

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LO/OVRAL-28 safely and effectively. See full prescribing information for LO/OVRAL-28.

LO/OVRAL<sup>®</sup>-28 (norgestrel and ethinyl estradiol tablets and ferrous fumarate tablets) for oral use  
Initial U.S. Approval: 1979

### WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See Full Prescribing Information for complete boxed warning.

- LO/OVRAL-28 is contraindicated in women over 35 years old who smoke. (4)
- Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. (4)

### RECENT MAJOR CHANGES

Warnings and Precautions (5.10)

04/2022

### INDICATIONS AND USAGE

LO/OVRAL-28 is a progestin/estrogen COC indicated for use by females of reproductive potential to prevent pregnancy. (1) The efficacy of LO/OVRAL-28 in women with a body mass index (BMI) of > 35 kg/m<sup>2</sup> 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/OVRAL-28 consists of 28 tablets in the following order (3):

- 21 white tablets (active), each containing 0.3 mg norgestrel and 0.03 mg ethinyl estradiol
- 7 brown tablets (inactive), 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)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Breast cancer (4)

- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

### WARNINGS AND PRECAUTIONS

- **Thrombotic Disorders and Other Vascular Problems:** Stop LO/OVRAL-28 if a thrombotic event occurs. Stop at least 4 weeks before through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- **Liver disease:** Discontinue LO/OVRAL-28 if jaundice occurs. (5.2)
- **High blood pressure:** If used in women with well-controlled hypertension, monitor blood pressure and stop LO/OVRAL-28 if blood pressure rises significantly. (5.4)
- **Carbohydrate and lipid metabolic effects:** Monitor prediabetic and diabetic women taking LO/OVRAL-28. Consider an alternative contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- **Headache:** Evaluate significant change in headaches and discontinue LO/OVRAL-28 if indicated. (5.7)
- **Bleeding Irregularities and Amenorrhea:** Evaluate irregular bleeding or amenorrhea. (5.8)

### ADVERSE REACTIONS

The most common adverse reactions (≥ 2%) were: headache, nausea, acne, vaginal infection, vaginal discharge, dysmenorrhea, breast discomfort, depression, increased appetite, gastrointestinal symptoms, nervousness, backache, change in menstrual flow, chloasma/melasma, and exacerbation of varicose veins. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact 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 (for example 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

- Lactation: Advise use of another contraceptive method. LO/OVRAL-28 can decrease milk production. (8.2)

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

Revised: 04/2022

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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/OVRAL-28 is indicated for use by females of reproductive potential to prevent pregnancy.

The efficacy of LO/OVRAL-28 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 Start LO/OVRAL-28**

LO/OVRAL-28 is dispensed in a blister pack [see *How Supplied/Storage and Handling (16)*]. LO/OVRAL-28 may be started using either a Day 1 start or a Sunday start (see [Table 1](#)). For the first cycle of a Sunday Start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

## 2.2 How to Take LO/OVRAL-28

Table 1: Instructions for Administration of LO/OVRAL-28

<p><b>Starting COCs in women not currently using hormonal contraception (Day 1 Start or Sunday Start)</b></p> <p><b>Important:</b> Consider the possibility of ovulation and conception prior to initiation of this product.</p> <p><b>Tablet Color:</b></p> <ul style="list-style-type: none"><li>• Lo/Ovral-28 <b>active</b> tablets are <b>white</b> (Day 1 to Day 21).</li><li>• Lo/Ovral-28 <b>inactive</b> tablets are <b>brown</b> (Day 22 to Day 28).</li></ul>	<p><b>Day 1 Start:</b></p> <ul style="list-style-type: none"><li>• Take first <b>white active</b> tablet without regard to meals on the first day of menses.</li><li>• Take subsequent <b>white active</b> tablets once daily at the same time each day for a total of 21 days.</li><li>• Take one <b>brown inactive</b> tablet daily for 7 days and at the same time of day that active tablets were taken.</li><li>• Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last <b>brown inactive</b> tablet).</li></ul> <p><b>Sunday Start:</b></p> <ul style="list-style-type: none"><li>• Take the <b>first white active</b> tablet on the first Sunday after the onset of menses. <b>Due to the potential risk of becoming pregnant, use additional non-hormonal contraception (such as condoms or spermicide) for the first 7 days of the patient's first cycle pack of Lo/Ovral-28.</b></li><li>• Take subsequent <b>white active</b> tablets once daily at the same time each day for a total of 21 days.</li><li>• Take one <b>brown inactive</b> tablet daily for the following 7 days and at the same time of day that active tablets were taken.</li><li>• Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the Sunday after taking the last <b>brown inactive</b> tablet) and additional non-hormonal contraceptive is not needed.</li></ul>
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<b>Switching to Lo/Ovral-28 from another oral contraceptive</b>	Start Lo/Ovral-28 the day after the last tablet of previous oral contraceptive was taken. When switching from a progestin-only pill, Lo/Ovral-28 should be started the next day and a non-hormonal back-up method of contraception (such as condoms or spermicide) should be used for the first 7 days.
<b>Switching from another contraceptive method to Lo/Ovral-28</b>	<b>Start Lo/Ovral-28:</b>
• <b>Transdermal patch</b>	• On the day when next application would have been scheduled.
• <b>Vaginal ring</b>	• On the day when next insertion would have been scheduled
• <b>Injection</b>	• On the day when next injection would have been scheduled. A non-hormonal back-up method of contraception should be used if starting LATER than the next injection is due.
• <b>Intrauterine contraceptive</b>	• On the day of removal • If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraceptive (such as condoms or spermicide) is needed for the first seven days of the first cycle pack.
• <b>Implant</b>	• On the day of removal. A non-hormonal back-up method of contraception should be used if starting at a date after removal of implant.
<b>Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-approved Patient Labeling.</b>	

### **Starting LO/OVRAL-28 after Abortion or Miscarriage**

#### ***First-trimester***

- After a first-trimester abortion or miscarriage, LO/OVRAL-28 may be started immediately. An additional method of contraception is not needed if LO/OVRAL-28 is started within 5 days after termination of pregnancy.
- If LO/OVRAL-28 is not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms or spermicide) for the first 7 days of her first pack of LO/OVRAL-28.

