HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use levonorgestrel and ethinyl estradiol tablets safely and effectively. See full prescribing information for levonorgestrel and ethinyl estradiol tablets.

LEVONORGESTREL and ETHINYL ESTRADIOL tablets for oral use
Initial U.S. Approval: 1982

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **Levonorgestrel and ethinyl estradiol tablets are contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)**

----------RECENT MAJOR CHANGES----------

Warning and Precautions, Malignant Neoplasms (5.11) 04/2022

----------INDICATIONS AND USAGE----------

Levonorgestrel and ethinyl estradiol tablet is an estrogen/progestin COC indicated for use by women to prevent pregnancy. (1)

----------DOSAGE AND ADMINISTRATION----------

- Take one tablet daily by mouth at the same time every day for 91 days. (2.1)
- Take tablets in the order directed on the Extended-Cycle Wallet. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Levonorgestrel and ethinyl estradiol tablets USP consists of 84 pink, round, biconvex, film-coated tablets, each containing 0.15 mg of levonorgestrel and 0.03 mg of ethinyl estradiol, and 7 white to off white, round, biconvex, inert tablets. (3)

----------CONTRAINDICATIONS----------

- A high risk of arterial or venous thrombotic diseases (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

----------WARNINGS AND PRECAUTIONS----------

- Thrombotic disorders and other vascular problems: Stop levonorgestrel and ethinyl estradiol tablets if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue levonorgestrel and ethinyl estradiol tablets if jaundice occurs. (5.2)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop levonorgestrel and ethinyl estradiol tablets if blood pressure rises significantly. (5.3)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking levonorgestrel and ethinyl estradiol tablets. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.5)
- Headache: Evaluate significant change in headaches and discontinue levonorgestrel and ethinyl estradiol tablets if indicated. (5.6)
- Bleeding irregularities and amenorrhea: Evaluate irregular bleeding or amenorrhea. (5.7)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥2%) reported during clinical trials were headache, menorrhagia, nausea, dysmenorrhea, acne, migraine, breast tenderness, weight increased, and depression. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes (for example CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing Mothers: Advise use of another contraceptive method. Levonorgestrel and ethinyl estradiol tablets can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

Levonorgestrel and ethinyl estradiol tablets are indicated for use by females of reproductive potential to prevent pregnancy.

2 DOSAGE AND ADMINISTRATION

2.1 How to Start Levonorgestrel and Ethinyl Estradiol Tablets

Levonorgestrel and ethinyl estradiol tablets are dispensed in an Extended-Cycle Wallet *[see How Supplied/Storage and Handling (16)]*. Levonorgestrel and ethinyl estradiol tablets should be started on a Sunday (see Table 1). For the first cycle of a Sunday Start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

Instruct patients to take levonorgestrel and ethinyl estradiol tablets once a day by mouth at the same time every day for 91 days. To achieve maximum contraceptive effectiveness, levonorgestrel and ethinyl estradiol tablets should be taken exactly as directed and at intervals not exceeding 24 hours. For patient instructions regarding missed pills, see *FDA-approved patient labeling.*

2.2 How to Take Levonorgestrel and Ethinyl Estradiol Tablets

Table 1: Instructions for Administration of Levonorgestrel and Ethinyl Estradiol Tablets

Starting COCs in women not currently using hormonal contraception (Sunday Start) **Important:** Consider the possibility of ovulation and conception prior to initiation of this product. **Tablet Color:** • Levonorgestrel and ethinyl estradiol active tablets are pink (Day 1 to Day 84). • Levonorgestrel and ethinyl estradiol inactive tablets are white (Day 85 to Day 91).	**Sunday Start:** **For each 91-day course, take in the following order:** • Take the first **pink** tablet (0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol) on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, take the tablet on that day. **Due to the potential risk of becoming pregnant, use additional non-hormonal contraception (such as condoms or spermicide) for the first 7 days of treatment.** • Take subsequent pink tablets once daily at the same time each day for a total of 84 days. • Take one **white** tablet (inert) daily for the following 7 days and at the same time of day that active tablets were taken. A scheduled period should occur during the 7 days that the white tablets are taken. • Begin the next and all subsequent 91-day courses of levonorgestrel and ethinyl estradiol tablets without interruption on the same day of the week (i.e., Sunday) on which the patient began her first

	dose. Follow the same schedule as the initial 91-day course: a pink tablet once a day for 84 days, and a white tablet once a day for 7 days. If the patient does not immediately start her next pill pack, instruct her to protect herself from pregnancy by using a non-hormonal back-up method of contraception until she has taken a pink tablet daily for 7 consecutive days.
Switching to levonorgestrel and ethinyl estradiol tablets from another oral contraceptive	Start on the same day that a new pack of the previous oral contraceptive would have started.
Switching from another contraceptive method to levonorgestrel and ethinyl estradiol tablets	**Start levonorgestrel and ethinyl estradiol tablets:**
• **Transdermal patch**	• On the day when the next application would have been scheduled.
• **Vaginal ring**	• On the day when the next insertion would have been scheduled.
• **Injection**	• On the day when the next injection would have been scheduled.
• **Intrauterine contraceptive (IUD)**	• On the day of removal. • If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraception (such as condoms or spermicide) is needed for the first seven days of the first 91-day course.
• **Implant**	• On the day of removal.
Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-approved patient labeling.	

