

# LO LOESTRIN FE- norethindrone acetate and ethinyl estradiol, ethinyl estradiol and ferrous fumarate

Allergan, Inc.

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lo Loestrin Fe safely and effectively. See full prescribing information for Lo Loestrin Fe.

Lo Loestrin<sup>®</sup> Fe (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets)

Initial U.S. Approval: 1968

### WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

*See Full Prescribing Information for complete boxed warning.*

- Women over 35 years old who smoke should not use Lo Loestrin Fe (4)
- Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use (4)

### RECENT MAJOR CHANGES

Contraindications (4)

08/2017

Warnings (5.4)

08/2017

### INDICATIONS AND USAGE

- Lo Loestrin Fe is an estrogen/progestin COC indicated for use by women to prevent pregnancy (1)
- The efficacy of Lo Loestrin Fe in women with a body mass index of  $> 35 \text{ kg/m}^2$  has not been evaluated (1, 8.8)

### DOSAGE AND ADMINISTRATION

- Take one tablet by mouth at the same time every day for 28 days (2.1)
- Take tablets in the order directed on the blister pack (2.1)

### DOSAGE FORMS AND STRENGTHS

Lo Loestrin Fe consists of 28 tablets in the following order (3):

- 24 blue tablets (active), each containing 1 mg norethindrone acetate and 10 mcg ethinyl estradiol
- 2 white tablets (active), each containing 10 mcg ethinyl estradiol
- 2 brown tablets (non-hormonal placebo), each containing 75 mg ferrous fumarate. The ferrous fumarate tablets do not serve any therapeutic purpose

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- Vascular risks: Stop Lo Loestrin Fe if a thrombotic event occurs. Stop Lo Loestrin Fe at least 4 weeks before through 2 weeks after major surgery. Start Lo Loestrin Fe no earlier than 4 weeks after delivery, in women who are not breastfeeding (5.1)
- Liver disease: Discontinue Lo Loestrin Fe if jaundice occurs (5.3)
- High blood pressure: Do not prescribe Lo Loestrin Fe for women with uncontrolled hypertension or hypertension with vascular disease (5.5)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Lo Loestrin Fe. Consider an alternative contraceptive method for women with uncontrolled dyslipidemia (5.7)
- Headache: Evaluate significant change in headaches and discontinue Lo Loestrin Fe if indicated (5.8)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea (5.9)

----- **ADVERSE REACTIONS** -----

The most common adverse reactions ( $\geq 2$  percent) are nausea/vomiting (7 percent), headache (7 percent), bleeding irregularities (5 percent), dysmenorrhea (4 percent), weight change (4 percent), breast tenderness (4 percent), acne (3 percent), abdominal pain (3 percent), anxiety (2 percent) and depression (2 percent) (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-678-1605 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

----- **DRUG INTERACTIONS** -----

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

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

- Nursing mothers: Not recommended; can decrease milk production (8.3)

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

Revised: 8/2017

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**FULL PRESCRIBING INFORMATION: CONTENTS\***

**WARNING: CIGARETTE SMOKING AND SERIOUS  
CARDIOVASCULAR EVENTS**

**1 INDICATIONS AND USAGE**

**2 DOSAGE AND ADMINISTRATION**

**2.1 How to Take Lo Loestrin Fe**

**2.2 How to Start Lo Loestrin Fe**

**2.3 Switching from another Hormonal Method of Contraception**

**2.4 Advice in Case of Gastrointestinal Disturbances**

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

**5.1 Thrombotic and Other Vascular Events**

**5.2 Carcinoma of the Breast and Cervix**

**5.3 Liver Disease**

**5.4 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment**

**5.5 High Blood Pressure**

**5.6 Gallbladder Disease**

**5.7 Carbohydrate and Lipid Metabolic Effects**

**5.8 Headache**

**5.9 Bleeding Irregularities and Amenorrhea**

**5.10 COC Use before or during Early Pregnancy**

**5.11 Depression**

**5.12 Interference with Laboratory Tests**

**5.13 Monitoring**

**5.14 Other Conditions**

**6 ADVERSE REACTIONS**

**6.1 Clinical Trial Experience**

**7 DRUG INTERACTIONS**

**7.1 Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products**

**7.2 Increase in Plasma Levels of Ethinyl Estradiol Associated with Co-Administered Drugs**

- 7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation
- 7.4 Changes in Plasma Levels of Co-Administered Drugs
- 8 USE IN SPECIFIC POPULATIONS
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers
  - 8.4 Pediatric Use
  - 8.5 Geriatric Use
  - 8.6 Renal Impairment
  - 8.7 Hepatic Impairment
  - 8.8 Body Mass Index
- 10 OVERDOSAGE
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
  - 12.1 Mechanism of Action
  - 12.2 Pharmacodynamics
  - 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
  - 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 14 CLINICAL STUDIES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
  - 16.1 How Supplied
  - 16.2 Storage Conditions
- 17 PATIENT COUNSELING INFORMATION

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

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## 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 should not be used by women who are over 35 years of age and smoke [see Contraindications (4)].

## 1 INDICATIONS AND USAGE

Lo Loestrin<sup>®</sup> Fe is indicated for use by women to prevent pregnancy [see Clinical Studies (14)].

The efficacy of Lo Loestrin Fe in women with a body mass index (BMI) of > 35 kg/m<sup>2</sup> has not been evaluated.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 How to Take Lo Loestrin Fe

To achieve maximum contraceptive effectiveness, Lo Loestrin Fe must be taken exactly as directed. Take one tablet by mouth at the same time every day. Tablets must be taken in the order directed on the blister pack. Tablets should not be skipped or taken at intervals exceeding 24 hours. For patient instructions for missed pills, see FDA-Approved Patient Labeling. Lo Loestrin Fe tablets may be

administered without regard to meals [*see Clinical Pharmacology (12.3)*].

## 2.2 How to Start Lo Loestrin Fe

Instruct the patient to begin taking Lo Loestrin Fe on Day 1 of her menstrual cycle (that is, the first day of her menstrual bleeding) [*see FDA-Approved Patient Labeling*]. One blue tablet should be taken daily for 24 consecutive days, followed by one white tablet daily for 2 consecutive days, followed by one brown tablet daily for 2 consecutive days. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days if she starts taking Lo Loestrin Fe other than on the first day of her menstrual cycle.