#### ***Second-trimester***

Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start LO/OVRAL-28 following the instructions in [Table 1](#) for Sunday Start, as desired. If using Sunday Start, use additional non-hormonal contraception (such as condoms or spermicide) for the first 7 days of the patient's first pack of LO/OVRAL-28 [see *Contraindications (4)*, *Warnings and Precautions (5.1)*, and *FDA-approved Patient Labeling*].

### Starting LO/OVRAL-28 after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with LO/OVRAL-28 following the instructions in [Table 1](#) for women not currently using hormonal contraception.
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of LO/OVRAL-28 [see *Contraindications (4)*, *Warnings and Precautions (5.1)*, *Use in Specific Populations (8.1Pregnancy)*, and *FDA-approved Patient Labeling*].

## 2.3 Missed Tablets

**Table 2: Instructions for Missed Lo/Ovral-28 Tablets**

<ul style="list-style-type: none"> <li>• If one <b>white active</b> tablet is missed in Weeks 1, 2 or 3</li> </ul>	<p>Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.</p>
<ul style="list-style-type: none"> <li>• If two <b>white active</b> tablets are missed in Week 1 or Week 2</li> </ul>	<p>Take the two missed tablets as soon as possible and the next two active tablets the next day. Continue taking one tablet a day until the pack is finished. <b>Additional non-hormonal contraception (such as condoms or spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.</b></p>
<ul style="list-style-type: none"> <li>• If two <b>white active</b> tablets are missed in Week 3 or three or more consecutive <b>white active</b> tablets are missed in a row in Weeks 1, 2 or 3</li> </ul>	<p><b>Day 1 Start:</b> Throw out the rest of the pack and start a new pack that same day.</p> <p><b>Sunday Start:</b> Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day.</p> <p><b>Additional non-hormonal contraception (such as condoms or spermicide) should be used as back-up if the patient has sex within 7 days after missing 3 tablets.</b></p>

## 2.4 Advice in Case of Gastrointestinal Disturbances

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

## 3 DOSAGE FORMS AND STRENGTHS

LO/OVRAL-28 (norgestrel and ethinyl estradiol tablets and ferrous fumarate tablets) is available in blister packs.

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

- 21 white, round (active) tablets imprinted with “78 on one side and “Wyeth” on the other and each containing 0.3 mg norgestrel and 0.03 mg ethinyl estradiol.
- 7 brown, round (inactive) tablets each containing 75 mg ferrous fumarate. The ferrous fumarate tablets do not serve any therapeutic purpose.

## 4 CONTRAINDICATIONS

LO/OVRAL-28 is contraindicated in females who are known to have the following conditions to women who are known to have or develop the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 [see *Boxed Warning and Warnings and Precautions (5.1)*]
  - Have deep vein thrombosis or pulmonary embolism, now or in the past [see *Warnings and Precautions (5.1)*]
  - Have inherited or acquired hypercoagulopathies [see *Warnings and Precautions (5.1)*]
  - Have cerebrovascular disease [see *Warnings and Precautions (5.1)*]
  - Have coronary artery disease [see *Warnings and Precautions (5.1)*]
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see *Warnings and Precautions (5.1)*]
  - Have uncontrolled hypertension [see *Warnings and Precautions (5.4)*]
  - Have diabetes mellitus with vascular disease [see *Warnings and Precautions (5.6)*]
  - Have headaches with focal neurological symptoms or have migraine headaches with aura [see *Warnings and Precautions (5.7)*]
    - Women over age 35 with any migraine headaches [see *Warnings and Precautions (5.7)*]]
- Liver tumors, benign or malignant, or liver disease [see *Warnings and Precautions (5.2)*]
- Undiagnosed abnormal uterine bleeding [see *Warnings and Precautions (5.8)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [see *Use in Specific Populations (8.1)*]
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive [see *Warnings and Precautions (5.10)*]
- Are receiving Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations [(see *Warnings and Precautions (5.3)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Thrombotic Disorders and Other Vascular Problems

- Stop LO/OVRAL-28 if an arterial thrombotic event or venous thromboembolic (VTE) event occurs.
- Stop LO/OVRAL-28 if there is unexplained loss of vision, proptosis, diplopia, papilledema. Evaluate for retinal vein thrombosis immediately [see *Adverse Reactions (6.2)*].
- If feasible, stop LO/OVRAL-28 at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during and following prolonged immobilization.
- Start LO/OVRAL-28 no earlier than 4 weeks after delivery in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of a COCs and when restarting oral contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after COC use is discontinued.  
  
Use of COCs also increases the risk of arterial thromboses that result in strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and

attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.

- Use COCs with caution in women with cardiovascular disease risk factors.

## 5.2 Liver Disease

### Impaired Liver Function

Do not use LO/OVRAL-28 in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver [see *Contraindications (4)*]. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue LO/OVRAL-28 if jaundice develops.

### Liver Tumors

LO/OVRAL-28 is contraindicated in women with benign and malignant liver tumors [see *Contraindications (4)*]. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases 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 risk of liver cancers in COC users is less than one case per million users.

## 5.3 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains 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 subjects using ethinyl estradiol-containing medications such as COCs. Discontinue Lo/Ovral-28 prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [see *Contraindications (4)*]. Lo/Ovral-28 can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

## 5.4 High Blood Pressure

LO/OVRAL-28 is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease [see *Contraindications (4)*]. For women with well-controlled hypertension, monitor blood pressure and stop LO/OVRAL-28 if blood pressure rises significantly.

