

The Applicant, Exeltis, is seeking a 505(b)(2) regulatory pathway with reference to the approved product Alesse® 28 Tablets. Alesse is a combined oral contraceptive (non-chewable) containing 21 pink active tablets, each containing 0.10 mg of levonorgestrel, a totally synthetic progestogen, and 0.02 mg of ethinyl estradiol. The inactive ingredients present are cellulose, hypromellose, iron oxide, lactose, magnesium stearate, polacrilin potassium, polyethylene glycol, titanium dioxide, and montanic ester wax.

EV402 has the same active ingredients, but differs from the listed drug, in the route of administration since EV402 is chewed.

2.4 Comments on Novel Excipients

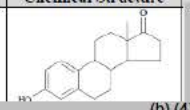
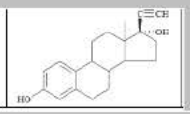
There were no novel excipients in the manufacturing of Levonorgestrel / Ethinyl Estradiol 0.10 mg / 0.02 mg, chewable tablets.

2.5 Comments on Impurities/Degradants of Concern

Drug substance: ethinyl estradiol (DMF no. (b) (4)

The actual total impurities for ethinyl estradiol was much lower than proposed levels of NMT (b) (4)% under long term storage conditions from the available stability data. The acce nce criteria for the related substances including each specified and unspecified and the total are the same as the approved Lutera.

Impurity	Comment
Organic impurities	Potential impurities derived from representative batches: (b) (4)
Inorganic impurities	(b) (4)
Residual solvents	It was confirmed that (b) (4) complies with the current ICH Q3C guideline regarding the requirements for Residual Solvents, as well as with the General Chapter <467> of the current USP.

Name	Chemical Structure	Source/Origin	Limit
Estrone		(b) (4)	
17β-ethinyl estradiol			

Comparison of the results obtained from the drug substance manufacturer

(b) (4)

[Table provided by the Applicant]

Drug substance: levonorgestrel (DMF no. (b) (4)

The actual total impurities for levonorgestrel was much lower than proposed levels of NMT (b) (4)% under long term storage conditions from the available stability data. The acceptance criteria for the related substances including each specified and unspecified and the total are the same as the approved Lutera. The known impurities of levonorgestrel are shown below.

List of impurities and source/origin information

Name	Chemical Structure	Source/Origin
		(b) (4)

summary of the batch analysis of Levonorgestrel drug substance.

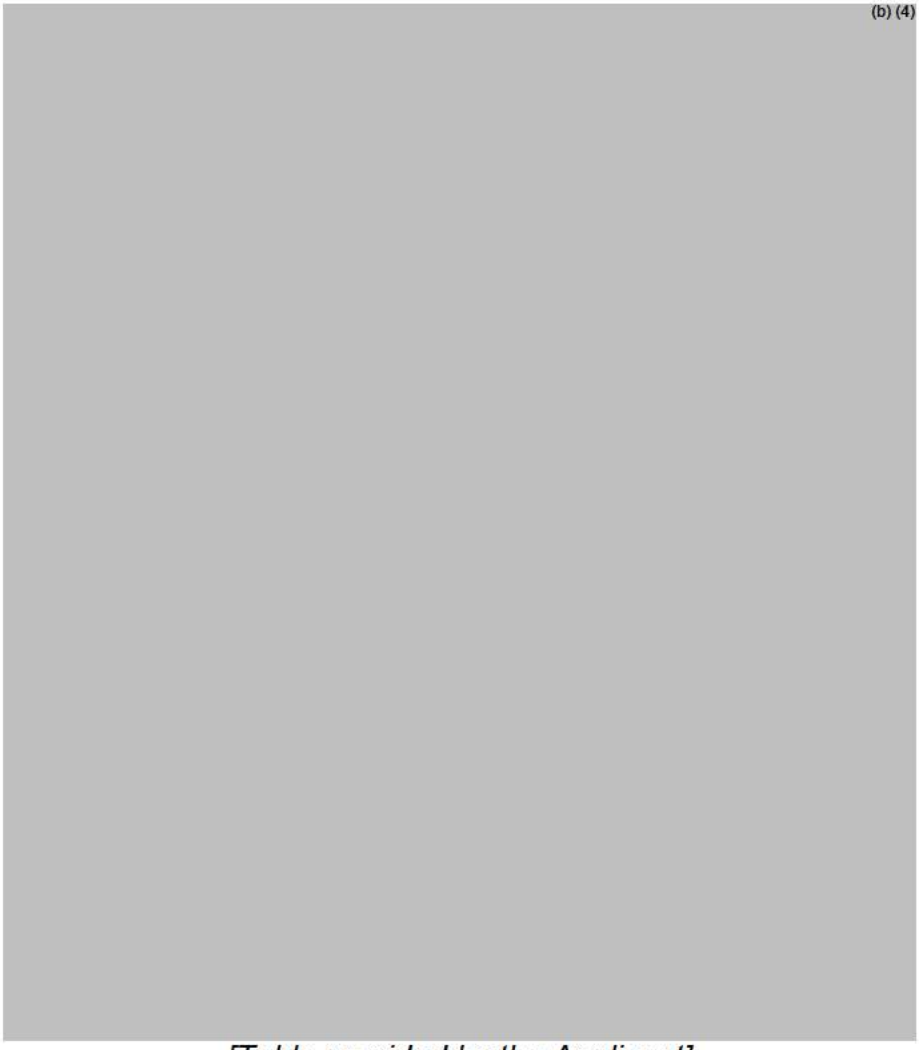
(b) (4)

