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: 1968 (norgestrel and ethinyl estradiol)

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
See full prescribing information for complete boxed warning.

- **Levonorgestrel and Ethinyl Estradiol Tablets is contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular side effects from combination hormonal contraceptive (CHC) use. (5.1)**

----------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)

----------DOSAGE AND ADMINISTRATION----------
- Take LNG/EE Tablets in one of two ways: (1) swallow whole on an empty stomach or (2) chew and then immediately swallow with a full glass of 240 mL water on an empty stomach. (2.1)
  - Start on Day 1 and take each tablet at the same time every day in the order directed on the blister pack, or (2)
  - Start on a Sunday and take each tablet at the same time every day in the order directed on the blister pack. (2)
- Take one tablet daily for 28 consecutive days: one white active tablet daily during the first 21 consecutive days, followed by one peach inactive tablet daily during the 7 following days. (2)

----------DOSAGE FORMS AND STRENGTHS----------
A LNG/EE Tablets pack consists of 28 tablets:
- 21 white tablets (active), each containing levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg.
- 7 peach-colored tablets (inactive placebo).

----------CONTRAINDICATIONS----------
- High risk of arterial or venous thrombotic diseases. (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer. (4)
- Liver tumors, acute viral hepatitis or decompensated cirrhosis. (4)
- Undiagnosed abnormal uterine bleeding. (4)
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. (4)

----------WARNINGS AND PRECAUTIONS----------
- Vascular risks: Stop if a thrombotic or thromboembolic event occurs. Stop LNG/EE Tablets at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in females who are not breast-feeding. Consider cardiovascular risk factors before initiating in all females, particularly those over 35 years. (5.1, 5.4)
- Liver disease: Discontinue LNG/EE Tablets if jaundice occurs. (5.2)
- Hypertension: If used in females with well-controlled hypertension, monitor blood pressure. Stop use of Levonorgestrel and Ethinyl Estradiol Tablets if blood pressure rises significantly. (5.3)
- Gallbladder disease: May cause or worsen gallbladder disease. (5.5)
- Adverse carbohydrate and lipid effect: Monitor glucose in prediabetic and diabetic females using LNG/EE Tablets. Consider an alternate contraceptive method for females with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue LNG/EE Tablets if indicated. (5.7)
- Uterine bleeding: May cause irregular bleeding or amenorrhea. Evaluate for other causes if symptoms persist. (5.8)

----------ADVERSE REACTIONS----------
Common adverse reactions are: headache, abdominal pain, nausea, metrorrhagia, vaginal moniliasis and pain, acne, and vaginitis. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Exeltis USA, Inc. at 1-877-324-9349 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
Enzyme inducers (e.g., CYP3A4): May decrease the effectiveness of LNG/EE Tablets or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with LNG/EE Tablets. (7.1, 7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise use of another method; LNG/EE Tablets can decrease milk production. (8.2)

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

Revised: 3/2020

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 combined hormonal contraceptive (CHC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, CHCs, including Levonorgestrel and Ethinyl Estradiol Tablets, are contraindicated in women who are over 35 years of age and smoke [*see Contraindications (4) and Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Levonorgestrel and Ethinyl Estradiol Tablets (LNG/EE Tablets) is indicated for use by females of reproductive potential to prevent pregnancy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Take Levonorgestrel and Ethinyl Estradiol Tablets (LNG/EE Tablets) in one of two ways: (1) swallow whole on an empty stomach or (2) chew and then immediately swallow with a full glass of 240 mL of water on an empty stomach *[see Dosage and Administration (2.2)]*.

2.2 Additional Administration Information

To achieve maximum contraceptive effectiveness, take LNG/EE Tablets exactly as directed (one tablet orally at the same time every day) and at intervals not exceeding 24 hours. The failure rate may increase when tablets are missed or taken incorrectly. The recommended dosage of LNG/EE Tablets is one tablet daily for 28 consecutive days: one white active tablet daily during the first 21 consecutive days, followed by one peach inactive tablet daily during the 7 following days (see Table 1).