For postpartum women who do not breastfeed or after a second trimester abortion, Lo Loestrin Fe may be started no earlier than 4 weeks postpartum. Recommend use of a non-hormonal back-up method for the first 7 days. When COCs are used during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered [*see Warnings and Precautions (5.1)*]. The possibility of ovulation and conception before starting COCs should also be considered.

Lo Loestrin Fe may be initiated immediately after a first-trimester abortion or miscarriage; if the patient starts Lo Loestrin Fe immediately, additional contraceptive measures are not needed.

## 2.3 Switching from another Hormonal Method of Contraception

If the patient is switching from a combination hormonal method such as:

- Another pill
- Vaginal ring
- Patch
  - Instruct her to take the first blue tablet on the day she would have taken her next COC pill. She should not continue taking the tablets from her previous birth control pack, and should not skip any days between packs. If she does not have a withdrawal bleed, rule out pregnancy before starting Lo Loestrin Fe.
  - If she previously used a vaginal ring or transdermal patch, she should start using Lo Loestrin Fe on the day she would have resumed the previous product.

If the patient is switching from a progestin-only method such as a:

- Progestin-only pill
- Implant
- Intrauterine system
- Injection
  - Instruct her to take the first blue tablet on the day she would have taken her next progestin-only pill, or had her next injection or on the day of removal of her implant.
  - If switching from an IUD, depending on the timing of removal, back-up contraception may be needed.

## 2.4 Advice in Case of Gastrointestinal Disturbances

If the patient vomits or has diarrhea (within 3 to 4 hours after she takes a blue or white pill), she should follow the instructions in the “What to Do if You Miss Pills” section [*see FDA-Approved Patient Labeling*].

## 3 DOSAGE FORMS AND STRENGTHS

Lo Loestrin Fe (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) is available in blister packs.

Each blister pack (28 tablets) contains in the following order:

- 24 blue, round (active) tablets imprinted with “WC” on one side and “421” on the other and each containing 1 mg norethindrone acetate and 10 mcg ethinyl estradiol.
- 2 white, hexagonal (active) tablets imprinted with “WC” on one side and “422” on the other and each containing 10 mcg ethinyl estradiol.
- 2 brown, round (non-hormonal placebo) tablets imprinted with “WC” on one side and “624” on the other and each containing 75 mg ferrous fumarate. The ferrous fumarate tablets do not serve any therapeutic purpose.

## 4 CONTRAINDICATIONS

Do not prescribe Lo Loestrin Fe to women who are known to have 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 cerebrovascular disease [*see Warnings and Precautions (5.1)*]
    - Have coronary artery disease [*see Warnings and Precautions (5.1)*]
    - Have thrombotic valvular or thrombotic 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 [*see Warnings and Precautions (5.5)*]
    - Have diabetes mellitus with vascular disease [*see Warnings and Precautions (5.7)*]
    - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 [*see Warnings and Precautions (5.8)*]
  - Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.2)*]
  - Liver tumors, benign or malignant, or liver disease [*see Warnings and Precautions (5.3)*]
  - Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.9)*]
  - Pregnancy, because there is no reason to use COCs during pregnancy [*see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)*]
- 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 (5.4)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thrombotic and Other Vascular Events

Stop Lo Loestrin Fe if an arterial or deep venous thrombotic event occurs. Although use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. The risk is highest during the first year of use of a COC. 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. The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

If feasible, stop Lo Loestrin Fe at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Lo Loestrin Fe no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest in older (> 35 years of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Lo Loestrin Fe if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

## **5.2 Carcinoma of the Breast and Cervix**

Women who currently have or have had breast cancer should not use Lo Loestrin Fe because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

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

## **5.3 Liver Disease**

Discontinue Lo Loestrin Fe if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. 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.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases per 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.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

## **5.4 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. Discontinue Lo Loestrin Fe prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [see *Contraindications (4)*]. Lo Loestrin Fe can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

## **5.5 High Blood Pressure**

For women with well-controlled hypertension, monitor blood pressure and stop Lo Loestrin Fe if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely

in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

## **5.6 Gallbladder Disease**

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

## **5.7 Carbohydrate and Lipid Metabolic Effects**

Carefully monitor prediabetic and diabetic women who are taking Lo Loestrin Fe. COCs may decrease glucose tolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. 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.

## **5.8 Headache**

If a woman taking Lo Loestrin Fe develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Lo Loestrin Fe if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

## **5.9 Bleeding Irregularities and Amenorrhea**

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, 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.

The clinical trial that evaluated the efficacy of Lo Loestrin Fe also assessed unscheduled bleeding and/or spotting. The participants in this 12-month clinical trial (N = 1,582 who had at least one post-treatment evaluation) completed over 15,000 cycles of exposure.

A total of 1,257 women (85.9 percent) experienced unscheduled bleeding and/or spotting at some time during Cycles 2 to 13 of this study. The incidence of unscheduled bleeding and/or spotting was highest during Cycle 2 (53 percent) and lowest at Cycle 13 (36 percent). Among these women, the mean number of days of unscheduled bleeding and/or spotting during a 28-day cycle ranged from 1.8 to 3.2 days.

Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over the one year study, with an average of less than 2 days per cycle.

Women who are not pregnant and use Lo Loestrin Fe may experience amenorrhea (absence of scheduled and unscheduled bleeding/spotting). In the clinical trial with Lo Loestrin Fe, the incidence of amenorrhea increased from 32 percent in Cycle 1 to 49 percent by Cycle 13. If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more 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 take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

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

## **5.10 COC Use before or during Early Pregnancy**

Extensive epidemiologic 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. Lo Loestrin Fe use should be discontinued 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)*].

### **5.11 Depression**

Women with a history of depression should be carefully observed and Lo Loestrin Fe discontinued if depression recurs to a serious degree.

### **5.12 Interference with Laboratory Tests**

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid binding globulin increase with use of COCs.

### **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 healthcare.

### **5.14 Other Conditions**

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

## **6 ADVERSE REACTIONS**

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

- Serious cardiovascular events and smoking [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [see *Warnings and Precautions (5.1)*]
- Liver disease [see *Warnings and Precautions (5.3)*]

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 practice.

A multicenter phase 3 clinical trial evaluated the safety and efficacy of Lo Loestrin Fe for pregnancy prevention. The study was a one year, open-label, single-arm, uncontrolled study. A total of 1,660 women aged 18 to 45 were enrolled and took at least one dose of Lo Loestrin Fe [see *Clinical Studies (14.1)*].