Starting Levonorgestrel and Ethinyl Estradiol Tablets after Abortion or Miscarriage

First-trimester

- After a first-trimester abortion or miscarriage, levonorgestrel and ethinyl estradiol tablets may be started immediately. An additional method of contraception is not needed if levonorgestrel and ethinyl estradiol tablets are started immediately.
- If levonorgestrel and ethinyl estradiol tablets are not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms or spermicide) for the first seven days of her first 91-day course of levonorgestrel and ethinyl estradiol tablets.

Second-trimester

- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start levonorgestrel and ethinyl estradiol tablets following the instructions in Table 1 for Sunday start. Use additional non-hormonal contraception (such as condoms or spermicide) for the first seven days of the patient's first 91-day course of levonorgestrel and ethinyl estradiol tablets *[see Contraindications (4), Warnings and Precautions (5.1), and FDA-approved Patient Labeling]*.

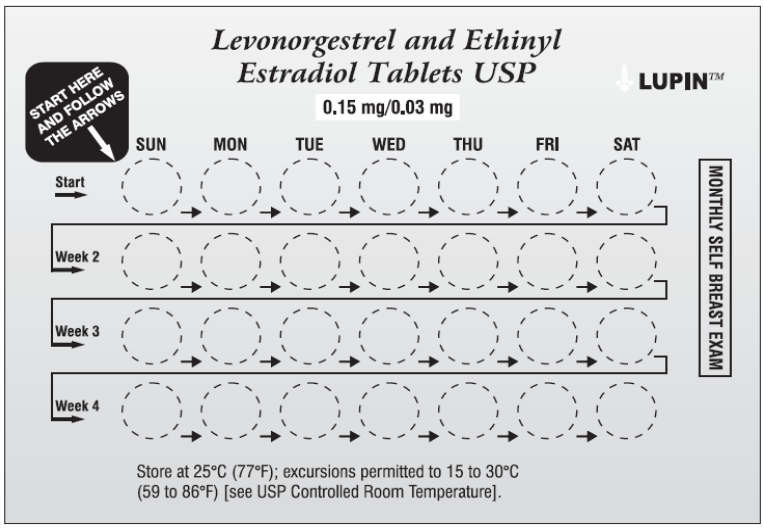
Starting Levonorgestrel and Ethinyl Estradiol Tablets after Childbirth

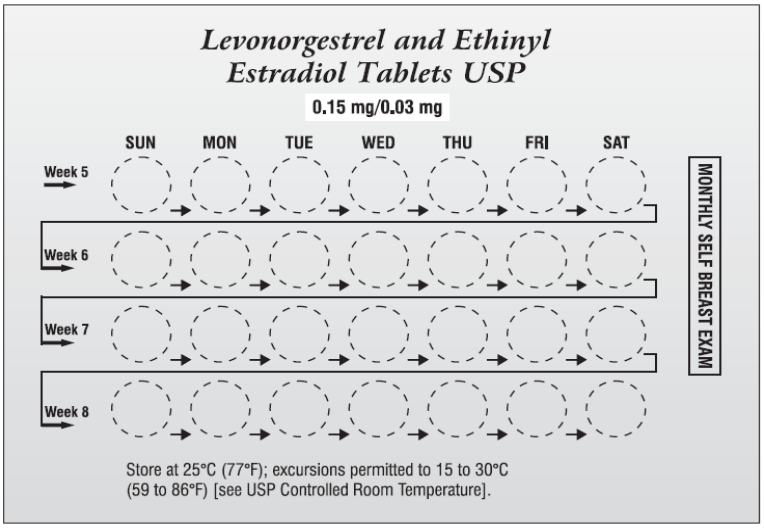
- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with levonorgestrel and ethinyl estradiol tablets following the instructions in Table 1 for women not currently using hormonal contraception.
- Levonorgestrel and ethinyl estradiol tablets are not recommended for use in lactating women *[see Use in Specific Populations (8.3) and FDA-Approved Patient Labeling]*.
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of levonorgestrel and ethinyl estradiol tablets *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1 and 8.3), and FDA-approved Patient Labeling]*.