Table 1 Instructions for Administration of LNG/EE Tablets

Starting LNG/EE Tablets in females with no current use of hormonal contraception (start on Day 1 or Sunday)
Day 1 start • Take first tablet without food (i.e. empty stomach) on the first day of menses • Take subsequent tablets once daily at the same time each day • Begin each subsequent 28-day pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet)
Sunday start • Take first tablet without food (i.e. empty stomach) on the first Sunday after the onset of menstrual period • Take subsequent tablets once daily at the same time each day • Use additional nonhormonal contraception for the first seven days of LNG/EE Tablets use

• Begin each subsequent 28-day pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet)	
Switching to LNG/EE Tablets from another contraceptive method	
	Start LNG/EE Tablets:
• A combined oral contraceptive (COC)	• On the day when the new pack of the previous COC would have been started
• Transdermal system	• On the day when next application would have been scheduled
• Vaginal ring	• On the day when next insertion would have been scheduled
• Injection	• On the day when next injection would have been scheduled
• Intrauterine system	• On the day of removal
• Implant	• On the day of removal
Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-Approved Patient Labeling (Instructions for Use).	

2.3 Missed Doses

Instruct patients about the handling of missed doses (e.g., to take a missed tablet as soon as possible) and to follow the dosing instructions provided in the FDA-approved patient labeling (Instructions for Use).

Table 2 Instructions for Missed LNG/EE Tablets

• If one white active tablet is missed in Weeks 1, 2, or 3	Take the missed active tablet as soon as possible, even if two active tablets are taken in one day. Continue taking one tablet a day until the pack is finished.
• If two white active tablets are missed in Week 1 or Week 2	Take two active tablets as soon as possible. Then, take two active tablets the next day. This means taking 4 tablets in 2 days. Continue taking one tablet a day until the pack is finished. Additional nonhormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.
• If two white active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	Day 1 start: Throw out the rest of the 28-day pack and start a new pack that same day. Sunday start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. Additional nonhormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.
• If one or more peach (inactive) tablets are missed in the fourth week	Throw away the missed inactive tablets. Keep taking one tablet each day until the pack is empty. Back-up nonhormonal birth-control method is not needed but take the next pack on time.

2.4 Administration Recommendations after Vomiting or Acute Diarrhea

If vomiting or acute diarrhea occurs within 3 to 4 hours after taking an active tablet, take the new active tablet (scheduled for the next day) as soon as possible. If more than two active tablets are missed, see the recommendations in Table 2 *[see Dosage and Administration (2.3)]*.

3 DOSAGE FORMS AND STRENGTHS

One pack of Levonorgestrel and Ethinyl Estradiol Tablets consists of 28 tablets:

- 21 active tablets are white, round, and debossed with 30 on one side and L2 on the other side. Each active tablet contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg.
- 7 inactive tablets (placebo) are peach-colored, round, and debossed with 1 on one side and L2 on the other side.

4 CONTRAINDICATIONS

Levonorgestrel and Ethinyl Estradiol Tablets (LNG/EE Tablets) is contraindicated in females who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include females who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have current or history of deep vein thrombosis or pulmonary embolism [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 inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension or hypertension with vascular disease *[see Warnings and Precautions (5.3)]*
  - Have diabetes mellitus and are over age 35, diabetes mellitus with hypertension or vascular disease or other end-organ damage, or diabetes mellitus of > 20 years duration *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms, migraine headaches with aura, or over age 35 with any migraine headaches *[see Warnings and Precautions (5.7)]*
- Current or history of breast cancer or other estrogen- or progestin-sensitive cancer
- Liver tumors, acute viral hepatitis, or severe (decompensated) cirrhosis *[see Warnings and Precautions (5.2)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- 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 (5.14)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Before starting Levonorgestrel and Ethinyl Estradiol Tablets (LNG/EE Tablets) evaluate any past medical history or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy. LNG/EE Tablets is contraindicated in females with a high risk of arterial or venous thrombotic/thromboembolic diseases *[see Contraindications (4)]*.