[Table provided by the Applicant]

Drug product: EE + Levo

According to current DMFs of Levonorgestrel (DMF no. (b) (4) and Ethinyl Estradiol (DMF no. (b) (4) several impurities could be regarded as potential impurities in the drug product Levonorgestrel / Ethinyl Estradiol 0.10 mg / 0.02 mg, chewable tablets as degradation products of the drug substances. In order to define drug product impurities profile, forced degradation study was performed during development of the product as part of analytical method validation (For additional information, please refer to Section 3.2.P.5.3 (*Levonorgestrel / Ethinyl Estradiol 0.10 mg / 0.02 mg, chewable tablets*)).

(b) (4)



[Table provided by the Applicant]

Stability testing

Stability studies have been carried out on a total of 4 batches stored under different conditions of temperature and relative humidity (long term condition: 25±2ºC and 60±5% RH; intermediate condition (30±2ºC and 65±5% RH) and accelerated condition (40±2ºC and 75±5%RH), using the to-be-marketed formulation. The long-term stability (24 months) and accelerated stability (6 months) studies are completed and detailed in Section 3.2.P.8 (*Levonorgestrel / Ethinyl Estradiol 0.10 mg / 0.02 mg, chewable tablets*).

Based on the stability results, it may be concluded that the tablets of the drug product Levonorgestrel / Ethinyl Estradiol 0.10 mg / 0.02 mg, chewable tablets maintain their physical, pharmaceutical and chemical characteristics within specifications after 24 months of storage at long-term conditions (25±2ºC and 60±5% RH) and 6 months of accelerated conditions (40±2ºC and 75±5%RH). Therefore, based on the data generated, it appears appropriate to request a shelf-life of (b) (4) months.

Summary of long-term and accelerated stability studies of batches LFD0031A,

Tests	Accelerated Conditions: 40±2°C and 75±5%RH 0, 1, 3 and 6 months	Long-term Conditions: 25±2°C and 60±5% RH 0, 3, 6, 9, 12, 18 and 24 months
Appearance	All conform	All conform
Levonorgestrel assay		(b) (4)
Ethinyl Estradiol assay		
Levonorgestrel dissolution		
Ethinyl Estradiol dissolution		
Levonorgestrel related substances: (b) (4) - Unknown individual impurities - Total impurities		
Ethinyl Estradiol related substances: (b) (4) - Unknown individual impurities - Total impurities		
Hardness		
Microbial Control - Total Aerobic Microbial Count (TAMC): - Total yeast and mold count (TYMC): - *Escherichia coli*		

[Table provided by the Applicant]

The proposed related substances limits in the drug product specification for both APIs are acceptable from a Pharm/Tox perspective.

Proposed Shelf-life specifications

Test	Shelf-life Specification
Appearance	Round white tablets with L2 and 30 debossed on opposite sides
Levonorgestrel assay	(b) (4) %
Ethinyl Estradiol assay	%
Levonorgestrel dissolution	Q = (b) (4)
Ethinyl Estradiol dissolution	Q =
Levonorgestrel related substances: (b) (4) - Unknown individual impurities - Total impurities	(b) (4)
Ethinyl Estradiol related substances: (b) (4) - Unknown individual impurities - Total impurities	(b) (4)
Hardness*	(b) (4)
Microbial Control** - Total Aerobic Microbial Count (TAMC): - Total yeast and mold count (TYMC): - *Escherichia coli*	(b) (4)

[Table provided by the Applicant]

2.6 Proposed Clinical Population and Dosing Regimen

The intended administration is one tablet daily; 1 active tablet for 21 days followed by 1 inactive tablet for 7 days. Females are instructed to chew and swallow immediately with water.