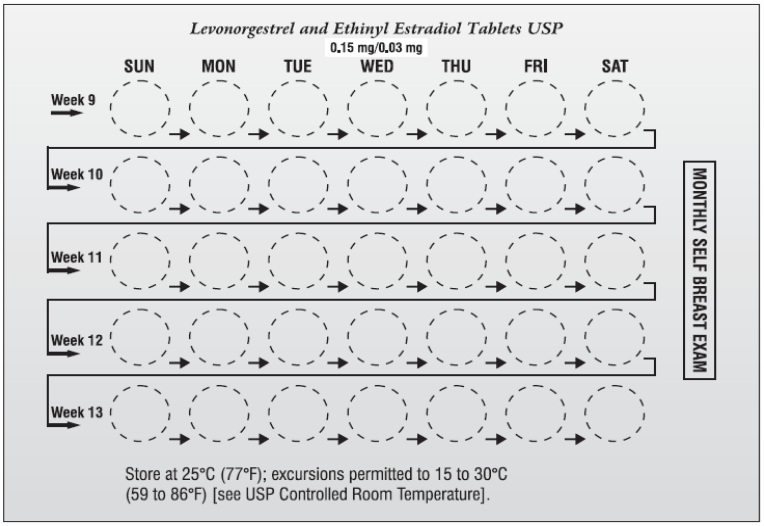
Wallet Instructions:

- The Wallet consists of blister strips that hold 91 individually sealed pills (a 13-week, or 91-day, cycle). The 91 pills consist of 84 pink pills (active pills with hormones) and 7 white pills (inactive pills without hormone).
- Blister strip 1 and 2 each contain 28 pink pills (4 rows of 7 pills). **See Figure A.**
- Blister strip 3 contains 35 pills consisting of 28 pink pills (4 rows of 7 pills) and 7 white pills (1 row of 7 pills). **See Figure A**

Figure A


Levonorgestrel and Ethinyl Estradiol Tablets USP
LUPIN™
0.15 mg/0.03 mg
START HERE AND FOLLOW THE ARROWS
SUN MON TUE WED THU FRI SAT
Start
Week 2
Week 3
Week 4
MONTHLY SELF BREAST EXAM
Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].


Levonorgestrel and Ethinyl Estradiol Tablets USP
0.15 mg/0.03 mg
SUN MON TUE WED THU FRI SAT
Week 5
Week 6
Week 7
Week 8
MONTHLY SELF BREAST EXAM
Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].


Levonorgestrel and Ethinyl Estradiol Tablets USP
0.15 mg/0.03 mg
SUN MON TUE WED THU FRI SAT
Week 9
Week 10
Week 11
Week 12
Week 13
MONTHLY SELF BREAST EXAM
Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

- Advise the patient to remove the first pill in the upper left corner at the start arrow by pushing down on the pill. The pill will come out through a hole in the back of the Wallet.
- Advise the patient to wait 24 hours to take the next pill, and continue to take one pill each day until all the pills have been taken.
- Advise the patient, after taking the last white pill, to start taking the first pink pill from a new Wallet the very next day, regardless of when their period started.

2.3 Missed Tablets

Table 2: Instructions for Missed Levonorgestrel and Ethinyl Estradiol Tablets

• If one active tablet (pink) is missed in Days 1 through 84	Take the tablet as soon as possible. Take the next tablet at the regular time and continue taking one tablet a day until the 91-day course is finished.
• If two consecutive active tablets (pink) are missed in Days 1 through 84	Take 2 tablets on the day remembered and 2 tablets the next day. Then continue taking one tablet a day until the 91-day course is finished. **Additional non-hormonal contraception (such as condoms or spermicide) should be used as back-up if the patient has sex within 7 days after missing 2 tablets.**
• If three or more consecutive active tablets (pink) are missed in Days 1 through 84	Do not take the missed tablets. Continue taking one tablet a day until the 91-day course is finished. **Additional non-hormonal contraception (such as condoms or spermicide) must be used as back-up if the patient has sex within 7 days after missing 3 tablets.**

2.4 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting or diarrhea occurs within 3 to 4 hours after taking a pink tablet, handle this as a missed tablet *[see FDA-approved patient labeling]*.

3 DOSAGE FORMS AND STRENGTHS

Levonorgestrel and ethinyl estradiol tablets USP are available in Extended-Cycle Wallets, each containing a 13-week supply of tablets in the following order:

- 84 pink, round, biconvex, film-coated tablets, each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol; debossed with LU on one side and U21 on the other side
- 7 white to off white, round, biconvex, inert tablets debossed with LU on one side and U22 on the other side.