- Stop Levonorgestrel and Ethinyl Estradiol Tablets (LNG/EE Tablets) if an arterial or venous thrombotic/thromboembolic event occurs.
- Stop LNG/EE Tablets if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately.
- Discontinue LNG/EE Tablets during prolonged immobilization. If feasible, stop LNG/EE Tablets at least four weeks before and through two weeks after major surgery, or other surgeries known to have an elevated risk of thromboembolism.
- Start LNG/EE Tablets no earlier than four weeks after delivery in females who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the likelihood of ovulation increases after the third postpartum week.

Arterial Events

CHCs increase the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke. The risk is greater among older women (> 35 years of age), smokers, and females with hypertension, dyslipidemia, diabetes, or obesity.

LNG/EE Tablets is contraindicated in women over 35 years of age who smoke *[see Contraindications (4)]*. Cigarette smoking increases the risk of serious cardiovascular events from CHC use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked.

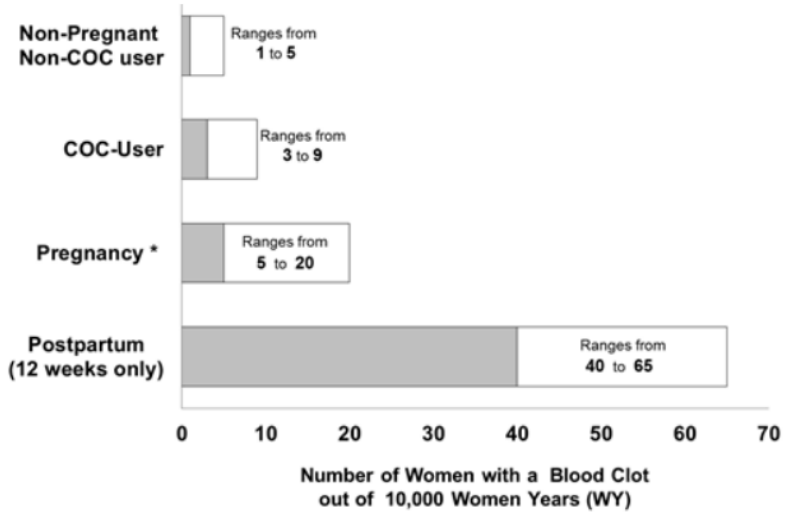
Venous Events

Use of CHCs increases the risk of venous thromboembolic events (VTEs), such as deep vein thrombosis and pulmonary embolism. Risk factors for VTEs include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of CHCs *[see Contraindications (4)]*. While the increased risk of VTE associated with use of CHCs is well-established, the rates of VTE are even greater during pregnancy, and especially during the postpartum period (see Figure 1). The rate of VTE in females using COCs has been estimated to be 3 to 9 cases per 10,000 woman-years.

The risk of VTE is highest during the first year of use of a CHC and when restarting hormonal contraception after a break of four weeks or longer. Based on results from a few studies, there is some evidence that this is true for non-oral products as well. The risk of thromboembolic disease due to CHCs gradually disappears after CHC use is discontinued.

Figure 1 shows the risk of developing a VTE for females who are not pregnant and do not use oral contraceptives, for females who use oral contraceptives, for pregnant females, and for females in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 females who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these females will develop a VTE.

Figure 1 Likelihood of Developing a VTE



*Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

5.2 Liver Disease

Elevated Liver Enzymes

LNG/EE Tablets is contraindicated in females with acute viral hepatitis or severe (decompensated) cirrhosis of the liver *[see Contraindications (4)]*. Discontinue LNG/EE Tablets if jaundice develops. Acute liver test abnormalities may necessitate the discontinuation of CHC use until the liver tests return to normal and CHC causation has been excluded.