Common Adverse Reactions (≥ 2 percent of all Treated Subjects): The most common adverse reactions reported by at least 2 percent of the 1,660 women using Lo Loestrin Fe were the following in order of



decreasing incidence: nausea/vomiting (7 percent), headache (7 percent), bleeding irregularities (including metrorrhagia, irregular menstruation, menorrhagia, vaginal hemorrhage and dysfunctional uterine bleeding) (5 percent), dysmenorrhea (4 percent), weight fluctuation (4 percent), breast tenderness (4 percent), acne (3 percent), abdominal pain (3 percent), anxiety (2 percent), and depression (2 percent).

Adverse Reactions Leading to Study Discontinuation: 10.7 percent of the women discontinued from the clinical trial due to an adverse reaction. Adverse reactions occurring in  $\geq 1$  percent of subjects leading to discontinuation of treatment were in decreasing order: menstrual irregularities (including metrorrhagia, irregular menstruation, menorrhagia and vaginal hemorrhage) (4 percent), headache/migraine (1 percent), mood disorder (including mood swings, depression, anxiety) (1 percent), and weight fluctuation (1 percent).

Serious Adverse Reactions: deep vein thrombosis, ovarian vein thrombosis, cholecystitis.

## 7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted with Lo Loestrin Fe.

### 7.1 Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors or of non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

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

### 7.2 Increase in Plasma Levels of Ethinyl Estradiol Associated with Co-Administered Drugs

Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20 percent. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

### **7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation**

Do not co-administer Lo Loestrin Fe with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations [*see Warnings and Precautions (5.4)*].

### **7.4 Changes in Plasma Levels of Co-Administered Drugs**

COCs containing some synthetic estrogens (for example, ethinyl estradiol) may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

## **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.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed should not start COCs earlier than 4 weeks postpartum.

### **8.3 Nursing Mothers**

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs 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 Lo Loestrin Fe have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 18 years as for users 18 years and older. Use of this product before menarche is not indicated.

### **8.5 Geriatric Use**

Lo Loestrin Fe has not been studied in postmenopausal women and is not indicated in this population.

### **8.6 Renal Impairment**

The pharmacokinetics of Lo Loestrin Fe has not been studied in subjects with renal impairment.

### **8.7 Hepatic Impairment**

No studies have been conducted to evaluate the effect of hepatic impairment on the disposition of Lo Loestrin Fe. However, steroid hormones may be poorly metabolized in patients with impaired liver function. 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 (5.3)*].

### **8.8 Body Mass Index**

The safety and efficacy of Lo Loestrin Fe in women with a body mass index (BMI) > 35 kg/m<sup>2</sup> has not been evaluated [see *Clinical Studies (14)*].

## 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

Lo Loestrin Fe (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) provides an oral contraceptive regimen consisting of 24 blue active tablets and 2 white active tablets that contain the active ingredients specified for each tablet below, followed by 2 non-hormonal placebo tablets:

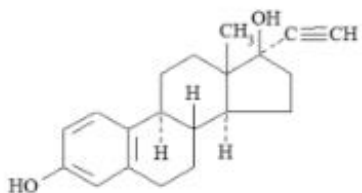
- 24 blue, round tablets each containing 1 mg norethindrone acetate and 10 mcg ethinyl estradiol
- 2 white, hexagonal tablets each containing 10 mcg ethinyl estradiol
- 2 brown, round tablets each containing 75 mg ferrous fumarate

Each blue tablet also contains the inactive ingredients mannitol, microcrystalline cellulose, FD&C Blue No. 1 Aluminum Lake, sodium starch glycolate, magnesium stearate, povidone, vitamin E and lactose monohydrate.

Each white tablet also contains the inactive ingredients mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, povidone, vitamin E and lactose monohydrate.

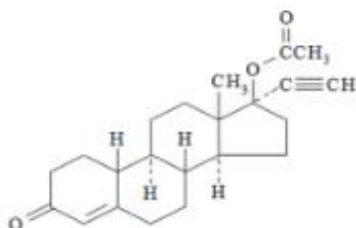
Each brown tablet contains ferrous fumarate, mannitol, povidone, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, sucralose and spearmint flavor. The ferrous fumarate tablets do not serve any therapeutic purpose. Ferrous fumarate tablets are not USP for dissolution and assay.

The empirical formula of ethinyl estradiol is C<sub>20</sub>H<sub>24</sub>O<sub>2</sub> and the structural formula is:



The chemical name of ethinyl estradiol is [19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 $\alpha$ )-].

The empirical formula of norethindrone acetate is C<sub>22</sub>H<sub>28</sub>O<sub>3</sub> and the structural formula is:



The chemical name of norethindrone acetate is [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17 $\alpha$ )-].

## 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 Lo Loestrin Fe.

## 12.3 Pharmacokinetics

### *Absorption*

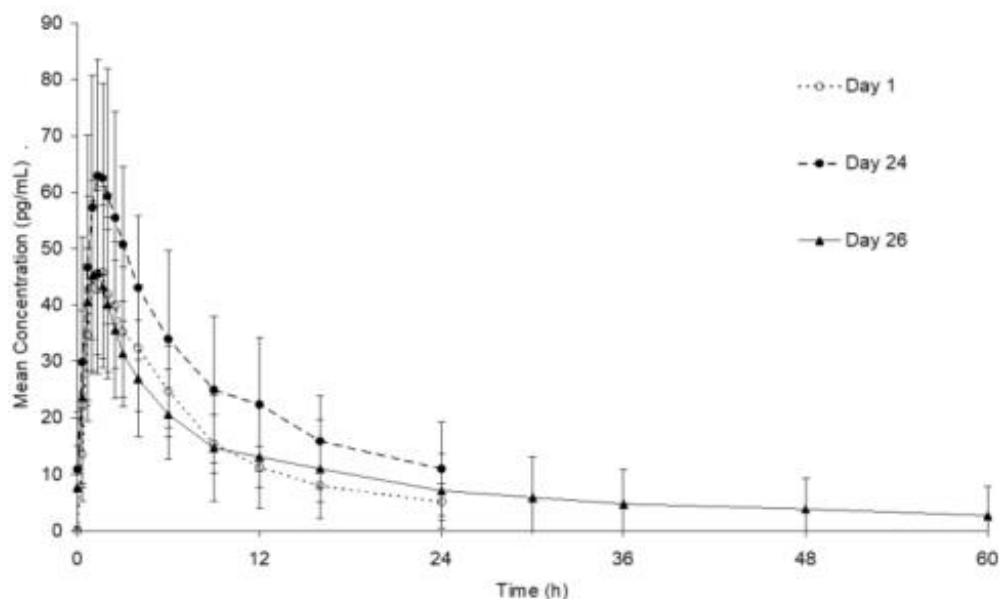
Norethindrone acetate is deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol are absorbed from Lo Loestrin Fe, with maximum plasma concentrations of norethindrone and ethinyl estradiol generally occurring 1 to 2 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64 percent for norethindrone and 55 percent for ethinyl estradiol.