4 CONTRAINDICATIONS

Levonorgestrel and Ethinyl Estradiol Tablets is contraindicated in females who are known to have or develop the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*.
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*.

- Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*.
- Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*.
- Have coronary artery disease *[see Warnings and Precautions (5.1)]*.
- Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*.
- Have uncontrolled hypertension *[see Warnings and Precautions (5.3)]*.
- Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.5)]*.
- Have headaches with focal neurological symptoms or migraine headaches with aura *[see Warnings and Precautions (5.6)]*.
  - Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.6)]*.

- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)]*.
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.7)]*.
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.8) and Use in Specific Populations (8.1)]*.
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive*[see Warnings and Precautions (5.11)]*.
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic Disorders and Other Vascular Problems

- Stop levonorgestrel and ethinyl estradiol tablets if an arterial thrombotic event or venous thromboembolic (VTE) event occurs.
- Stop levonorgestrel and ethinyl estradiol tablets if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.
- If feasible, stop levonorgestrel and ethinyl estradiol tablets at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during and following prolonged immobilization.
- Start levonorgestrel and ethinyl estradiol tablets no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued.
- Use of levonorgestrel and ethinyl estradiol tablets provide women with more hormonal exposure on a yearly basis than conventional monthly COCs containing the same strength synthetic estrogens and progestins (an additional 9 weeks of exposure per year). In the clinical

trial, one case of pulmonary embolism was reported. Postmarketing adverse reactions of VTE have been reported in women who used levonorgestrel and ethinyl estradiol tablets.

- Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. Stroke has been reported in women associated with the use of levonorgestrel and ethinyl estradiol tablets. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.
- Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function

Do not use levonorgestrel and ethinyl estradiol tablets in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of the liver *[see Contraindications (4)]*. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue levonorgestrel and ethinyl estradiol tablets if jaundice develops.

Liver Tumors

Levonorgestrel and ethinyl estradiol tablets are contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)]*. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

5.3 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains obmitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as COCs. Discontinue levonorgestrel and ethinyl estradiol tablets prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4*)]. Levonorgestrel and ethinyl estradiol tablets can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.4 High Blood Pressure

Levonorgestrel and ethinyl estradiol tablets are contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop levonorgestrel and ethinyl estradiol tablets if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may worsen existing gallbladder disease.

A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC-related cholestasis.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking levonorgestrel and ethinyl estradiol tablets. COCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.
Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache

If a woman taking levonorgestrel and ethinyl estradiol tablets develop new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue levonorgestrel and ethinyl estradiol tablets if indicated.

Consider discontinuation of levonorgestrel and ethinyl estradiol tablets in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) *[see Contraindications (4)]*.

5.8 Bleeding Irregularities and Amenorrhea

Bleeding and/or spotting that occurs at any time while taking the first 84 tablets of each extended-cycle regimen is considered “unscheduled” bleeding/spotting. Bleeding that occurs during the time a woman takes the seven white inert tablets is considered “scheduled” bleeding.

<u>Unscheduled and Scheduled Bleeding and Spotting</u>
Unscheduled (breakthrough) bleeding and spotting sometimes occur in patients on COCs, especially during the first 3 months of use. If unscheduled bleeding persists or occurs after previously regular cycles on levonorgestrel and ethinyl estradiol tablets, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Before prescribing levonorgestrel and ethinyl estradiol tablets, advise the woman to weigh the convenience of fewer scheduled menses (4 per year instead of 13 per year) against the inconvenience of increased unscheduled bleeding and/or spotting.

The clinical trial of the efficacy of levonorgestrel and ethinyl estradiol tablets (91-day cycles) in preventing pregnancy also assessed scheduled and unscheduled bleeding. The participants in the study were composed primarily of women who had used oral contraceptives previously as opposed to new users. Women with a history of breakthrough bleeding/spotting ≥ 10 consecutive days on oral contraceptives were excluded from the study. More levonorgestrel and ethinyl estradiol tablets subjects, compared to subjects on the comparator 28-day cycle regimen, discontinued prematurely for unacceptable bleeding (7.7% [levonorgestrel and ethinyl estradiol tablets] vs. 1.8% [28-day cycle regimen]).

Unscheduled bleeding and unscheduled spotting decreased over successive 91-day cycles. Table 3 below presents the number of days with unscheduled bleeding and/or spotting for each respective 91-day cycle.