Liver Tumors

LNG/EE Tablets is contraindicated in females with benign or malignant liver tumors *[see Contraindications (4)]*. CHCs increase the risk of hepatic adenomas. An estimate of the attributable risk is 3.3 cases/100,000 CHC users. Rupture of hepatic adenomas may cause death from abdominal hemorrhage.

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

5.3 Hypertension

LNG/EE Tablets is contraindicated in females with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For all females, including those with

well-controlled hypertension, monitor blood pressure at routine visits and stop LNG/EE Tablets if blood pressure rises significantly.

An increase in blood pressure has been reported in females using CHCs, and this increase is more likely in older women with extended duration of use. The effect of CHCs on blood pressure may vary according to the progestin in the CHC.

5.4 Age-related Considerations

The risk for cardiovascular disease and prevalence of risk factors for cardiovascular disease increase with age. Certain conditions, such as smoking and migraine headache without aura, that do not contraindicate CHC use in younger females, are contraindications to use in women over 35 years of age *[see Contraindications (4) and Warnings and Precautions (5.1)]*. Consider the presence of underlying risk factors that may increase the risk of cardiovascular disease or VTE, particularly before initiating a CHC for women over 35 years, such as:

- Hypertension
- Diabetes
- Dyslipidemia
- Obesity

5.5 Gallbladder Disease

Studies suggest an increased risk of developing gallbladder disease among CHC users. Use of CHCs may also worsen existing gallbladder disease.

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

5.6 Adverse Carbohydrate and Lipid Metabolic Effects

Hyperglycemia

LNG/EE Tablets is contraindicated in diabetic women over age 35, or females who have diabetes with hypertension, nephropathy, retinopathy, neuropathy, other vascular disease, or females with diabetes of > 20 years duration *[see Contraindications (4)]*. LNG/EE Tablets may decrease glucose tolerance. Carefully monitor prediabetic and diabetic females who are using LNG/EE Tablets.

Dyslipidemia

Consider alternative contraception for females with uncontrolled dyslipidemia. LNG/EE Tablets may cause adverse lipid changes.

Females with hypertriglyceridemia, or a family history thereof, may have an increase in serum triglyceride concentrations when using LNG/EE Tablets, which may increase the risk of pancreatitis.

5.7 Headache

LNG/EE Tablets is contraindicated in females who have headaches with focal neurological symptoms or have migraine headaches with aura, and in women over age 35 years who have migraine headaches with or without aura *[see Contraindications (4)]*.

If a woman using LNG/EE Tablets develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue LNG/EE Tablets if indicated. Consider discontinuation of LNG/EE Tablets if there is an increased frequency or severity of migraines during CHC use (which may be prodromal of a cerebrovascular event).

5.8 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Females using LNG/EE Tablets may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first three months of use. Bleeding irregularities may resolve over time or by changing to a different contraceptive product. If bleeding persists or occurs after previously regular cycles, evaluate for causes such as pregnancy or malignancy.

Amenorrhea and Oligomenorrhea

Females who use LNG/EE Tablets may experience absence of scheduled (withdrawal) bleeding, even if they are not pregnant.

If scheduled bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or two active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and perform appropriate diagnostic measures. If the patient has adhered to the prescribed dosing schedule and misses two consecutive periods, rule out pregnancy.

After discontinuation of a CHC, amenorrhea or oligomenorrhea may occur, especially if these conditions were pre-existent.

5.9 Depression

Carefully observe females with a history of depression and discontinue LNG/EE Tablets if depression recurs to a serious degree. Data on the association of CHCs with onset of depression or exacerbation of existing depression are limited.

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.

5.11 Effect on Binding Globulins

The estrogen component of LNG/EE Tablets 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.

5.12 Hereditary Angioedema

In females with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.13 Chloasma

Chloasma may occur with LNG/EE Tablets use, especially in females with a history of chloasma gravidarum. Advise females with a history of chloasma to avoid exposure to the sun or ultraviolet radiation while using LNG/EE Tablets.