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

## 5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may worsen existing gallbladder disease. A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC related cholestasis.

## 5.6 Carbohydrate and Lipid Metabolic Effect

Carefully monitor prediabetic and diabetic women who are taking LO/OVRAL-28. COCs may decrease glucose tolerance.

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.

## 5.7 Headache

If a woman taking LO/OVRAL-28 develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue LO/OVRAL-28 if indicated.

Consider discontinuation of LO/OVRAL-28 in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event).

## 5.8 Bleeding Irregularities and Amenorrhea

### Unscheduled Bleeding and Spotting

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 contraceptive product.

The frequency and duration of unscheduled bleeding and/or spotting was assessed in 1,343 subjects across nine studies. Unscheduled bleeding and spotting occurred in 15% of women in the first cycle on treatment, 9% in Cycle 3, 5% in Cycle 6, 5% in Cycle 9 and 5% in Cycle 12. In 1287 subjects, LO/OVRAL-28 was discontinued in 1% of subjects due to breakthrough bleeding and 1% of subjects discontinued due to spotting. .

### Amenorrhea and Oligomenorrhea

Women who use LO/OVRAL-28 may experience amenorrhea, absence of withdrawal bleeding, even if they are not pregnant. In the clinical trials with LO/OVRAL-28, amenorrhea was reported in 3% of subjects in the first cycle, 2% in Cycle 3, 2% in Cycle 6, 1% in Cycle 9 and 2% in Cycle 12. Amenorrhea was the reason for study discontinuation in < 1% of subjects.

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

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.

## 5.9 Depression

Carefully observe women with a history of depression and discontinue LO/OVRAL-28 if depression recurs to a serious degree.

## 5.10 Malignant Neoplasms

### Breast Cancer

Lo/Ovral-28 is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive [see Contraindications (4)].

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

### Cervical Cancer

Some studies suggest that 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.

## 5.11 Effect on Binding Globulins

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

## 5.12 Hereditary Angioedema

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

### 5.13 Chloasma

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 LO/OVRAL-28.

## 6 ADVERSE REACTIONS

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

- Serious cardiovascular events and stroke [see *Boxed Warning and Warnings and Precautions (5.1)*]
- Vascular events [see *Warnings and Precautions (5.1)*]
- Liver disease [see *Warnings and Precautions (5.2)*]

The following adverse reactions are commonly reported by COC users. Because these reactions are voluntarily reported by from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- 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.

The safety of LO/OVRAL-28 was evaluated in nine clinical investigations with a cumulative total of 1,343 subjects aged 15 to 40 and followed for a total of 11,085 cycles (852 women years of study). The subjects were recruited from a wide geographical distribution in the United States and including all socio-economic groups. The ethnic distribution of study volunteers was: 69% white; 28% black; 1.0% Asian; and 2% other backgrounds. 28% nulligravidas and 72% gravidas.

Common Adverse Reactions ( $\geq 2\%$  of all subjects): The most common adverse reactions were headache (6%), nausea (5%), acne (4%), vaginal infection (4%), vaginal discharge (4%), dysmenorrhea (4%) breast discomfort (3%), depression (3%), increased appetite (3%), gastrointestinal symptoms (3%), nervousness (3%), backache (2%), change in menstrual flow (2%), chloasma/melasma (2%), exacerbation of varicose veins (2%).

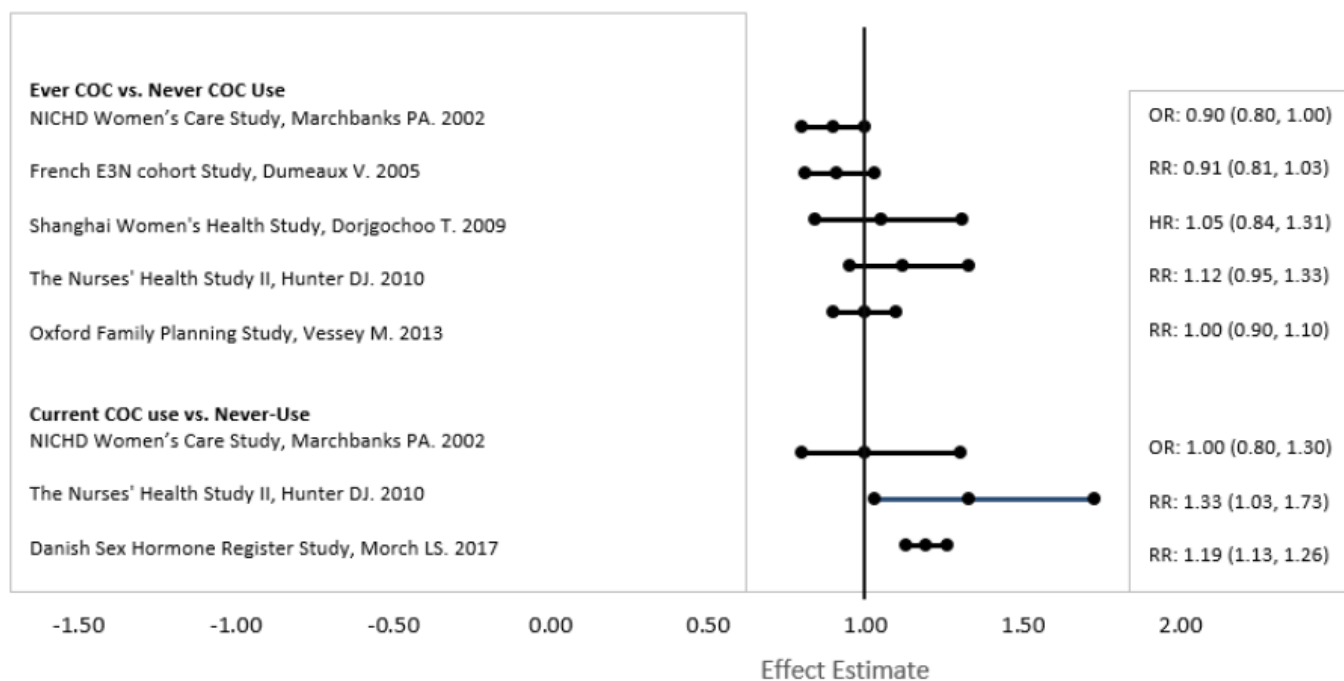
Adverse Reactions Leading to Study Discontinuation: A total of 103 subjects (8%) dropped out of the trials due to adverse reactions, including unscheduled bleeding (breakthrough bleeding 1%; spotting 1%), and the following each in  $< 1\%$ , headache including migraine, amenorrhea, nausea, acne, change in menstrual flow, nervousness, increase in weight, depression, and high blood pressure.