Table 3: Number of Unscheduled Bleeding and/or Spotting Days per 91-day Cycle

Cycle (N)	**Days of Unscheduled Bleeding and/or Spotting per 84-Day Interval**				**Median Days Per Subject-Month**
	Mean	**Q1**	**Median**	**Q3**	
1 (446)	15.1	3.0	12	23.0	3.0
2 (368)	11.6	2.0	6	17.5	1.5
3 (309)	10.6	1.0	6	15.0	1.5
4 (282)	8.8	1.0	4	14.0	1.0

Q1=Quartile 1: 25% of women had ≤ this number of days of unscheduled bleeding/spotting
Median: 50% of women had ≤ this number of days of unscheduled bleeding/spotting
Q3=Quartile 3: 75% of women had ≤ this number of days of unscheduled bleeding/spotting

Table 4 shows the percentages of women with ≥ 7 days and ≥ 20 days of unscheduled spotting and/or bleeding in the levonorgestrel and ethinyl estradiol tablets and the 28-day cycle treatment groups.

Table 4: Percentage of Subjects with Unscheduled Bleeding and/or Spotting

Days of unscheduled bleeding and/or spotting	Percentage of Subjects[a]	
Levonorgestrel and ethinyl estradiol tablets	Cycle 1 (N=385)	Cycle 4 (N=261)
≥ 7 days	65%	42%
≥ 20 days	35%	15%
28-day regimen	Cycles 1 to 4 (N=194)	Cycles 10 to 13 (N=158)
≥ 7 days	38%	39%
≥ 20 days	6%	4%

a Based on spotting and/or bleeding on days 1 to 84 of a 91 day cycle in the levonorgestrel and ethinyl estradiol tablets subjects and days 1 to 21 of a 28 day cycle over 4 cycles in the 28-day dosing regimen.

Total days of bleeding and/or spotting (scheduled plus unscheduled) were similar over one year of treatment for levonorgestrel and ethinyl estradiol tablets subjects and subjects on the 28-day cycle regimen.

Amenorrhea and Oligomenorrhea

Women who are not pregnant and use levonorgestrel and ethinyl estradiol tablets may experience amenorrhea. Based on data from the clinical trial, amenorrhea occurred in approximately 0.8% of women during Cycle 1, 1.2% of women during Cycle 2, 3.7% of women during Cycle 3, and 3.4% of women during Cycle 4. Because women using levonorgestrel and ethinyl estradiol tablets will likely have scheduled bleeding only 4 times per year, rule out pregnancy at the time of any missed menstrual period.

Some women may experience amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was pre-existent.

5.9 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue levonorgestrel and ethinyl estradiol tablets use if pregnancy is confirmed.

Administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Depression associated with the use of levonorgestrel and ethinyl estradiol tablets has been reported. Carefully observe women with a history of depression and discontinue levonorgestrel and ethinyl estradiol tablets if severe depression recurs.

5.11 Malignant Neoplasms

Breast Cancer

Levonorgestrel and ethinyl estradiol tablets is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see Contraindications (4)]*.

Epidemiology studies have not found a consistent association between use of combined oral contraceptives (COCs) and breast cancer risk. Studies do not show an association between ever (current or past) use of COCs and risk of breast cancer. However, some studies report a small increase in the risk of breast cancer among current or recent users (<6 months since last use) and current users with longer duration of COC use *[see Postmarketing Experience (6.2)]*.

Cervical Cancer

Some studies suggest that COC use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

5.12 Effect on Binding Globulins
The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.13 Monitoring
A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated health care.

5.14 Hereditary Angioedema
In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.15 Chloasma
Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to develop chloasma should avoid prolonged exposure to the sun or ultraviolet radiation while taking levonorgestrel and ethinyl estradiol tablets.

6 ADVERSE REACTIONS
The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:
- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*

Adverse reactions commonly reported by COC users are:
- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The clinical trial that evaluated the safety and efficacy of levonorgestrel and ethinyl estradiol tablets was a 12-month, randomized, multicenter, open-label study, which enrolled women aged 18 to 40, of whom 456 took at least one dose of levonorgestrel and ethinyl estradiol tablets (345.14 woman-years of exposure) *[see Clinical Studies (14)]*.

Adverse Reactions Leading to Study Discontinuation: 14.9% of the women discontinued from the clinical trial due to an adverse reaction; the most common adverse reactions (≥ 1% of women)

leading to discontinuation in the levonorgestrel and ethinyl estradiol tablets group were menorrhagia (5.7%), mood swings (1.9%), weight/appetite increase (1.5%), and acne (1.3%).

Common Adverse Reactions (≥ 2% of women): headache (20.6%), menorrhagia (11.6%), nausea (7.5%), dysmenorrhea (5.7%), acne (4.6%), migraine (4.4%), breast tenderness (3.5%), weight increased (3.1%), and depression (2.1%).