5.14 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/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. COCs are contraindicated for use with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. Discontinue LNG/EE Tablets prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir.

LNG/EE Tablets can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of CHCs are discussed elsewhere in labeling:

- Serious cardiovascular events *[see Boxed Warning and Warnings and Precautions (5.1 and 5.4)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*
- Hypertension *[see Warnings and Precautions (5.3)]*
- Gallbladder disease *[see Warnings and Precautions (5.5)]*
- Adverse carbohydrate and lipid metabolic effects *[see Warnings and Precautions (5.6)]*
- Headache *[see Warnings and Precautions (5.7)]*
- Bleeding irregularities and amenorrhea *[see Warnings and Precautions (5.8)]*
- Depression *[see Warnings and Precautions (5.9)]*
- Cervical cancer *[see Warnings and Precautions (5.10)]*
- Effect on binding globulins *[see Warnings and Precautions (5.11)]*
- Hereditary angioedema *[see Warnings and Precautions (5.12)]*
- Chloasma *[see Warnings and Precautions (5.13)]*
- Risk of liver enzyme elevations with concomitant hepatitis C treatment *[see Warnings and Precautions (5.14)]*

The following adverse reactions associated with the use of oral CHCs were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Common adverse reactions associated with oral CHCs are headache, abdominal pain, nausea, metrorrhagia, vaginal moniliasis and pain, acne, and vaginitis.

Additional adverse reactions that have been reported include the following:

Eye disorder: intolerance to contact lenses, steepening of corneal curvature

Gastrointestinal disorders: Abdominal bloating, vomiting

General disorders and administration site condition: Edema, fluid retention

Hepatobiliary disorders: Cholestatic jaundice

Psychiatric disorders: Change in libido, mood changes

Reproductive system and breast disorders: Amenorrhea, breast tenderness, breast pain, breast enlargement, increased cervical mucous, change in menstrual flow, unscheduled bleeding

Skin and subcutaneous tissue disorders: Acne, melasma [see Warnings and Precautions (5.13)]

Vascular disorders: Budd-Chiari syndrome, aggravation of varicose veins

7 DRUG INTERACTIONS

The sections below provide information on substances for which data on drug interactions with CHCs are available. There is little information available about the clinical effect of most drug interactions that may affect CHCs. However, based on the known pharmacokinetic effects of these drugs, clinical strategies to minimize any potential adverse effect on contraceptive effectiveness or safety are suggested.

Consult the approved product labeling of all concurrently used drugs to obtain further information about interactions with CHCs or the potential for metabolic enzyme or transporter system alterations.

No drug-drug interaction studies were conducted with LNG/EE Tablets.

7.1 Effects of Other Drugs on Combined Hormonal Contraceptives

Substances decreasing the Plasma Concentration of CHCs and Potentially Diminishing the Efficacy of CHCs

Table 3 Significant Drug Interactions Involving Substances That Affect CHCs

Metabolic Enzyme Inducers	
Clinical effect	• Concomitant use of CHCs with metabolic enzyme inducers may decrease the plasma concentrations of the estrogen and/or progestin component of CHCs *[see Clinical Pharmacology (12.3)]*. • Decreased exposure of the estrogen and/or progestin component of CHCs may potentially diminish the effectiveness of CHCs and may lead to contraceptive failure or an increase in breakthrough bleeding.
Prevention or management	• Counsel females to use an alternative method of contraception or a backup method when enzyme inducers are used with CHCs. • Continue backup contraception for 28 days after discontinuing the enzyme inducer to maintain contraceptive reliability.
Examples	Aprepitant, barbiturates, bosentan, carbamazepine, efavirenz, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, primidone, phenylbutazone, rifabutin, rufinamide, topiramate, products containing St. John's wort, and certain protease inhibitors (see separate section on protease inhibitors below).
Colesevelam	
Clinical effect	• Concomitant use of CHCs with colesevelam significantly decreases systemic exposure of ethinyl estradiol *[see Clinical Pharmacology (12.3)]*. • Decreased exposure of the estrogen component of CHCs may potentially reduce contraceptive efficacy or result in an increase in breakthrough bleeding, depending on the strength of ethinyl estradiol in the CHC.
Prevention or management	Administer 4 or more hours apart to attenuate this drug interaction.