The rate of norethindrone and ethinyl estradiol absorption from Lo Loestrin Fe tablets containing the combination of 1 mg norethindrone acetate and 10 mcg ethinyl estradiol is slower than that from a norethindrone suspension/ethinyl estradiol solution, but the extent of absorption is equivalent.

Ethinyl estradiol bioavailability from Lo Loestrin Fe tablets containing 10 mcg ethinyl estradiol alone is equivalent to that from an ethinyl estradiol solution.

The plasma norethindrone and ethinyl estradiol pharmacokinetic profiles and serum sex hormone binding globulin (SHBG) concentrations following multiple-dose administration of Lo Loestrin Fe were characterized in 15 healthy female volunteers. The mean plasma concentrations are shown below (Figures 1 and 2), and pharmacokinetic parameters are found in Table 1.

Ethinyl estradiol and norethindrone  $C_{max}$  values increase by a factor of 1.4 and 1.9, respectively, following 24 days administration of Lo Loestrin Fe combination tablets as compared to single-dose administration. Ethinyl estradiol and norethindrone  $AUC_{0-24h}$  values increase by a factor of 1.6 and 2.5, respectively, following 24 days administration of Lo Loestrin Fe combination tablets as compared to single-dose administration. Norethindrone concentrations more than double by Day 24 due to both accumulation and increased SHBG concentration. Steady state with respect to ethinyl estradiol and norethindrone is reached by Day 5 and Day 13, respectively.



**Figure 1. Mean ( $\pm$  SD) plasma ethinyl estradiol concentration versus time profiles following single- and**

multiple-dose oral administration of Lo Loestrin Fe to healthy female volunteers (n = 15)

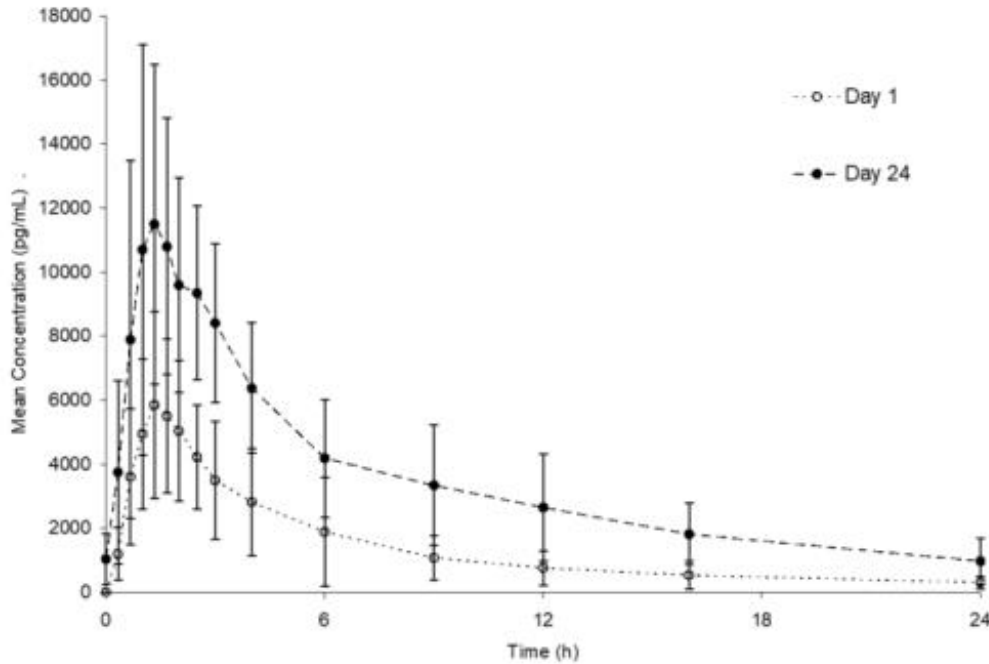


Figure 2. Mean ( $\pm$  SD) plasma norethindrone concentration versus time profiles following single- and multiple-dose oral administration of Lo Loestrin Fe to healthy female volunteers (n = 15)

Table 1. Summary of Norethindrone (NE) and Ethinyl Estradiol (EE) Pharmacokinetic Parameter Values Following Oral Administration of Lo Loestrin Fe to Healthy Female Volunteers (n = 15)

Regimen	Study Day	Analyte	Arithmetic Mean <sup>a</sup> (Percent CV) by Pharmacokinetic Parameter				
			C <sub>max</sub>	t <sub>max</sub>	AUC <sub>0-24h</sub>	C <sub>min</sub>	C <sub>avg</sub>
Single Dose Lo Loestrin Fe combination tablet <sup>c</sup>	1	NE	7360 (21)	1.7 (1.3-6.0)	33280 (33)	--	--
		EE	50.9 (27)	1.3 (1.0-6.0)	389.9 (27)	--	--
		SHBG	--	--	--	54.8 (33) <sup>b</sup>	--
Multiple Dose Lo Loestrin Fe combination tablet <sup>c</sup> x 24 days	24	NE	13900 (34)	1.3 (0.7-3.0)	84160 (41)	917 (84)	3510 (41)
		EE	71.3 (33)	1.3 (0.3-2.0)	621.3 (41)	10.0 (92)	25.9 (41)
		SHBG	--	--	--	109 (38)	--
Multiple Dose Lo Loestrin Fe combination tablet <sup>c</sup> x 24 days and ethinyl estradiol alone tablet <sup>d</sup> x 2 days	26	EE	49.9 (34)	1.3 (0.7-3.0)	403.6 (50)	--	--

$C_{max}$  = Maximum plasma concentration (pg/mL);  $t_{max}$  = Time of  $C_{max}$  (h);  $AUC_{0-24h}$  = Area under plasma concentration versus time curve from 0 to 24 hours (pg·h/mL);  $C_{min}$  = Minimum plasma concentration (pg/mL);  $C_{avg}$  = Average plasma concentration =  $AUC_{0-24h}/24$  (pg/mL)  
Percent CV = Coefficient of Variation (percent); SHBG = Sex hormone binding globulin (nmol/L)

<sup>a</sup>The median (range) is reported for  $t_{max}$

<sup>b</sup>The  $C_{min}$  concentration reported for SHBG is the pre-dose concentration

<sup>c</sup>Lo Loestrin Fe combination tablets contain 1 mg norethindrone acetate and 10 mcg ethinyl estradiol

<sup>d</sup>Lo Loestrin Fe ethinyl estradiol alone tablets contain 10 mcg ethinyl estradiol

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#### *Food Effect:*

Lo Loestrin Fe tablets may be administered without regard to meals.