2.7 Regulatory Background

Regulatory Background

- Type B pre-NDA meeting was held on 02/08/18. There was no nonclinical issue.

Sponsor's Question

NONCLINICAL

Question 5: Module 4 will not contain any original nonclinical studies since the Sponsor did not perform any non-clinical studies. The non-clinical safety will be based on the referenced listed drug (Alesse®) and also summarized in Modules 2.4 and 2.6. The Sponsor will rely upon the Agency's prior findings of safety from the reference listed product. Appropriate literature references will be provided in Module 4, if any. Is this acceptable?

FDA Response:
Your approach is generally acceptable provided that there is adequate clinical data to bridge your product to the listed drug (Alesse®) and that the impurity profile of EV402 is adequately assessed. Submit all referenced literature at the time of NDA submission.

In addition, we remind you that your application must conform to the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR), see PRESCRIBING INFORMATION section below.

External meeting was held on February 8, 2018. There was no further discussion with regards to nonclinical at the meeting.

- This NDA was first submitted 01/07/19 (SN0001). This submission resulted in a Refusal to File (letter dated 03/08/19), attributed to incomplete and inconsistent clinical datasets.
- This NDA was resubmitted on 5/30/19 (SN0006).

3 Studies Submitted

3.1 Studies Reviewed

No nonclinical study was conducted.

3.2 Studies Not Reviewed

N/A

3.3 Previous Reviews Referenced

IND 119353 pre-NDA memo (02/14/18)

4 Pharmacology

Pharmacology

With the long history of ethinyl estradiol (EE) and levonorgestrel (LNG) use and established safety, the pharmacology of ethinyl estradiol and levonorgestrel is very well described in the scientific literature, and estrogens and progestins have been reviewed extensively. No new studies on preclinical pharmacology have been conducted by the Applicant as the dose levels proposed in the EV402 drug product are equivalent to commercial drug products. A review of the published literature was provided by the Applicant. The text below was extracted from the Module 2.6.2. Pharmacology Written Summary.

- EE

Estrogens act synergistically with progestins in suppressing cyclic pituitary follicle stimulating hormone (FSH) and luteinizing hormone (LH). In addition, estrogens maintain the endometrium and help to prevent bleeding. EE has a high estrogenic activity and binds with a comparable affinity to the estrogen receptors as the endogenous hormone 17β-estradiol (E2) and induces similar responses as E2 in target tissues.

In addition to the involvement in hypothalamic-pituitary regulation and direct effects on gonads, estrogens exert a variety of effects due to the extensive distribution of estrogen receptors across various tissues. These effects include modulation of calcium influx in various cells, activation of adenyl cyclase and inhibition of guanyl cyclase in vascular smooth muscles, and augmentation of the effects of excitatory amino acids such as glutamate and aspartate.

Secondary effects of clinical relevance are primarily those in respect to arteriosclerosis, bone mineral density, endometriosis and tumor protection. Various activities may contribute to the protective effect including those on lipid metabolism and endothelial function as well as antioxidative and anti-inflammatory effects.

- LNG

LNG is a second-generation progestin that shows potent progestin and androgenic effects but it lacks estrogenic activity. LNG is the active levorotatory enantiomer of the racemic mixture norgestrel, which both compounds are potent inhibitors of ovulation.

LNG acts on the secretory transformation of an estrogen-primed endometrium by preventing the over-proliferation of the endometrial tissue. The degree to which this effect is achieved depends upon the dose and duration of treatment. LNG suppresses ovulation and is often combined with estrogens like ethinyl estradiol in most hormonal combined oral contraceptives, by suppressing gonadotropins.

Even though the primary mechanism of this action is inhibition of ovulation, there are other secondary effects including changes in the cervical mucus and endometrium that contribute to increasing the difficulty of sperm entering the uterus and decreasing the likelihood of implantation.

- EE + LNG

The product monograph for ALESSE®21 and ALESSE®28 tablets, consisting of 20 µg EE and 100 µg of LNG, notes that in combination the LNG tends to ameliorate the effects of the EE, while the EE modifies the effects of the LNG.

In rats, suppression of fertility is followed by recovery of normal fertility and fecundity upon withdrawal of drug administration. The combination product caused metrotropic effects (uterine glandular development and growth) in rats. Blockade of pituitary gonadotropins can be produced by clinical doses of EE; the effect is not modified by addition of LNG.