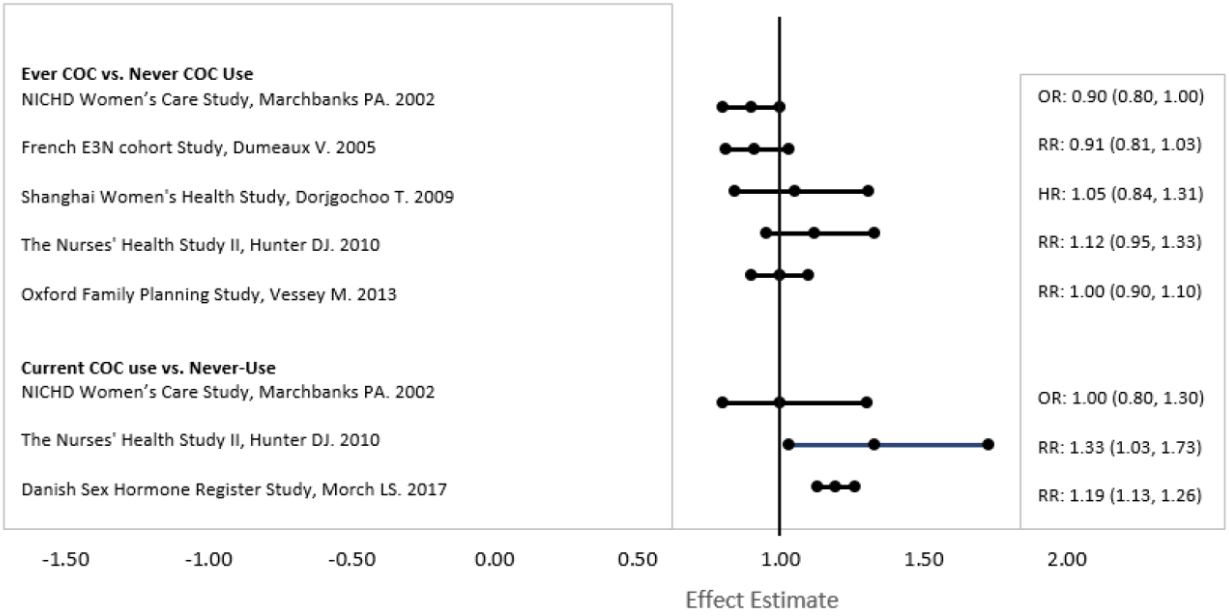
Serious Adverse Reactions: pulmonary embolus, cholecystitis.

6.2 Postmarketing Experience

Five studies that compared breast cancer risk between ever-users (current or past use) of COCs and never-users of COCs reported no association between ever use of COCs and breast cancer risk, with effect estimates ranging from 0.90 - 1.12 (Figure C).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure C). One of these studies reported no association between breast cancer risk and COC use. The other two studies found an increased relative risk of 1.19 - 1.33 with current or recent use. Both of these studies found an increased risk of breast cancer with current use of longer duration, with relative risks ranging from 1.03 with less than one year of COC use to approximately 1.4 with more than 8-10 years of COC use.

Figure C: Relevant Studies of Risk of Breast Cancer with Combined Oral Contraceptives



RR = relative risk; OR = odds ratio; HR = hazard ratio. "ever COC" are females with current or past COC use; "never COC use" are females that never used COCs.

The following adverse reactions have been identified during post-approval use of levonorgestrel and ethinyl estradiol tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: abdominal distension, vomiting

General disorders and administration site conditions: chest pain, fatigue, malaise, edema peripheral, pain

Immune system disorder: hypersensitivity reactions, including itching, rash, and angioedema

Investigations: blood pressure increased

Musculoskeletal and connective tissue disorders: muscle spasms, pain in extremity

Nervous system disorders: dizziness, loss of consciousness

Psychiatric disorders: insomnia

Reproductive and breast disorders: dysmenorrhea

Skin and subcutaneous tissue disorders: alopecia

Vascular disorders: thrombosis, pulmonary embolism, pulmonary thrombosis

7 DRUG INTERACTIONS

Consult the labeling of concurrently used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances decreasing the plasma concentrations of COCs and potentially diminishing the efficacy of COCs:

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of COCs and potentially diminish the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Colesevelam: Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of EE. The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Substances increasing the plasma concentrations of COCs:

Co-administration of atorvastatin or rosuvastatin and certain COCs containing ethinyl estradiol (EE) increase AUC values for EE by approximately 20 to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:
Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV protease inhibitors(decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

7.2 Effects of Combined Oral Contraceptives on Other Drugs
COCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations.

COCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs *[see Warnings and Precautions (5.11)]*.