Administration of food with a single-dose of a Lo Loestrin Fe combination tablet did not affect the maximum concentration of norethindrone and increased the extent of absorption by 24 percent; it decreased the maximum concentration of ethinyl estradiol by 23 percent and did not affect the extent of absorption.

Administration of food with a single-dose of a Lo Loestrin Fe ethinyl estradiol alone tablet decreased the maximum concentration of ethinyl estradiol by 31 percent and did not affect the extent of absorption.

#### *Distribution*

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95 percent); norethindrone binds to both albumin and SHBG, whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

#### *Metabolism*

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites. A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol.

Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

#### *Excretion*

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Elimination half-lives of norethindrone and ethinyl estradiol following administration of 1 mg norethindrone acetate/10 mcg ethinyl estradiol tablets are approximately 10 hours and 16 hours, respectively.

#### *Specific populations*

The pharmacokinetics of Lo Loestrin Fe in presence of renal or hepatic impairment has not been evaluated [see *Use in Specific Populations (8.6) and (8.7)*].

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

[See *Warnings and Precautions (5.2, 5.3) and Use in Specific Populations (8.1)*.]

## 14 CLINICAL STUDIES

In a one year (thirteen 28-day cycles) multicenter open-label clinical trial, 1,270 women 18 to 35 years of age, were studied to assess the efficacy of Lo Loestrin Fe, completing the equivalent of 12,482 28-day evaluable cycles of exposure. The racial demographic of all enrolled women was: Caucasian (74.9 percent), African-American (11.8 percent), Hispanic (9.8 percent), Asian (1.3 percent), and Other (2.2 percent). Women with body mass index (BMI) greater than 35 mg/m<sup>2</sup> were excluded from the study. The weight range for those women treated was 89 to 260 lbs., with a mean weight of 150 lbs. Among the women in the trial, 51 percent had not used hormonal contraception immediately prior to enrolling in this study. Of treated women, 13.7 percent were lost to follow-up, 10.7 percent discontinued due to an adverse event, and 8.9 percent discontinued by withdrawing their consent.

**The pregnancy rate (Pearl Index [PI]) in women 18 to 35 years of age was 2.92 pregnancies per 100 women-years of use (95 percent confidence interval 1.94 – 4.21)**, based on 28 pregnancies that occurred after the onset of treatment and extending through the 7 days following the last dose of Lo Loestrin Fe. Cycles in which conception did not occur, but which included the use of backup contraception, were not included in the calculation of the PI. The PI includes women who did not take the drug correctly.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Lo Loestrin<sup>®</sup> Fe (norethindrone acetate and ethinyl estradiol tablets, ethinyl estradiol tablets and ferrous fumarate tablets) is available in blister cards (dispensers) containing 28 tablets:

NDC 0430-0420-14            Cartons of 5 blister cards (dispensers)

NDC 0430-0420-60            Cartons of 30 blister cards (dispensers)

Each blister card (28 tablets) contains in the following order:

- 24 blue, round tablets (active) imprinted with “WC” on one side and “421” on the other and each containing 1 mg norethindrone and 10 mcg ethinyl estradiol
- 2 white, hexagonal tablets (active) imprinted with “WC” on one side and “422” on the other and each containing 10 mcg ethinyl estradiol
- 2 brown, round tablets (non-hormonal placebo) imprinted with “WC” on one side and “624” on the other and each containing 75 mg ferrous fumarate

### 16.2 Storage Conditions

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

Keep this drug and all drugs out of the reach of children.

## 17 PATIENT COUNSELING INFORMATION

- Counsel patients that 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.
- Counsel patients that Lo Loestrin Fe does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on the Warnings and Precautions associated with COCs.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. See “What to Do if You Miss Pills” section in FDA-Approved Patient Labeling.

- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with Lo Loestrin Fe.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum, and who has not yet had a period, to use an additional method of contraception until she has taken a blue tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.

## **FDA-Approved Patient Labeling**

### **Guide for Using Lo Loestrin Fe**

#### **WARNING TO WOMEN WHO SMOKE**

**Do not use Lo Loestrin Fe if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.**

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

#### **What is Lo Loestrin Fe?**

Lo Loestrin Fe is a birth control pill. It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called norethindrone acetate.