At doses approximating the clinical range, the following high-dose combination effects were not observed: parturition delay in pregnant rats; estrogenic changes in mouse vaginal cytology; antiestrogenic effects in mouse uterine growth or vaginal smear tests; androgenic, myotrophic or fetal masculizing effects in rats; claudogenic (antinidatory) effects in rats; thymolymphatic involution in mice; mineralocorticoid effects in rats and dogs and antimineralocorticoid effects in rats. There were no glucocorticoid (rat liver glycogen) or anti-inflammatory (Selye pouch, TBR-arthritis) effects observed at any combined dose of ethinyl estradiol and levonorgestrel.

Safety Pharmacology

No safety pharmacology studies have been performed by the Applicant or described in the Lutera package insert. However, the extensive clinical experience with the combination of EE and LNG is indicative that there are no drug-related clinical effects on renal, respiratory or cardiovascular systems.

5 Pharmacokinetics/ADME/Toxicokinetics

The absorption and bioavailability of the chewable formulation EV402 in nonclinical species has not been studied. However, the metabolism of both EE and LNG have been studied extensively and described in the scientific literature. A review of the published literature was provided by the Applicant. The text below was extracted from the Module 2.6.4. Pharmacokinetics Written Summary.

EE

EE is poorly bioavailable in rats (3%), rhesus monkeys (0.6%) and beagle dogs (9%), most likely due to extensive first-pass metabolism.

EE is metabolized by the monooxygenase system in the liver and the metabolism depends on substrate specificities of P450 isoforms (primarily CYP3A4). Estrogens are oxidized to catechol estrogens and then to highly reactive semiquinone and quinone metabolites.

EE undergoes enterohepatic circulation and is excreted as glucuronide and sulfate in the urine and feces in humans. EE has rates of clearance higher than hepatic blood flow, suggesting high rates of metabolic clearance.

LNG
LNG is not generally bioavailable in nonclinical species (9% in rats and rhesus monkeys, 22% in beagle dogs), most likely due to extensive first-pass metabolism. LNG is excreted primarily in urine (45%) and feces (32%) in women.

LNG is transformed primarily to α3,5β-tetrahydro-, 16β- hydroxy- and 2α-hydroxy-derivatives. Monooxygenases may also oxidize the triple bond of the 17α-ethinyl group.

The primary human urinary metabolite is the glucuronide whereas the sulfate conjugate is the predominant circulating metabolite. LNG undergoes extensive metabolism prior to excretion. Humans excrete similar levels of glucuronide conjugates compared to Rhesus monkeys, but >10% of the urinary metabolites in humans were sulfate conjugates that were not found in the primate. Like EE, LNG has rates of clearance higher than hepatic blood flow, suggesting high rates of metabolic clearance.

Human PK of Alesse

Below texts are taken from the Clinical Overview in Module 2.5.

EE
The Alesse® label indicates that EE is rapidly absorbed but is subject to first-pass metabolism with a bioavailability of 38-48%. Study EXS-P3-239 showed that exposure estimates (Cmax and AUC) of EE after administration of the to-be-marketed formulation of EV402 (Batch LF09251A) were within the bioequivalence (BE) criteria of both the reference comparator product, Lutera®, and the second EV402 batch LFD0556A that was used in study EXS-P3-239.

A food-effect study assessing a different formulation of the LNG/EE 0.10mg/0.02mg chewable tablets showed that administration with a high-fat meal reduced absorption (Cmax) of EE ~44% but had no impact on overall exposure (AUC). A similar trend is anticipated with the to-be-marketed formulation in this application, and while the difference is not anticipated to be clinically relevant, the product will be directed to be administered without food.

LNG
The Alesse® label indicates that the kinetics of total LNG are non-linear due to an increase in binding of LNG to sex hormone binding globulin (SHBG), which is attributed to increased SHBG levels induced by the daily administration of EE. Study EXS-P3-239 showed that exposure estimates (Cmax and AUC) of LNG after administration of the to be-marketed formulation of EV402 (Batch LF09251A) were within the BE criteria of both the reference product, Lutera®, and the second EV402 batch LFD0556A that was used in study EXS-P3-239.

A food-effect study assessing a different formulation of the LNG/EE 0.10mg/0.02mg chewable tablets showed that administration with a high-fat meal reduced absorption (Cmax) of LNG ~66% but had no impact on overall exposure (AUC). A similar trend is anticipated with the to-be-marketed formulation in this application, and while the difference is not anticipated to be clinically relevant, the product will be directed to be administered without food.

Clinical BA studies

Below texts are taken from the Clinical Summary in Module 2.7.2.