### 6.2 Postmarketing Experience

Five studies that compared breast cancer risk between ever-users (current or past use) of COCs and never-users of COCs reported no association between ever use of COCs and breast cancer risk, with effect estimates ranging from 0.90 - 1.12 (Figure 1).

Three studies compared breast cancer risk between current or recent COC users ( $< 6$  months since last use) and never users of COCs (Figure 1). One of these studies reported no association between breast cancer risk and COC use. The other two studies found an increased relative risk of 1.19 - 1.33 with current or recent use. Both of these studies found an increased risk of breast cancer with current use of longer duration, with relative risks ranging from 1.03 with less than one year of COC use to approximately 1.4 with more than 8-10 years of COC use.

**Figure 1: Relevant Studies of Risk of Breast Cancer with Combined Oral Contraceptives**



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

The following adverse reactions have been identified during post approval use of LO/OVRAL-28. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

*Arterial events:* myocardial infarction, arterial thromboembolism, and cerebral hemorrhage.

*Eye disorders:* retinal vein thrombosis, change in corneal curvature (steepening).

*GI disorders:* nausea, pancreatitis.

*Hepatobiliary disorders:* gallbladder disease and cholestatic jaundice.

*Immune system disorders:* anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.

*Metabolism and nutrition disorders:* change in weight or appetite (increase or decrease), carbohydrate and lipid effects.

*Neoplasms, Benign, Malignant, and Unspecified:* Carincoma of the reproductive organs and breasts, Hepatic neoplasia (including hapatic adenomas, or benign liver tumors).

*Skin and subcutaneous disorders:* hirsutism, erythema multiforme, erythema nodosum, hemorrhagic eruption, and melasma/chloasma, which may persist

*Nervous system disorders:* headache, migraine.

*Psychiatric disorders:* mood swings.

*Reproductive system and breast disorders:* breast changes (tenderness, pain, enlargement, and secretion), premenstrual syndrome.

*Vascular disorders:* venous thrombosis, pulmonary embolism, cerebral thrombosis, mesenteric thrombois, and retinal vascular thrombosis.

## 7 DRUG INTERACTIONS

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

### 7.1 Effects of Other Drugs on Combined Oral Contraceptives

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

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

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

#### Substances increasing the plasma concentrations of COCs:

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

#### Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:

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

### 7.2 Concomitant use with HCV combination therapy – Liver enzyme elevation

Do not co-administer Lo/Ovral-28 with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations [see *Warnings and Precautions (5.3)*].

### 7.3 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. COCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, and temazepam. A significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

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

### 7.4 Interactions with Laboratory Tests

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

There is little or no increased risk of birth defects in the children of females who inadvertently use COCs during early pregnancy. Animal data, along with epidemiologic studies, do not show an increased risk of birth defects with use of COCs prior to pregnancy or during early pregnancy.

Discontinue LoOvral use if pregnancy is confirmed.

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

#### *Animal Data*

Several studies were conducted in rodents and rabbits to evaluate the potential reproductive toxicity of Norgestrel in combination with Ethinyl Estradiol (Norgestrel/EE) during pregnancy or lactation at doses approximately up to 25-fold over the clinical dose.

In rats administered Norgestrel/EE from Day 8-21 of gestation, there were no maternal adverse effects and no effects on embryofetal development or reproductive potential of the offspring. In rabbits, Norgestrel/EE administered from Day 8-18 of gestation showed a decrease in maternal body weight gain and litter size. There was no indication of teratogenicity in either rats or rabbits.

Administration of Norgestrel/EE in mice and rats to suppress fertility was followed by a recovery of reproductive function and fertility. In lactating female rats administered Norgestrel/EE at doses up to 25-fold the clinical dose from delivery to 21 days post-delivery or weaning, there were no adverse maternal effects, no effect on the lactation process, and no effect on offspring growth.

## **8.2 Lactation**

### Risk Summary

Contraceptive hormones and/or metabolites are present in human milk in small amounts. The effects of Lo/Ovral-28 on the breastfed child is unknown. COCs can reduce milk production in lactating women. Advise the nursing mother to use a non-COC contraception, when possible, until she has weaned her child. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Lo/Ovral-28 and any potential adverse effects on the breast-fed child from Lo-Ovral-28 or from the underlying maternal condition.

## **8.4 Pediatric Use**

Safety and efficacy of LO/OVRAL-28 have been established in women of reproductive age. Efficacy is expected to be the same in postpubertal adolescents under the age of 18 years as for users 18 years and older. Use of this LO/OVRAL-28 before menarche is not indicated.

## **8.5 Geriatric Use**

LO/OVRAL-28 has not been studied in postmenopausal women and is not indicated in this population.