[a] Induction potency of St. John's wort may vary widely based on preparation.

Substances increasing the systemic exposure of CHCs:
Co-administration of atorvastatin or rosuvastatin and CHCs containing ethinyl estradiol increase systemic exposure of ethinyl estradiol by approximately 20 to 25 percent. Ascorbic acid and acetaminophen may increase systemic exposure of ethinyl estradiol, possibly by inhibition of conjugation. CYP3A inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice*, or ketoconazole may increase systemic exposure of the estrogen and/or progestin component of CHCs.

* The effect of grapefruit juice on CYP3A4 enzymes (e.g., strong vs. moderate inhibition) depends on its brand, concentration, and preparation.

Human immunodeficiency virus (HIV)/hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:
Significant decreases in systemic exposure of the estrogen and/or progestin have been noted when CHCs are co-administered with some HIV protease inhibitors (e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir), some HCV protease inhibitors (e.g., boceprevir and telaprevir), and some non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine).

In contrast, significant increases in systemic exposure of the estrogen and/or progestin have been noted when CHCs are co-administered with certain other HIV protease inhibitors (e.g., indinavir and atazanavir/ritonavir) and with other non-nucleoside reverse transcriptase inhibitors (e.g., etravirine).

7.2 Effects of Combined Hormonal Contraceptives on Other Drugs

Table 4 provides significant drug interaction information for drugs co-administered with LNG/EE Tablets.

Table 4 Significant Drug Interaction Information for Drugs Co-Administered with CHCs

Lamotrigine	
Clinical effect	• Concomitant use of CHCs with lamotrigine may significantly decrease systemic exposure of lamotrigine due to induction of lamotrigine glucuronidation [see *Clinical Pharmacology (12.3)*]. • Decreased systemic exposure of lamotrigine may reduce seizure control.
Prevention or management	Dose adjustment may be necessary. Consult the approved product labeling for lamotrigine.
Thyroid Hormone Replacement Therapy or Corticosteroid Replacement Therapy	
Clinical effect	Concomitant use of CHCs with thyroid hormone replacement therapy or corticosteroid replacement therapy may increase systemic exposure of thyroid-binding and cortisol-binding globulin [see *Warnings and Precautions (5.11)*].
Prevention or management	The dose of replacement thyroid hormone or cortisol therapy may need to be increased. Consult the approved product labeling for the therapy in use. [See *Warnings and Precautions (5.11)*].
Other Drugs	
Clinical effect	Concomitant use of CHCs may decrease systemic exposure of acetaminophen, morphine, salicylic acid, and temazepam. Concomitant use with ethinyl estradiol-containing CHCs may increase systemic exposure of other drugs (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole).
Prevention or management	The dosage of drugs that can be affected by this interaction may need to be increased. Consult the approved product labeling for the concomitantly used drug.

7.3 Effect on Laboratory Tests

The use of CHCs may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

7.4 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

CHCs are contraindicated for use with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. Discontinue LNG/EE Tablets prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. LNG/EE Tablets can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

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.

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.

8.4 Pediatric Use

The safety and effectiveness of LNG/EE Tablets have been established in females of reproductive potential. Efficacy is expected to be the same for post-menarchal females under the age of 17 as for users 17 years and older. The use of LNG/EE Tablets before menarche is not indicated.

8.5 Geriatric Use
LNG/EE Tablets has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment
The pharmacokinetics of LNG/EE Tablets have not been studied in women 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 Body Mass Indexes
Data on differences in safety and effectiveness (if any) of LNG/EE Tablets between patients with high BMI and lower BMI are not available.