- EHE-P4-469

This study was a single center, randomized, single dose, 3-period, 6 sequence crossover design in 36 healthy female subjects designed to assess the relative bioavailability of EV402 (LNG/EE 0.10mg/0.02mg chewable tablet) compared to the reference tablet, Lutera® (LNG/EE 0.10mg/0.02mg tablet) and to evaluate the effect of food on the bioavailability of EV402. Note that the EV402 formulation used in this study (Formulation A) was modified after this study and has not been bridged to the current formulation (Formulation B).

Study findings: 1) Food Effect: Administration with food significantly reduced absorption (maximal concentration [C_{max}]) of EE (~44%) and of LNG (~66%), but not the overall exposure (area under the concentration versus time curve [AUC]) of either analyte. 2) Relative Bioavailability: Compared to the reference standard Lutera®, Exeltis' EV402 Formulation A (LFD0293A batch) had similar systemic exposures (AUC) of both EE and LNG and comparable absorption (C_{max}) of LNG. Compared to the reference standard Lutera®, Exeltis' EV402 Formulation A (LFD0293A batch) had slightly higher absorption (C_{max}) of EE; however, the difference has minimal clinical relevance.

- EXS-P3-821

This study was a single center, randomized, single dose, 3-period, 3-sequence, crossover design in 36 healthy female subjects designed to assess the relative bioavailability of EV402 (LNG/EE 0.10mg/0.02mg chewable tablet) under different conditions (chewed with and without water) compared to the conventional tablet, Lutera® (LNG/EE 0.10mg/0.02mg tablet).

Study findings: 1) Administration of EV402 without water increases exposures of EE (~ 50% for C_{max} and ~30% for AUC) relative to the reference tablet Lutera® but has no impact on LNG exposures. 2) Administration of EV402 with water increases C_{max} of EE (~ 23%), but not overall exposures (AUC) relative to the reference tablet Lutera®.

- EXS-P3-239

The study was a single center, randomized, single dose, 3-period, 6-sequence, crossover design in 36 healthy female subjects designed to evaluate the relative bioavailability of two different batches of EV402 (LNG/EE 0.10mg/0.02mg chewable tablet) compared with the reference standard Lutera® (LNG/EE 0.10mg/0.02mg tablet).

Study findings: 1) Compared to the reference standard Lutera®, Exeltis' EV402 (LF09251A batch) had comparable exposures (C_{max} and AUCs) of EE and LNG. 2) Compared to the reference standard Lutera®, Exeltis' EV402 (LFD0556A batch) had comparable absorption (C_{max}) of LNG and systemic exposures (AUC) of both EE and LNG. 3) Compared to the reference standard Lutera®, Exeltis' EV402 (LFD0556A batch) had a slightly higher absorption (C_{max}) of EE (~22%); however, the difference has minimal clinical relevance. 4) EV402 batches LFD0556A and LF09251A had comparable exposures (Cmax and AUCs) of EE and LNG.

Study	Study Title	Evaluated EV402 Formulation	Dose Evaluated
EHE-P4-469	Single-dose Crossover Comparative Bioavailability Under Fasting-Conditions and Food Effect Study of Ethinylestradiol/Levonorgestrel 0.02 mg/0.1 mg Chewable Tablets Compared to Tablets in Healthy Female Volunteers	Formulation A (Batch LFD0293A)	EV402: 1 x EE/LNG 0.02 mg/0.1 mg Reference: 1 x Lutera® 0.02 mg/0.1 mg
EXS-P3-821	Single-dose Crossover Comparative Bioavailability Under Fasting-Conditions of Ethinylestradiol/Levonorgestrel 0.02 mg/0.1 mg Chewable Tablets Compared to Tablets in Healthy Female Volunteers	Formulation B* (Batch LFD0415A)	EV402: 1 x EE/LNG 0.02 mg/0.1 mg Reference: 1 x Lutera® 0.02 mg/0.1 mg
EXS-P3-239	Single-dose Crossover Comparative Bioavailability Study of Ethinylestradiol/Levonorgestrel 0.02 mg/0.1 mg Chewable Tablets Compared to Tablets in Healthy Female Volunteers	Formulation B* (batches LFD0556A and LF09251A)	EV402: 1 x EE/LNG 0.02 mg/0.1 mg Reference: 1 x Lutera® 0.02 mg/0.1 mg

*Formulation B is the to-be-marketed formulation.