## **8.6 Hepatic Impairment**

The pharmacokinetics of LO/OVRAL-28 has not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded [*see Contraindications (4) and Warnings and Precautions (5.2)*].

## **8.7 Renal Impairment**

The pharmacokinetics of LO/OVRAL-28 has not been studied in women with renal impairment.

## **8.8 Body Mass Index**

The safety and efficacy of LO/OVRAL-28 in women with a body mass index (BMI) > 35 kg/m<sup>2</sup> has not been evaluated [*see Clinical Studies (14)*].

## **10 OVERDOSAGE**

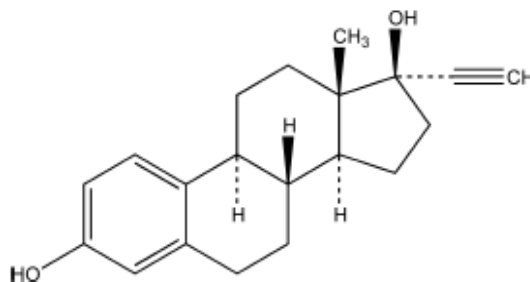
There have been no reports of serious ill effects from overdose of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

## 11 DESCRIPTION

LO/OVRAL-28 is a combination oral contraceptive for oral administration consisting of active white tablets containing norgestrel, a progestin, and ethinyl estradiol, an estrogen, and brown inactive tablets containing ferrous fumarate, which serve no therapeutic purpose.

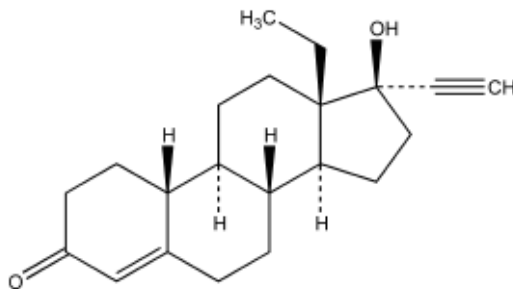
- Each active white tablet contains 0.3 mg norgestrel and 0.03 mg ethinyl estradiol. Inactive ingredients include lactose monohydrate, magnesium stearate, microcrystalline cellulose, and polacrillin potassium.
- Each brown inactive tablet contains 75 mg ferrous fumarate, methylcellulose starch, lactose anhydrous, and magnesium stearate. The ferrous fumarate tablets do not serve any therapeutic purpose. Ferrous Fumarate Tablets are not USP for dissolution and assay.

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



**Ethinyl Estradiol**  
M.W. 296.40

The chemical name of norgestrel is 18, 19-Dinorepregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-, (17 $\alpha$ )-(±)-, a totally synthetic progesterone. The empirical formula of norgestrel is C<sub>21</sub>H<sub>28</sub>O<sub>2</sub> and the structural formula is:



**Norgestrel**  
M.W. 312.45

## 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.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.10) and Use in Specific Populations (8.1).]

## 14 CLINICAL STUDIES

Nine clinical trials in different parts of the United States recruited subjects aged 15 to 40. A total of 1,287 subjects completed at least one cycle, 1,062 three cycles, 766 six cycles, 429 twelve cycles, and 244 fifteen cycles, making a total of 11,085 cycles (852 women-years of study). The racial demographic of subjects LO/OVRAL-28 was: 69% Caucasian, 28% African-American, 1% Asian and < 1% Native American.

The pregnancy rate was approximately 1 pregnancy per 100 women-years of use.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

LO/OVRAL<sup>®</sup>-28 (norgestrel and ethinyl estradiol tablets and ferrous fumarate tablets) is available in cartons of 100 blister packs containing 28 tablets:

NDC 0080-2526-01          Cartons of 100 blister packs

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

- 21 white, round (active) tablets imprinted with “78” on one side and “Wyeth” on the other and each containing 0.3 mg norgestrel and 0.03 mg ethinyl estradiol.
- 7 brown, round (inactive) 75 mg ferrous fumarate

### 16.2 Storage Conditions

- Store at controlled room temperature 20° to 25°C (68°F to 77° F); excursions permitted from 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*].
- Protect from light.

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

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling ([Patient Information](#) and [Instructions for Use](#)).

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs [*see Boxed Warning*].
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC [*see Warnings and Precautions (5.1)*].
- LO/OVRAL-28 does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
- LO/OVRAL-28 is not to be used during pregnancy; if pregnancy occurs during use of LO/OVRAL-28 instruct the patient to stop further use [*see Specific Populations (8.1)*].
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed [*see Dosage and Administration (2.2)*].
- Use a back-up or alternative method of contraception when enzyme inducers are used with LO/OVRAL-28 [*see Drug Interactions (7.1)*].
- COCs may reduce breast milk production; this is less likely to occur if breastfeeding is well established [*see Use in Specific Populations (8.2)*].

- Women who start COCs postpartum, and who have not yet had a period, should use an additional method of contraception until she has taken a white tablet for 7 consecutive days [see *Dosage and Administration (2.2)*].
- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea at the time of the first missed period. Rule out pregnancy if amenorrhea persists beyond two consecutive cycles [see *Warnings and Precautions (5.8)*].