#### **How well does Lo Loestrin Fe work?**

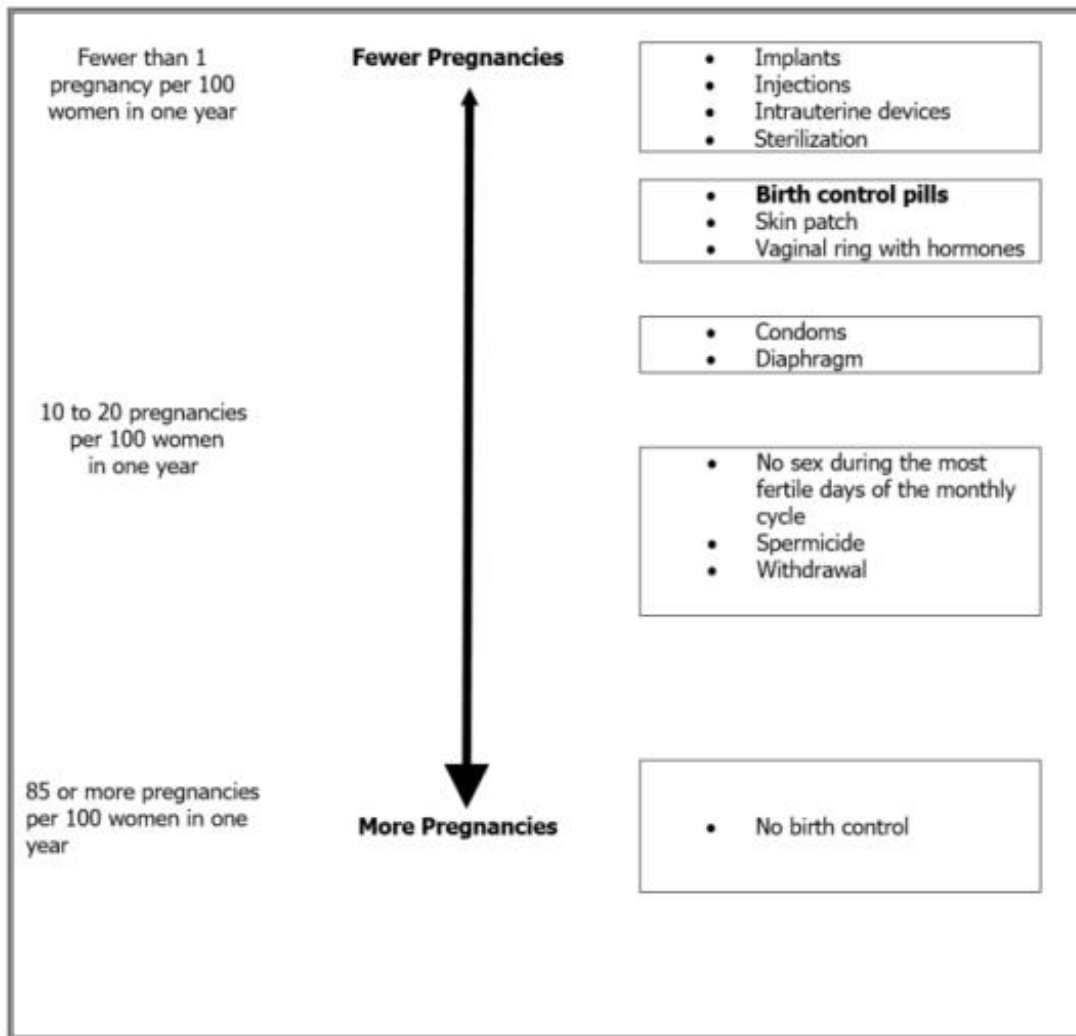
Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of one clinical study, about 2 to 4 out of 100 women may get pregnant during the first year they use Lo Loestrin Fe.

Women with a BMI above 35 kg/m<sup>2</sup> were not studied in the clinical trial, so it is not known how well Lo Loestrin Fe protects against pregnancy in such women. If you are overweight, discuss with your healthcare provider whether Lo Loestrin Fe is the best choice for you.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.





### How do I take Lo Loestrin Fe?

- Take one pill every day at the same time. If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
- You may have spotting or light bleeding, or may feel sick to your stomach during the first few months of taking Lo Loestrin Fe. If you have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your healthcare provider.
- Missing pills can also cause spotting or light bleeding, even when you take these missed pills later. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
- If you have trouble remembering to take Lo Loestrin Fe, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.
- If you have vomiting or diarrhea (within 3 to 4 hours after you take your pill), you should follow the instructions for "What to Do if You Miss Pills".
- If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

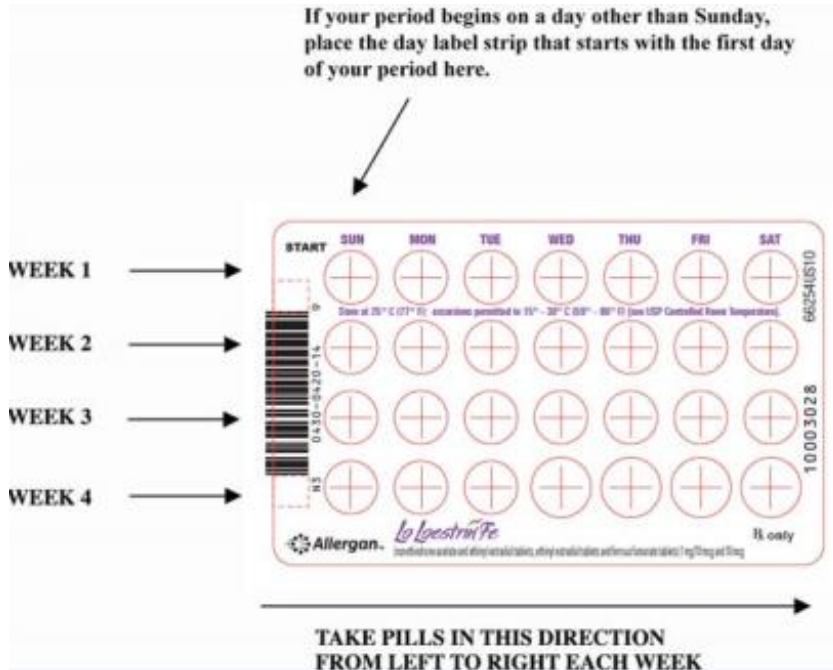
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### ***Before you start taking Lo Loestrin Fe***

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1. Decide what time of day you want to take your pill. It is important to take it at the same time every day.

2. Look at your pill pack: The Lo Loestrin Fe pill pack has 24 "active" blue pills (with hormones) and 2 "active" white pills (with hormones) for Weeks 1, 2, 3 and part of Week 4. The pill pack also has 2 "reminder" brown pills (without hormones) for the last part of Week 4.



3. Find:

- Where on the pack to start taking pills,
- In what order to take the pills (follow the arrows), and
- The week numbers as shown in the picture above

4. Have ready at all times:

- Another kind of birth control (such as a condom and spermicide) to use as a back-up in case you miss pills
- An extra pill pack

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### When to start the *first* pack of Lo Loestrin Fe

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1. Take the day label strip that starts with the first day of your period. (This is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins.)
2. Place the day label strip on the tablet dispenser over the area that has the days of the week (starting with Sunday) printed on the plastic.
3. Take the first blue pill of the first pack during the first 24 hours of your period.
4. You will not need to use a back-up method of birth control, because you are starting the pill at the beginning of your period. However, if you start Lo Loestrin Fe later than the first day of your period, or if you start after having a baby and you have not yet resumed your periods, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 blue pills.