[Extracted from Module 2.7.2. Summary-Clin-Pharm]

6 General Toxicology

The sponsor conducted a comprehensive literature search using the RTECS and Toxnet databases and for all available chemical names associated with both ethinyl estradiol (EE) and levonorgestrel (LNG). A review of the published literature was provided by the Applicant. The text below was extracted from the Module 2.6.6. Toxicology Written Summary.

- Single dose toxicity

Single-dose toxicity studies showed that the LD_{50} values for the combination of EE and LNG were > 1.32 g/kg, more than 11,000-fold higher than the clinical dose of 0.12 mg total dose for EV042.

Single Dose LD50 Studies on EV402

Species	Route of Administration	LD_{50} (g/kg)		
		Levonorgestrel	Ethinyl Estradiol	Levonorgestrel + Ethinyl Estradiol
Mice	Oral	> 4.0	> 2.5	> 2.5
Mice	i.p.	> 3.9	0.69	1.32-1.65
Mice	s.c.	> 4.0	> 2.6	> 2.5
Rats	Oral	> 4.0	Suspension >5.0 Solution 1.5	> 2
Rats	i.p.	> 5.0	0.97	~ 2
Rats	s.c.	>4.0; hair loss		
Dogs	oral		> 1.0	

[Table provided by the Applicant]

- Repeat dose toxicity

Repeat-dose oral toxicity studies in rats, dogs and rhesus monkeys have been conducted through 10 years of dosing with EE, norgestrel (of which LNG is the active isomer), LNG and a combination of EE and LNG. No general toxicity was observed in any preclinical species from 26 weeks through 10 years of dosing, although some studies showed evidence of an increase in benign and malignant tumor formation.

Repeat-dose Toxicity Studies on Ethinyl Estradiol alone or in combination with Norgestrel or Levonorgestrel

Species	Drugs, Dose and Route of Administration	Duration of Administration	Effects	Histopathology
Mice 40/sex/group	Norgestrel Ethinyl Estradiol Norgestrel + Ethinyl estradiol (10 + 1) Oral, mg/kg 0.02 + 0.002 0.7 + 0.007 2.0 + 0.2 3.0 + 0.3	80 weeks	Ethinyl estradiol depressed weight gain in 3 highest dose groups. Norgestrel + ethinyl estradiol depressed weight gain in 3 highest dose groups. No effects in norgestrel dose group.	Ethinyl estradiol: significant increase in malignant tumors. Lymphocarcinoma in males and interstitial tumors in females. Norgestrel + ethinyl estradiol: same tumor pattern as ethinyl estradiol alone. Norgestrel: no tumorigenic effects.
Rat 16/sex/group	Norgestrel Oral, mg/kg 0.001%, 0.005%, 0.0025%	26 weeks	No signs or symptoms of toxicity	No histopathological changes
	Levonorgestrel Oral, mg/kg 0.00005%, 0.00025%, 0.00125%	26 weeks	Significantly less weight gain in low dose females. No other signs of toxicity	No histopathological changes
Rat 40/sex/group	Norgestrel Ethinyl Estradiol Norgestrel + Ethinyl estradiol (10 + 1) Oral, mg/kg	104 weeks	Norgestrel: no effects. Ethinyl estradiol: dose-related decreases in body weight gain. Norgestrel and ethinyl	Significant increase vs controls in malignant and benign mammary tumors at mid-dose and high dose groups with ethinyl estradiol either alone or in

Species	Drugs, Dose and Route of Administration	Duration of Administration	Effects	Histopathology
	0.02 + 0.002 0.5 + 0.005 2.0 + 0.2		estradiol: dose-related decreases in body weight gain.	combination with Norgestrel. One incidence of leukemia in low dose group with norgestrel + ethinyl estradiol.
Dog 6/sex/group	Levonorgestrel Oral, mg/kg 0.05, 0.1, 0.5	26 weeks	No estrus in any dog, mammary enlargement in all but 2 females and 8 males. Dose related clitoral reddening and enlargement. Significant decrease in cholesterol in all dose groups.	No drug-related effects on ophthalmology, ECG, hemostasis, urinalysis or organ weights.
Dog 16 females/group	Norgestrel Oral, mg/kg 0, 0.003, 0.015, 0.0375	Continuous over 7 years	Estrus inhibited in all but low dose group. Urine enlargement and endometrial hyperplasia at 0.015 and 0.0375 mg/kg.	Norgestrel 0.0375 mg/kg group – many dogs with cysts and absence of luteal phase. One dog with mammary carcinoma at 0.0375 mg/kg.
	Levonorgestrel Oral, mg/kg 0.5	Cyclic over 7 years	Enlarged clitoris on majority of dogs. Low hematocrit and hemoglobin or SGPT increased significantly. Increased fibrinogen.	Increase in benign mammary adenomas. Adenocarcinoma in one dog. Multiple vaginal cysts and absence of luteal phase.
Dog 16 females/group	Levonorgestrel Oral, mg/kg 0.01, 0.05, 0.125	Cyclic over 7 years	No treatment-related adverse findings. Endocrine-related findings at the 0.05 and 0.125 mg/kg dose levels related to pharmacological effects of a progestin.	No treatment-related changes.
Dog 12 females/group	Norgestrel Ethinyl estradiol	7 years	Norgestrel: increases in body weights at 0.1 mg/kg, SGPT	Dose-related increases in mammary adenomas in