7.3 Concomitant Use with Hepatitis C Vaccine (HCV) Combination Therapy – Liver Enzyme Elevation
Do not co-administer levonorgestrel and ethinyl estradiol tablets with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations *[see Warnings and Precautions (5.3)]*.

7.4 Interactions with Laboratory Tests
The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

Do not administer COCs to induce withdrawal bleeding as a test for pregnancy. Do not use COCs during pregnancy to treat threatened or habitual abortion.

8.3 Nursing Mothers
Advise the nursing mother to use other forms of contraception, when possible, until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use
Safety and efficacy of levonorgestrel and ethinyl estradiol tablets have been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 as for users 18 years and older. Use of levonorgestrel and ethinyl estradiol tablets before menarche is not indicated.

8.5 Geriatric Use
Levonorgestrel and ethinyl estradiol tablet has not been studied in postmenopausal women and is not indicated in this population.

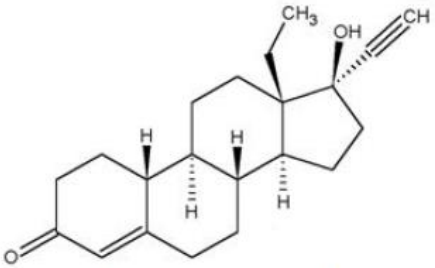
8.6 Hepatic Impairment
The pharmacokinetics of levonorgestrel and ethinyl estradiol tablets have not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

8.7 Renal Impairment
The pharmacokinetics of levonorgestrel and ethinyl estradiol tablets have not been studied in women with renal impairment.

10 OVERDOSAGE
There have been no reports of serious ill effects from overdose of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

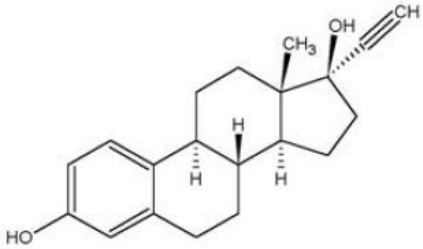
11 DESCRIPTION
Levonorgestrel and ethinyl estradiol tablets USP are an extended-cycle combination oral contraceptive consisting of 84 pink, round, biconvex, film-coated, active tablets, each containing 0.15 mg of levonorgestrel USP, a synthetic progestin and 0.03 mg of ethinyl estradiol USP, an estrogen , and 7 white to off white, round, biconvex, inert tablets (without hormones).

The structural formulas for the active components are:



Levonorgestrel
$C_{21}H_{28}O_2$ MW: 312.4

Levonorgestrel USP is chemically 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-, (-)-.



Ethinyl Estradiol
$C_{20}H_{24}O_2$ MW: 296.4

Ethinyl Estradiol USP is 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-.

- Each pink active tablet contains the following inactive ingredients: croscarmellose sodium, FD & C Blue # 1, FD & C Red # 40, hypromellose, lactose anhydrous, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide.
- Each white to off white inert tablet contains the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with levonorgestrel and ethinyl estradiol tablets.

12.3 Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of levonorgestrel and ethinyl estradiol tablets in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism. EE is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of EE is approximately 43%.

Following continuous dosing with once-daily administration of levonorgestrel and ethinyl estradiol tablets, plasma concentrations of levonorgestrel and EE reached steady-state within 7 days. The mean plasma pharmacokinetic parameters for levonorgestrel and ethinyl estradiol tablets under fasting conditions in normal healthy women following once-daily administration of one levonorgestrel/EE combination tablet for 10 days are summarized in Table 5.

Table 5: Mean ±SD Pharmacokinetic Parameters Under Fasting Conditions in Healthy Women Following 10 Days Administration of One Tablet of Levonorgestrel and Ethinyl Estradiol (n=44)

Analyte	$AUC_{0\ to\ 24}$	C_{max}	C_{min}	C_{avg}[a]	T_{max}
Levonorgestrel	54.6 ± 16.5 ng*hr/mL	5.0 ±1.5 ng/mL	1.6 ± 0.5 ng/mL	2.3 ±0.7 ng/mL	1.4 ± 0.7 hours
Ethinyl estradiol	935.5 ± 346.9 pg*hr/mL	106.1 ± 41.2 pg/mL	18.5 ± 9.4 pg/mL	38.9 ± 14.4 pg/mL	1.6 ± 0.6 hours

[a] $C_{avg} = AUC_{0\ to\ 24/24}$

Food Effect

The effect of food on the rate and the extent of levonorgestrel and EE absorption following oral administration of levonorgestrel and ethinyl estradiol tablets has not been evaluated.