### When You Switch from a Different Method of Hormonal Contraception

- When you switch from another birth control pill, start Lo Loestrin Fe on the first day you would have started your previous birth control pack.
- When you switch from a vaginal ring or skin patch, finish the 21 days of use, and wait 7 days after removal of the ring or patch before starting Lo Loestrin Fe.
- When you switch from a progestin-only pill, start Lo Loestrin Fe the next day.
- When you switch from an implant, start Lo Loestrin Fe on the day of implant removal.

- If you switch from an injectable contraceptive, start Lo Loestrin Fe on the day on which the next injection would be due.
- If you switch from an IUD, discuss with your healthcare provider when to start Lo Loestrin Fe.

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### What to do during the month

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- Take one pill at the same time every day until the pack is empty.
  - Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
  - Do not skip pills even if you do not have sex very often.
- When you finish a pack of Lo Loestrin Fe, start the next pack on the day after your last brown "reminder" pill. Do not skip any days between packs.

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### What to do if you miss pills

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Birth control pills may not be as effective if you miss any blue or white pills, especially if you miss the first few or the last few blue pills in a pack.

**If you miss ONE blue pill, follow these steps:**

- Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in 1 day.
- You do not need to use a back-up birth control method if you have sex.

**If you miss TWO blue pills in a row in Week 1 or Week 2 of your pack, follow these steps:**

- Take
  1. Two pills on the day you remember and two pills the next day.
  2. One pill a day until you finish the pack.
- You could become pregnant if you have sex during the first **7 days** after you restart your pills. You **MUST** use a non-hormonal birth control method (such as a condom and spermicide) as a back-up for those **7 days**.

**If you miss TWO pills (blue or white) in a row in Week 3 or Week 4 of your pack, follow these steps:**

- Throw out the rest of the pill pack and start a new pack that same day.
- You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your healthcare provider because you might be pregnant.
- You could become pregnant if you have sex during the first **7 days** after you restart your pills. You **MUST** use a non-hormonal birth control method (such as a condom and spermicide) as a back-up for those **7 days** after you restart your pills.

**If you miss THREE OR MORE pills (blue or white) in a row at any time, follow these steps:**

- Throw out the rest of the pill pack and start a new pack that same day.
- You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your healthcare provider because you might be pregnant.
- You could become pregnant if you have sex on the days when you missed pills or during the first **7 days** after restarting your pills. You **MUST** use a non-hormonal birth control method (such as a condom and spermicide) as a back-up the next time you have sex and for the first **7 days** after you restart your pills.

**If you forget either of the 2 brown "reminder" pills in Week 4, follow these steps:**

- Throw away the pills you missed.
- Keep taking one pill each day until the pack is empty.

- You do not need to use a back-up method of birth control.

**If you are still not sure what to do about the pills you have missed:**

- Use a back-up method of birth control anytime you have sex.
- Keep taking one pill each day until you can reach your healthcare provider.

**Who should not take Lo Loestrin Fe?**

Your healthcare provider will not give you Lo Loestrin Fe if you have:

- Ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
- Ever had a stroke
- Ever had a heart attack
- Certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- An inherited problem with your blood that makes it clot more than normal
- High blood pressure that medicine can't control
- Diabetes with kidney, eye, nerve, or blood vessel damage
- Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision
- Ever had breast cancer or any cancer that is sensitive to female hormones
- Liver disease, including liver tumors
- Take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are or suspect you are pregnant
- Are allergic to anything in Lo Loestrin Fe

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy, also called cholestasis of pregnancy.

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider may recommend another method of birth control).

**What else should I know about taking Lo Loestrin Fe?**

Birth control pills do ***not*** protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

Do not skip any pills, even if you do not have sex often.

**If you miss a period, you could be pregnant.** However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant
- Miss one period and have not taken your birth control pills every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

You should stop Lo Loestrin Fe at least four weeks before you have surgery and not restart it until at least two weeks after the surgery, due to an increased risk of blood clots.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Lo Loestrin Fe, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

Tell your healthcare provider about all medicines and herbal products that you take. Some medicines and herbal products may make birth control pills less effective, including:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- wort
- topiramate

Consider using another birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like a condom and spermicide, until you check with your healthcare provider.

If you are scheduled for any laboratory tests, tell your healthcare provider that you are taking birth control pills. Certain blood tests may be affected by birth control pills.

### **What are the most serious risks of taking Lo Loestrin Fe?**

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke.

Some examples of serious blood clots are blood clots in the:

- Legs (deep vein thrombosis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

A few women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

### **Call your healthcare provider right away if you have:**

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain or pressure in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking

- Yellowing of the skin or eyeballs

### **What are the common side effects of birth control pills?**

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol, triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself
- Problems tolerating contact lenses
- Weight gain

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

### **Do birth control pills cause cancer?**

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

### **What should I know about my period when taking Lo Loestrin Fe?**

When you take Lo Loestrin Fe you may have bleeding and spotting between periods, called unscheduled bleeding. Approximately half of the women who use Lo Loestrin Fe have unscheduled bleeding or spotting in the first months of use, and about one-third of users continue to have unscheduled bleeding or spotting after one year of use. If the unscheduled bleeding or spotting is heavy or lasts for more than a few days, you should discuss this with your healthcare provider.

### **What if I miss my scheduled period when taking Lo Loestrin Fe?**

It is not uncommon to miss your period. However, if you go two or more months in a row without a period, or you miss your period after a month where you did not take all your pills correctly, call your healthcare provider because you may be pregnant. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. Stop taking Lo Loestrin Fe if you are pregnant.

### **What if I want to become pregnant?**

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

### **General Advice about Lo Loestrin Fe**

Your healthcare provider prescribed Lo Loestrin Fe for you. Please do not share Lo Loestrin Fe with anyone else. Keep Lo Loestrin Fe out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your pharmacist for a more detailed label written for healthcare professionals.

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Irvine, CA 92612

Product of Germany

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Patented. See [www.allergan.com/patents](http://www.allergan.com/patents).