Species	Drugs, Dose and Route of Administration	Duration of Administration	Effects	Histopathology
	Norgestrel and ethinyl estradiol Oral, mg/kg 0.1-0.25 0.01 0.1 + 0.025 0.1 + 0.01 0.25 + 0.025		increases in all dose groups, some increases in fibrinogen. Suppression of estrus with norgestrel alone or in combination with ethinyl estradiol.	Norgestrel-treated dogs. Possible increase in benign adenomas and intraductal papillomas in Norgestrel high dose group.
Rhesus Monkey 16 females/group	Norgrestrel Oral, mg/kg 0, 0.003, 0.015, 0.075	Continuous over 10 years (120 months)	Red vaginal discharge, less frequent in 0.015 and 0.075 mg/kg groups.	Mammary nodules in 3 animals at 0.075 mg/kg. One animal with mammary nodules at 0.003 and 0.015 mg/kg.
	Levonorgestrel Oral, mg/kg 1.0	Cyclic (over 21 days) over 10 years (120 months)	Red vaginal discharge more frequent in withdrawal periods. Increased fibrinogen levels.	Mammary nodule in 1 animal.
Rhesus monkey 16 females/group	Norgestrel Ethinyl estradiol Norgestrel + ethinyl estradiol Oral, mg/kg 0.01, 0.1, 0.5 0.002, 0.02, 0.05 0.02 + 0.002 0.1 + 0.01 0.5 + 0.05	10 years	Increased body weight gain in Norgestrel 0.5 mg/kg group. Increased fibrinogen levels in monkeys receiving Norgestrel alone or in combination with ethinyl estradiol. Higher rate of retinal depigmentation in animals treated with ethinyl estradiol alone or in combination with Norgestrel.	No histopathology findings.

[Tables provided by the Applicant]

Clinical safety studies

Below texts are taken from the Clinical Summary in Module 2.7.4. Cumulatively, 1680 doses of Test drug were administered to 80 subjects over a period 21 day in two studies, EHE-P4-471 (n=40 test drug once daily for 21 days and n=40 placebo once daily for 7 days) and EXS-P1-531 (n=40 test drug once daily for 21 days and n=40 placebo once daily for 7 days).

Study findings: The proportion of subjects in study reporting AEs was similar across the studies. The majority of AEs were mild to moderate in severity. There were no serious AEs and No deaths reported.

Overview of Adverse Events in Subjects Who received Active Test Drug Across Clinical Studies

	EHE-P4-469[a] N=36		EXS-P3-239 N=36		EXS-P3-821 N=36		EHE-P4-471 N=40	EXS-P1-531 N=40
	T-1	T-3	T-1	T-2	T-1	T-2		
Adverse Events Reported, n	42	27	23	19	29	13	53	50
Subjects with at least one AE, n (%)	15 (44)	12 (38)	11 (32)	10 (29)	15 (44)	10 (30)	19 (48)	18 (45)
Subjects with related AE, n (%)	13 (38)	12 (38)	7 (21)	7 (21)	13 (38)	7 (21)	18 (45)	18 (45)
Serious Adverse Events Reported, n (%)	0	0	0	0	0	0	0	0
Deaths, n (%)		0	0	0	0	0	0	0

[a] EHE-P4-469: T-1=Test drug administered under fasting conditions; T-3=Test drug administered under fed conditions
[b] EXS-P3-239: T-1=Test drug; T-2=Test drug
[c] EXS-P3-821: T-1=Test drug chewed without water; T-2=Test chewed with water

[Table provided by the Applicant]

7 Genetic Toxicology

The sponsor conducted a comprehensive literature search using the RTECS and Toxnet databases and for all available chemical names associated with both ethinyl estradiol (EE) and levonorgestrel (LNG). A review of the published literature was provided by the Applicant. The text below was extracted from the Module 2.6.6. Toxicology Written Summary.