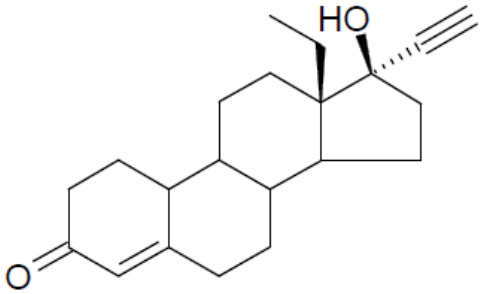
10 OVERDOSAGE
Overdose may cause nausea and uterine bleeding in females.

11 DESCRIPTION
Levonorgestrel and Ethinyl Estradiol Tablets is an oral contraceptive product. A LNG/EE Tablets pack consists of 21 white active tablets and 7 peach-colored inactive tablets.

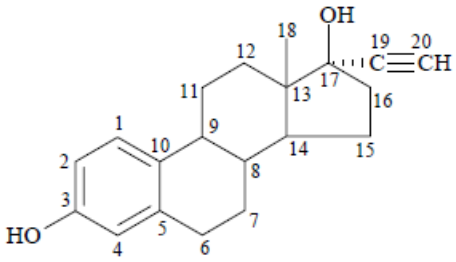
The twenty-one white active tablets each contain 0.1 mg of levonorgestrel, a progestin, and 0.02 mg of ethinyl estradiol, an estrogen. Each tablet also contains the following inactive ingredients: corn starch, crospovidone, lactose monohydrate, magnesium stearate, povidone, and pregelatinized starch.

Seven peach-colored inactive tablets, each contains anhydrous lactose, corn starch, crospovidone, D&C yellow No. 10 aluminum lake, FD&C Red No. 40 aluminum lake, magnesium stearate, and povidone.

The chemical name for levonorgestrel is [18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17α)-(-)-]. It has the molecular formula of $C_{21}H_{28}O_2$, the molecular weight of 312.5, and the structural formula is provided below:



The chemical name for ethinyl estradiol is [19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-]. It has the molecular formula of $C_{20}H_{24}O_2$, the molecular weight of 296.4, and the structural formula is provided below:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CHCs lower the risk of becoming pregnant primarily by suppressing ovulation.

12.2 Pharmacodynamics

No specific pharmacodynamics studies were conducted with LNG/EE Tablets.

12.3 Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of LNG/EE Tablets in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is between 38% and 48%.

The kinetics of total levonorgestrel are non-linear due to an increase in binding of levonorgestrel to sex hormone binding globulin (SHBG), which is attributed to increased SHBG levels that are induced by the daily administration of ethinyl estradiol.

Table 5 provides a summary of pharmacokinetics of levonorgestrel and ethinyl estradiol after a single dose of LNG/EE Tablets in 32 female subjects only under fasting condition.

Table 5 Summary Mean (CV%) Pharmacokinetic Parameters from Single Dose Administration of LNG/EE Tablets

Analyte	Sample Size	C_{max} (pg/mL)	T_{max} (h)[a]	AUC_{0-T} (pg*h/mL)	$AUC_{0-\infty}$ (pg*h/mL)	$T_{1/2}$ (h)
EE	n = 32	53.22 (33.9)	1.50 (1.00-2.25)	477.75 (32.5)	515.51 (31.0)	16.42 (25.0)
LNG	n = 32[b]	3225.0 (33.1)	0.75 (0.50-1.00)	27586.0 (39.0)	34099.0 (36.8)	33.67 (31.8)

[a] Median (min – max)

[b] n = 30 for $AUC_{0-\infty}$ and $T_{1/2}$

Distribution

Levonorgestrel in serum is primarily bound to SHBG. Ethinyl estradiol is about 97% bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis.

Elimination

Metabolism

Levonorgestrel: The most important metabolic pathway occurs in the reduction of the Δ4-3-oxo group and hydroxylation at positions 2α, 1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3α,5β-tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as 17β-sulfate. 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.