Distribution

The apparent volume of distribution of levonorgestrel and EE are reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively. Levonorgestrel is about 97.5 to 99% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. EE is about 95 to 97% bound to serum albumin. EE does not bind to SHBG, but induces SHBG synthesis, which leads to decreased levonorgestrel clearance. Following repeated daily dosing of levonorgestrel/EE oral contraceptives, levonorgestrel plasma concentrations accumulate more than predicted based on single-dose pharmacokinetics, due in part, to increased SHBG levels that are induced by EE, and a possible reduction in hepatic metabolic capacity.

Metabolism

Following absorption, levonorgestrel is conjugated at the 17β-OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3α,5β-tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3α,5α-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates

may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

First-pass metabolism of EE involves formation of EE-3-sulfate in the gut wall, followed by 2-hydroxylation of a portion of the remaining untransformed EE by hepatic cytochrome P-450 3A4 (CYP3A4). Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of EE hydroxylation. Hydroxylation at the 4-, 6-, and 16- positions may also occur, although to a much lesser extent than 2-hydroxylation. The various hydroxylated metabolites are subject to further methylation and/or conjugation.

Excretion

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The terminal elimination half-life for levonorgestrel after a single dose of levonorgestrel and ethinyl estradiol tablets was about 30 hours.

EE is excreted in the urine and feces as glucuronide and sulfate conjugates, and it undergoes enterohepatic recirculation. The terminal elimination half-life of EE after a single dose of levonorgestrel and ethinyl estradiol tablets was found to be about 15 hours.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[see Warnings and Precautions (5.2, 5.10) and Use in Specific Populations (8.1)].

14 CLINICAL STUDIES

In a 12-month, multicenter, randomized, open-label clinical trial, 456 women aged 18 to 40 were studied to assess the safety and efficacy of levonorgestrel and ethinyl estradiol tablets, completing 809 91-day cycles of exposure. The racial demographic of those enrolled was: Caucasian (77%), African-American (11%), Hispanic (7%), Asian (2%), and Other (3%).

There were no exclusions for body mass index (BMI) or weight. The weight range of those women treated was 84 to 304 pounds, with a mean weight of 157 pounds and a median weight of 147 pounds. Among the women in the trial, 63% were current or recent hormonal contraceptive users, 29% were prior users (who had used hormonal contraceptives in the past but not in the 6 months prior to enrollment), and 8% were new starts.

The pregnancy rate (Pearl Index [PI]) in the 397 women aged 18 to 35 years was 1.98 pregnancies per 100 women-years of use (95% CI: 0.54 to 5.03), based on 4 pregnancies that occurred after the onset of treatment and within 14 days after the last combination pill. Cycles in which conception did not occur, but which included the use of back-up contraception, were not included in the calculation of the PI.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Levonorgestrel and ethinyl estradiol tablets USP, 0.15 mg/0.03 mg are available in Extended-Cycle Wallet of 91 tablets each containing a 13-week supply of tablets which is packed in a pouch (NDC 68180-843-11). Such three pouches are packed in a carton (NDC 68180-843-13).

Each wallet (91 tablets) contains in the following order:

- 84 pink, round, biconvex, film-coated tablets, each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol; debossed with LU on one side and U21 on the other side
- 7 white to off white, round, biconvex, inert tablets debossed with LU on one side and U22 on the other side.

16.2 Storage Conditions

- Store at 25° C (77° F); excursions permitted to 15 to 30° C (59 to 86° F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).
Counsel patients on the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs *[see Boxed Warning]*.
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC *[see Warnings and Precautions (5.1)]*.
- Levonorgestrel and ethinyl estradiol tablets does not protect against HIV-infection (AIDS) and other sexually transmitted infections.
- Levonorgestrel and ethinyl estradiol tablets are not to be used during pregnancy; if pregnancy occurs during use of levonorgestrel and ethinyl estradiol tablets, instruct the patient to stop further use *[see Warnings and Precautions (5.8)]*.
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed *[see Dosage and Administration (2.3)]*.
- Use a back-up or alternative method of contraception when enzyme inducers are used with levonorgestrel and ethinyl estradiol tablets *[see Drug Interactions (7.1)]*.
- COCs may reduce breast milk production; this is less likely to occur if breastfeeding is well established *[see Use in Specific Populations (8.3)]*
- Women who start on COCs postpartum, and who have not yet had a period, should use an additional method of contraception until they have taken a pink tablet for 7 consecutive days *[see Dosage and Administration (2.2)]*.
- Amenorrhea may occur. Because women using levonorgestrel and ethinyl estradiol tablets will likely have scheduled bleeding only 4 times per year, rule out pregnancy at the time of any missed menstrual period *[see Warnings and Precautions (5.7)]*.

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