## PATIENT INFORMATION

### LO/OVRAL-28 [Low-O-Vral 28]

(norgestrel and ethinyl estradiol tablets and ferrous fumarate tablets)

#### What is the most important information I should know about LO/OVRAL-28?

**Do not use LO/OVRAL-28 if you smoke cigarettes and are over 35 years old.** Smoking increases your risk of serious cardiovascular side effects from hormonal birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

#### What is LO/OVRAL-28?

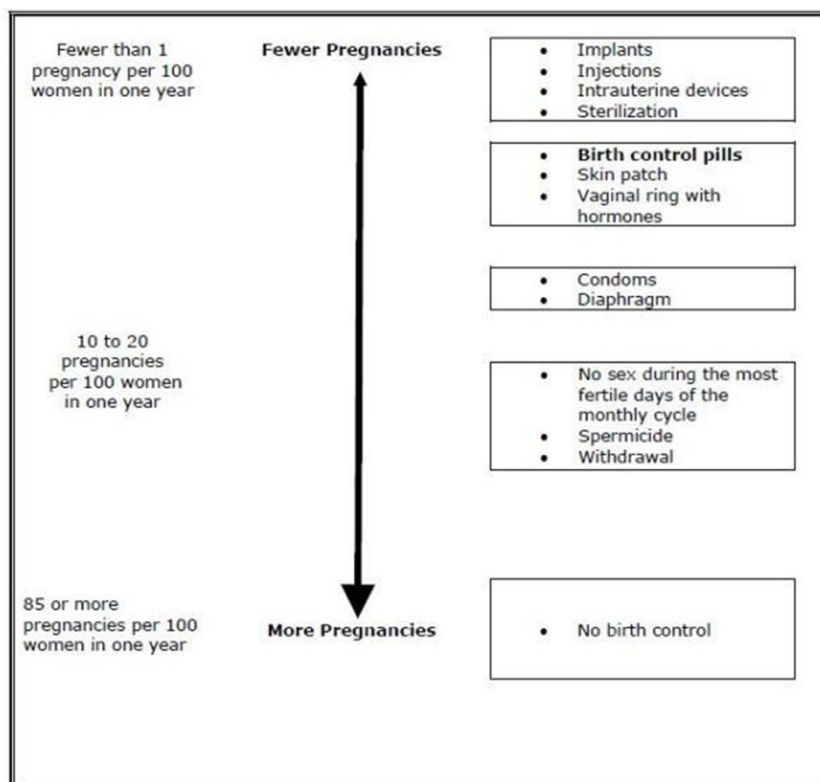
LO/OVRAL-28 is a birth control pill (oral hormonal contraceptive) used by women to prevent pregnancy.

#### How does LO/OVRAL-28 work for contraception?

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 from the clinical study, about 1 to 4 out of 100 subjects may get pregnant during the first year they use LO/OVRAL-28.

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.



## Who should not take LO/OVRAL-28?

### Do not take LO/OVRAL-28 if you:

- smoke and are over 35 years of age
- had blood clots in your arms, legs, lungs, or eyes
- had a problem with your blood that makes it clot more than normal
- have certain heart valve problems or irregular heart beat that increases your risk of having blood clots
- had a stroke
- had a heart attack
- have high blood pressure that cannot be controlled by medicine
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or any migraine headaches if you are over 35 years of age
- have liver problems, 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
- have any unexplained vaginal bleeding
- are pregnant
- had breast cancer or any cancer that is sensitive to female hormones

**If any of these conditions happen while you are taking LO/OVRAL-28, stop taking LO/OVRAL-28 right away and talk to your healthcare provider. Use non-hormonal contraception (such as condoms or spermicide) when you stop taking LO/OVRAL-28.**

## What should I tell my healthcare provider before taking LO/OVRAL-28?

### Tell your healthcare provider if you:

- are pregnant or think you may be pregnant
- are depressed now or have been depressed in the past
- had yellowing of your skin or eyes (jaundice) caused by pregnancy (cholestasis of pregnancy)
- are breastfeeding or plan to breastfeed. LO/OVRAL-28 may decrease the amount of breast milk you make. A small amount of the hormones in LO/OVRAL-28 may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins and herbal supplements.

LO/OVRAL-28 may affect the way other medicines work, and other medicines may affect how well LO/OVRAL-28 works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

## How should I take LO/OVRAL-28?

Read the [Instructions for Use](#) at the end of this Patient Information.

### **What are the possible serious side effects of LO/OVRAL-28?**

**Like pregnancy, LO/OVRAL-28 may cause serious side effects, including blood clots in your lungs, heart attack, or a stroke that may lead to death.** Some other examples of serious blood clots include blood clots in the legs or eyes.

Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age.

Serious blood clots are more likely to happen when you:

- first start taking birth control pills
- restart the same or different birth control pills after not using them for a month or more

### **Call your healthcare provider or go to a hospital emergency room right away if you have:**

- leg pain that will not go away
- sudden severe shortness of breath
- sudden change in vision or blindness
- chest pain
- a sudden, severe headache unlike your usual headaches
- weakness or numbness in your arm or leg
- trouble speaking

### **Other serious side effects include:**

- **liver problems, including:**
  - rare liver tumors
  - jaundice (cholestasis), especially if you previously had cholestasis of pregnancy. Call your healthcare provider if you have yellowing of your skin or eyes.
- **high blood pressure**
- **gallbladder problems**
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood**
- **new or worsening headaches including migraine headaches**
- **depression**
- **possible cancer in your breast and cervix**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider if you have a swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher if you have a history of angioedema.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Women who tend to get chloasma should avoid spending a long time in sunlight, tanning booths, and under sun lamps while taking LO/OVRAL-28. Use sunscreen if you have to be in the sunlight.

### **What are the most common side effects of LO/OVRAL-28?**

- headache
- nausea
- acne
- vaginal infections/discharge

- menstrual cramps
- breast tenderness
- depression
- increased appetite
- stomach discomfort
- nervousness
- backache
- irregular uterine bleeding
- skin discoloration
- worsening varicose veins

These are not all the possible side effects of LO/OVRAL-28. For more information, ask your healthcare provider or pharmacist.

You may report side effects to the FDA at 1-800-FDA-1088.

### **What else should I know about taking LO/OVRAL-28?**

- If you are scheduled for any lab tests, tell your healthcare provider you are taking LO/OVRAL-28. Certain blood tests may be affected by LO/OVRAL-28.
- LO/OVRAL-28 does not protect against HIV infection (AIDS) and other sexually transmitted infections.