**PRINCIPAL DISPLAY PANEL**

NDC 0430-0420-14

Lo Loestrin Fe

26 days of active therapy

5 blister cards of 28 tablets each

Rx Only



**PRINCIPAL DISPLAY PANEL**

NDC 0430-0420-95

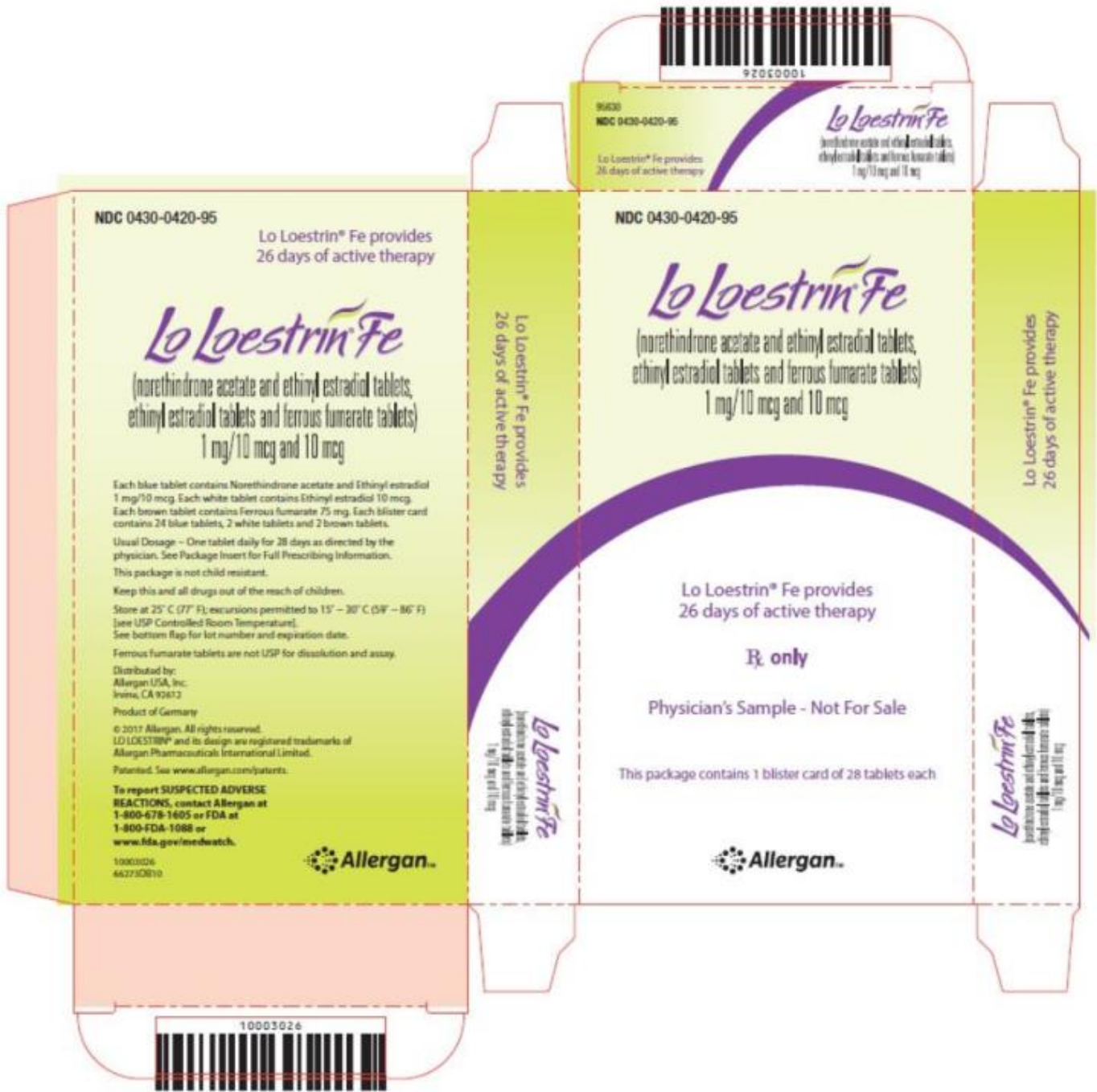
Lo Loestrin Fe

26 days of active therapy

1 blister card of 28 tablets each

Rx Only





## LO LOESTRIN FE

norethindrone acetate and ethinyl estradiol, ethinyl estradiol and ferrous fumarate kit

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:0430-0420
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### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0430-0420-14	5 in 1 CARTON	12/01/2010	
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:0430-0420-95	6 in 1 TRAY	12/01/2010	

2		1 in 1 CARTON	
2		1 in 1 BLISTER PACK; Type 0: Not a Combination Product	
3	NDC:0430-0420-60	8 in 1 TRAY	12/01/2010
3		30 in 1 CARTON	
3		1 in 1 BLISTER PACK; Type 0: Not a Combination Product	

### Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1		24
Part 2		2
Part 3		2

### Part 1 of 3

## NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL

norethindrone acetate and ethinyl estradiol tablet

### Product Information

**Route of Administration** ORAL

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NORETHINDRONE ACETATE (UNII: 9S44LIC7OJ) (NORETHINDRONE - UNII:T18F433X4S)	NORETHINDRONE ACETATE	1 mg
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.01 mg

### Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE (UNII: FZ989GH94E)	
ALPHA-TOCOPHEROL (UNII: H4N855PNZ1)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	

### Product Characteristics

<b>Color</b>	BLUE	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	6mm
<b>Flavor</b>		<b>Imprint Code</b>	WC;421
<b>Contains</b>			

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022501	12/01/2010	

## Part 2 of 3

### ETHINYL ESTRADIOL

ethinyl estradiol tablet

## Product Information

Route of Administration ORAL

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.01 mg

## Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE (UNII: FZ989GH94E)	
ALPHA-TOCOPHEROL (UNII: H4N855PNZ1)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	

## Product Characteristics

Color	WHITE	Score	no score
Shape	HEXAGON (6 SIDED)	Size	5mm
Flavor		Imprint Code	WC;422
Contains			

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022501	12/01/2010	

## Part 3 of 3

# FERROUS FUMARATE

ferrous fumarate tablet

## Product Information

**Route of Administration** ORAL

## Inactive Ingredients

Ingredient Name	Strength
FERROUS FUMARATE (UNII: R5L488RY0Q)	75 mg
MANNITOL (UNII: 3OWL53L36A)	
POVIDONE (UNII: FZ989GH94E)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
SODIUM STARCH GLYCOLATE TYPE A POTATO (UNII: 5856J3G2A2)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	
SPEARMINT (UNII: J7I2T6IV1N)	

## Product Characteristics

<b>Color</b>	BROWN	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	6mm
<b>Flavor</b>	SPEARMINT	<b>Imprint Code</b>	WC;624
<b>Contains</b>			

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022501	12/01/2010	

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA022501	12/01/2010	

**Labeler** - Allergan, Inc. (144796497)

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Allergan, Inc.