EE and LNG have both been tested in an Ames reverse bacterial mutation assay in the presence and absence of S9 (Lang and Reinmann, 1993). Neither compound caused bacterial mutation.

Sex steroids are generally negative in standard genotoxicity assays and have been considered to be epigenetic carcinogens. However, in a study of nine sex hormones (Martelli and Brambilla, 2002), including EE, in rat and human hepatocytes, induction of DNA repair indicating a positive response was noted in hepatocytes from 2/2 male and 1 of 2 female rats, but no hepatocytes from male or female human donors. The data suggests that the ability of steroids, in particular EE, to induce DNA repair may be different between rat and human hepatocytes and may be dependent on the sex of the donor.

8 Carcinogenicity

The sponsor conducted a comprehensive literature search using the RTECS and Toxnet databases and for all available chemical names associated with both ethinyl estradiol (EE) and levonorgestrel (LNG). A review of the published literature was provided by the Applicant. The text below was extracted from the Module 2.6.6. Toxicology Written Summary.

LNG plus EE was tested for carcinogenicity in mice and rats by oral administration. No increase in the incidence of tumors was observed in either species. *In vitro* and *in vivo* tests have demonstrated that LNG is not carcinogenic.

LNG did not increase the incidence of mammary tumors in dogs or the incidence of endometrial carcinomas in rabbits, nor did it enhance the incidence of renal dysplastic lesion or tumors in hamsters treated with N-nitroso(2-oxopropyl)amine.

However, in some studies in mice and rats, long-term, continuous administration of EE increased the frequency of cancers of the breast, cervix, liver, pancreas, testis, uterus, and vagina. The significance of this finding is unclear as there are conflicting studies in the literature.

9 Reproductive and Developmental Toxicology

The sponsor conducted a comprehensive literature search using the RTECS and Toxnet databases and for all available chemical names associated with both ethinyl estradiol (EE) and levonorgestrel (LNG). A review of the published literature was

provided by the Applicant. The text below was extracted from the Module 2.6.6. Toxicology Written Summary.

At doses in the clinical range, LNG, EE and their combinations have no noticeable effects on pregnant rats, their pregnancies, their offspring or the reproductive potential of the young. In addition, at doses approximating the clinical range, LNG and/or EE have no observable effects on lactating rats, the lactation process or the nursing young.

At doses above the clinical range, a small dose-related increase in the number of abnormal fetuses is observed in mice treated during pregnancy with norgestrel/EE combinations in a ratio of 5:1. Abnormalities included open eyes, cleft palates, exencephaly and umbilical hernia. Rabbits treated during pregnancy with doses of norgestrel and EE in the clinical range and greater did not show teratogenic effects.

10 Special Toxicology Studies

No studies on comparative systemic exposure have been conducted. No studies on tolerability or other special studies have been conducted.

Studies to evaluate local tolerance of EV402 for the new chewable tablet route of administration were conducted during clinical trials. No significant adverse effects were observed. No nonclinical studies were necessary.

11 Integrated Summary and Safety Evaluation

The acute toxicity of the ethinyl estradiol/levonorgestrel (EE/LNG) combination is low, based upon the requirement of doses much higher than those normally used in humans to produce significant changes in preclinical species. Repeated administration of high doses of exogenous progestins to rats, dogs and rhesus monkeys results in the extension of the pharmacologic activity. No significant toxicity was observed in any preclinical species from 26 weeks through 10 years of dosing, and findings were primarily pharmacologic. EE/LNG is not teratogenic nor mutagenic. Carcinogenic potential has not been detected after administering doses higher than that normally given to humans over prolonged periods of time.

The safe use of EE in combination with LNG is well established in the clinical literature. Long-term exposure to the proposed clinical doses has no toxicological consequence with respect to either organ toxicity or reproductive toxicity. Neither EE nor LNG, either alone or in combination, is directly genotoxic; sex steroid hormones are considered epigenetic carcinogens, but these effects appear to be species and sex-specific. Even though there are conflicting reports regarding the carcinogenicity of long-term use of EE and LNG, clinical experience thus far does not suggest increased incidence of breast cancer with low-dose EE use.

Taken together, the data indicate that the combination of 20 µg of EE and 100 µg of LNG does not raise any toxicological concern.

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/

MIYUN M TSAI-TURTON
02/04/2020 06:17:42 AM

KIMBERLY P HATFIELD
02/04/2020 09:04:47 AM
I concur with Dr. Tsai-Turton's review and recommendations.