### **How should I store LO/OVRAL-28?**

- Store LO/OVRAL-28 at room temperature between 68°F to 77°F (20°C to 25°C).
- Store away from light.
- Keep LO/OVRAL-28 and all medicines out of the reach of children.

### **General information about the safe and effective use of LO/OVRAL-28.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LO/OVRAL-28 for a condition for which it was not prescribed. Do not give LO/OVRAL-28 to other people.

This Patient Information summarizes the most important information about LO/OVRAL-28. You can ask your pharmacist or healthcare provider for information about LO/OVRAL-28 that is written for health professionals.

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

It is not known if hormonal birth control pills causes breast cancer. Some studies, but not all, suggest that there could be a slight increase in the risk of breast cancer among current users with longer duration of use.

If you have breast cancer now, or have had it in the past, do not use hormonal birth control because some breast cancers are sensitive to hormones.

### **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.

### **What should I know about my period when taking LO/OVRAL-28?**

Your periods may be lighter and shorter than usual. Some women may miss a period. Irregular vaginal bleeding or spotting may happen while you are taking LO/OVRAL-28, especially during the first few months of use. This usually is not a serious problem. It is important to continue taking your pills on a regular schedule to prevent a pregnancy.

### **What are the ingredients in LO/OVRAL-28?**

#### **Active ingredients:**

White pills: norgestrel and ethinyl estradiol

#### **Inactive ingredients:**

White pills: lactose monohydrate, magnesium stearate, microcrystalline cellulose, and polacrillin potassium.

Brown pills: ferrous fumarate, methylcellulose, starch, lactose anhydrous, and magnesium stearate.

## INSTRUCTIONS FOR USE

### LO/OVRAL-28 [*Low-O-Vral 28*]

(norgestrel and ethinyl estradiol tablets and ferrous fumarate tablets)

#### Important Information about taking LO/OVRAL-28

- Take **1** pill every day at the same time. Take the pills in the order directed on your blister pack.
- Do not skip your pills, even if you do not have sex often. If you miss pills (including starting the pack late), **you could get pregnant**. The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take LO/OVRAL-28, talk to your healthcare provider.
- When you first start taking LO/OVRAL-28, spotting or light bleeding in-between your periods may occur. Contact your healthcare provider if this does not go away after a few months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking LO/OVRAL-28. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If your nausea does not go away, call your healthcare provider.
- Missing pills can also cause spotting or light bleeding, even when you take the 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.
- It is not uncommon to miss a period. However, if you miss a period and have not taken LO/OVRAL-28 according to directions, or miss **2** periods in a row, or feel like you may be pregnant, call your healthcare provider. If you have a positive pregnancy test, you should stop taking LO/OVRAL-28.
- If you have vomiting or diarrhea within **3 to 4** hours of taking a white active pill, take another white pill from your extra blister pack. If you do not have an extra blister pack, take the next white pill in your blister pack. Continue taking all your remaining pills in order. Start the first pill of your next blister pack the day after finishing your current blister pack. This will be 1 day earlier than originally scheduled. Continue on your new schedule.
- If you have vomiting or diarrhea for more than 1 day, your birth control pills may not work as well. Use an additional birth control method, like condoms or a spermicide, until you check with your healthcare provider.
- Stop taking LO/OVRAL-28 at least **4** weeks before you have major surgery and do not restart after the surgery without asking your healthcare provider. Be sure to use other forms of contraception (like condoms or spermicide) during this time period.

#### Before you start taking LO/OVRAL-28:

- Decide what time of day you want to take your pill. It is important to take it at the same time every day and in the order as directed on your blister pack.
- Have backup contraception (condoms or spermicide) available and if possible, an extra full pack of pills as needed.

## When should I start taking LO/OVRAL-28?

**If you start taking LO/OVRAL-28 and you have not used a hormonal birth control method before:**

- There are 2 ways to start taking your birth control pills. You can either start on a Sunday (Sunday Start) or on the first day (Day 1) of your natural menstrual period (Day 1 Start). Your healthcare provider should tell you when to start taking your birth control pill.
- If you use the Sunday Start, use non-hormonal back-up contraception such as condoms or spermicide for the first 7 days that you take LO/OVRAL-28. You do not need back-up contraception if you use the Day 1 Start.

**If you start taking LO/OVRAL-28 and you are switching from another birth control pill:**

- Start your new LO/OVRAL-28 pack the day after the last tablet of your previous birth control method.
- Do not continue taking the pills from your previous birth control pack.

**If you start taking LO/OVRAL-28 and previously used a vaginal ring or transdermal patch:**

- Start using LO/OVRAL-28 on the day you would have reapplied the next ring or patch.

**If you start taking LO/OVRAL-28 and you are switching from a progestin-only method such as an implant or injection:**

- Start taking LO/OVRAL-28 on the day of removal of your implant or on the day when you would have had your next injection.

**If you start taking LO/OVRAL-28 and you are switching from an intrauterine device or system (IUD or IUS):**

- Start taking LO/OVRAL-28 on the day of removal of your IUD or IUS.
- You do not need back-up contraception if your IUD or IUS is removed on the first day (Day 1) of your period. If your IUD or IUS is removed on any other day, use non-hormonal back-up contraception such as condoms or spermicide for the first 7 days that you take LO/OVRAL-28.

**Keep a calendar to track your period:**

**If this is the first time** you are taking birth control pills, read, “**When should I start taking LO/OVRAL-28?**” above. Follow these instructions for either a **Sunday Start** or a **Day 1 Start**.

**Sunday Start:**

You will use a **Sunday Start** if your healthcare provider told you to take your first pill on a Sunday.