Ethinyl estradiol: Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Levels of Cytochrome P450 (CYP3A) vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation.

Excretion

The elimination half-life for levonorgestrel is approximately 36 ± 13 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in feces. The elimination half-life of ethinyl estradiol is 18 ± 4.7 hours at steady state.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[see Warnings and Precautions (5.10)]

14 CLINICAL STUDIES

In a clinical trial with Levonorgestrel and Ethinyl Estradiol Tablets (LNG/EE Tablets) (0.1 mg and 0.02 mg, respectively), 1,477 subjects had 7,720 cycles of use and a total of 5 pregnancies were reported. This represented an overall pregnancy rate of 0.84 per 100 woman-years. These data included patients who did not take LNG/EE Tablets correctly. One or more tablets were missed during 1,479 (19%) of the 7,870 cycles; thus all tablets were taken during 6,391 (81%) of the 7,870 cycles. Of the total 7,870 cycles, a total of 150 cycles were excluded from the calculation of the Pearl Index due to the use of backup contraception and/or missing 3 or more consecutive tablets.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Levonorgestrel and Ethinyl Estradiol Tablets are available as follows:

Each blister card contains 28 tablets in the following order: 21 active tablets and 7 inactive tablets. The 21 active tablets are white, round, and debossed with 30 on one side and L2 on the other side; each contains levonorgestrel 0.1 mg and ethinyl estradiol 0.02 mg. The 7 inactive tablets (placebo) are peach-colored, round, and debossed with 1 on one side and L2 on the other side.

- NDC 0642-7471-01, one carton containing 1 individual blister card
- NDC 0642-7471-03, one carton containing 3 individual blister cards
- NDC 0642-7471-06, one carton containing 6 individual blister cards

16.2 Storage and Handling

Store at controlled room temperature 20°C to 25°C (68°F to 77°F). Excursions are NOT permitted. Protect from light and excessive heat.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Cigarette Smoking

Advise women that cigarette smoking increases the risk of serious cardiovascular events from CHC use, and that women who are over 35 years old and smoke should not use LNG/EE Tablets *[see Boxed Warning and Warning and Precautions (5.1)]*.

Venous Thromboembolism

Advise women that the increased risk of VTE compared to non-users of CHCs is greatest after initially starting a CHC or restarting (following a 4-week or greater tablet-free interval) the same or a different CHC *[see Warnings and Precautions (5.1)]*.

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

Sexually Transmitted Infections
Advise women that LNG/EE Tablets does not protect against HIV-infection (AIDS) and other sexually transmitted infections.

Dosing, Administration and Missed Dose Instructions
Advise women to take LNG/EE Tablets in one of two ways: (1) swallow whole on an empty stomach or (2) chew and then immediately swallow with a full glass of 240 mL water on an empty stomach. Advise women to take one tablet daily by mouth at the same time every day *[see Dosage and Administration (2.1)]*.

Advise women about what to do in the event tablets are missed. See "What should I do if I miss any LNG/EE Tablets" section in FDA-approved patient labeling *[see Dosage and Administration (2.3)]*.

Need for Additional Contraception
- Advise women to use a back-up or alternative method of contraception when enzyme inducers are used with LNG/EE Tablets *[see Drug Interactions (7.1)]*.
- Advise a woman who starts CHCs postpartum and has not yet had a period that she should use an additional method of contraception until she has taken a white tablet for 7 consecutive days.

Lactation
CHCs may reduce breast milk production; this is less likely to occur if breastfeeding is well established *[see Use in Specific Populations (8.2)]*.

Amenorrhea and Possible Symptoms of Pregnancy
Advise women that amenorrhea may occur. Advise women to contact their health care provider in the event of amenorrhea in two or more consecutive cycles or in case of symptoms of pregnancy such as morning sickness or unusual breast tenderness *[see Warnings and Precautions (5.8)]*.

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

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