- Take pill **1** on the Sunday **after your period starts**.
- If your period starts on a Sunday, take pill “**1**” that day and refer to Day 1 Start instructions below.
- Take **1** pill every day in the order on the blister pack at the same time each day for **28** days.

- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack (Sunday). Take the first pill in the new pack whether or not you are having your period.
- Use non-hormonal back-up contraception such as condoms or spermicide for the first 7 days of the first cycle that you take LO/OVRAL-28.

### Day 1 Start:

You will use a **Day 1 Start** if your doctor told you to take your first pill (Day 1) on the **first day of your period**.

- Take **1** pill every day in the order of the blister pack, at the same time each day, for **28** days.
- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack. Take the first pill in the new pack whether or not you are having your period.

### Instructions for using your pill pack:

#### Step 1.

Look at your LO/OVRAL-28 pill pack. See **Figure A**.

The LO/OVRAL-28 pill pack has:

- **21** "active" white pills (with hormones) to be taken for **21** days
- **7** "inactive" brown pills (without hormones) to be taken for the next **7** days

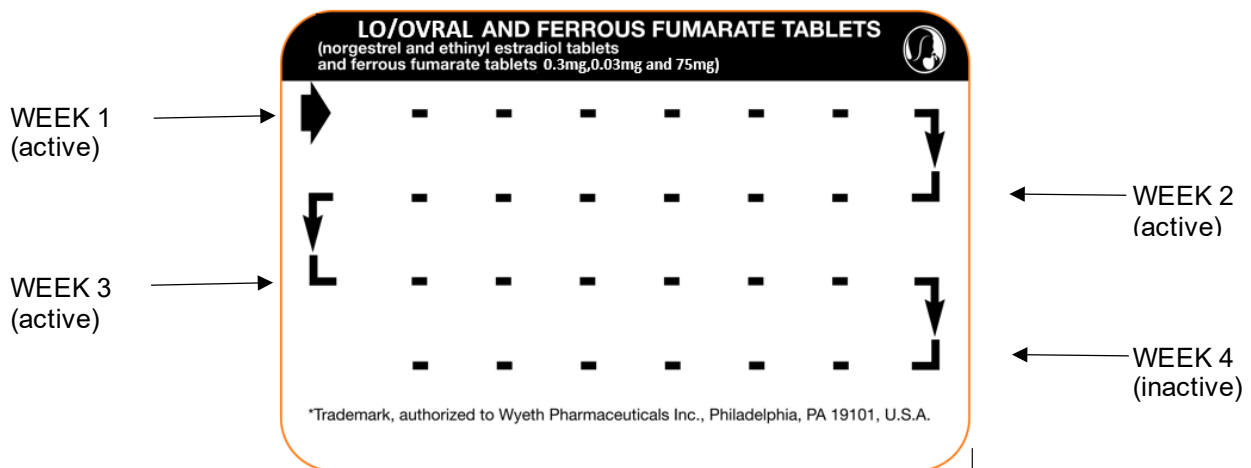


Figure A

#### Step 2.

Find:

- Where on the pack to start taking pills (look for white pill next to the large arrow)
- In what order to take the pills (follow the arrows). Follow the arrows shown in **Figure A**

### Step 3.

Remove the white pill by pressing the pill through the foil in the bottom of the pill pack. See **Figure B**. Continue taking the white pills for 21 days.

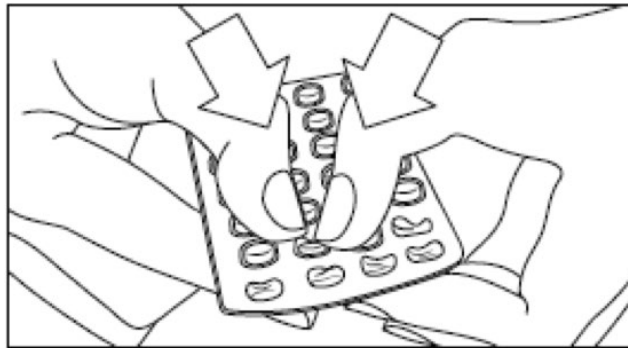


Figure B

### Step 4.

On the first day of **Week 4** start taking the brown pills. Take the brown pill for **7 days**. Your period should start during this time.

### Step 5.

When you have taken all of the brown pills in your pill pack, get a new pill pack and start taking the white pills.

- **For a Day 1 start:**

Begin your next pill pack on the same day of the week as your first cycle pill pack.

- **For a Sunday Start:**

Begin your next pill pack on Sunday.

### What should I do if I miss any LO/OVRAL-28 white pills?

#### If you miss 1 pill in Weeks 1, 2, or 3, follow these steps:

- Take it as soon as you remember. Take the next pill at your regular time. This means you may take **2 pills in 1 day**.
- Then continue taking **1 pill every day** until you finish the pack.
- You do not need to use a back-up birth control method if you have sex.

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

- Take the 2 missed pills as soon as possible and the next 2 pills the next day.
- Then continue to take 1 pill every day until you finish the pack.
- Use a non-hormonal birth control method (such as a condom or spermicide) as a back-up if you have sex during the first 7 days after missing your pills.

**If you miss 2 pills in a row in Week 3, or you miss 3 or more pills in a row at any time, follow these steps:**

- **If you are a Day 1 Starter:**
  - Throw out the rest of the pill pack and start a new pack that same day.
- **If you are a Sunday Starter:**
  - Keep taking 1 pill every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of pills 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 **SHOULD** use a non-hormonal birth control method (such as a condom or spermicide) as a back-up if you have sex during the first 7 days after you restart your pills.

**If you miss any of the 7 brown inactive pills in Week 4**, throw away the pills you missed and keep taking 1 pill each day until the pack is empty. You do not need to use a back-up method of birth control.

**If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.**

**Manufactured by: Wyeth Pharmaceuticals Inc.  
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This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

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