

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORTHO TRI-CYCLEN<sup>®</sup> Lo safely and effectively. See full prescribing information for ORTHO TRI-CYCLEN Lo.

ORTHO TRI-CYCLEN Lo (norgestimate/ethinyl estradiol) tablets for oral use

Initial U.S. Approval: 1989

### WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- ORTHO TRI-CYCLEN Lo 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)

### INDICATIONS AND USAGE

ORTHO TRI-CYCLEN Lo is an estrogen/progestin COC, indicated for use by women to prevent pregnancy. (1.1)

### DOSAGE AND ADMINISTRATION

- Take one tablet daily by mouth at the same time every day. (2.2)
- Take tablets in the order directed on the blister pack. (2.2)
- Do not skip or delay tablet intake. (2.2)

### DOSAGE FORMS AND STRENGTHS

ORTHO TRI-CYCLEN Lo consists of 28 round, convex, coated tablets in the following order (3):

- 7 white tablets each containing 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 light blue tablets each containing 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 dark blue tablets each containing 0.250 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 dark green tablets (inert)

### CONTRAINDICATIONS

- A high risk of arterial or venous thrombotic diseases (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)

### WARNINGS AND PRECAUTIONS

- **Thromboembolic Disorders and Other Vascular Problems:** Stop ORTHO TRI-CYCLEN Lo if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- **Liver disease:** Discontinue ORTHO TRI-CYCLEN Lo if jaundice occurs. (5.2)
- **High blood pressure:** If used in women with well-controlled hypertension, monitor blood pressure and stop ORTHO TRI-CYCLEN Lo if blood pressure rises significantly. (5.3)
- **Carbohydrate and lipid metabolic effects:** Monitor prediabetic and diabetic women taking ORTHO TRI-CYCLEN Lo. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.5)
- **Headache:** Evaluate significant change in headaches and discontinue ORTHO TRI-CYCLEN Lo if indicated. (5.6)
- **Bleeding Irregularities and Amenorrhea:** Evaluate irregular bleeding or amenorrhea. (5.7)

### ADVERSE REACTIONS

The most common adverse reactions reported during clinical trials ( $\geq 2\%$ ) were: headache/migraine, nausea/vomiting, breast issues, abdominal pain, menstrual disorders, mood disorders, acne, vulvovaginal infection, abdominal distension, weight increased, fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceutical, Inc. at 1-800-JANSSEN (1-800-526-7736) 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 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: 07/2015

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

#### 1 INDICATIONS AND USAGE

##### 1.1 Oral Contraception

#### 2 DOSAGE AND ADMINISTRATION

##### 2.1 How to Start ORTHO TRI-CYCLEN Lo

##### 2.2 How to Take ORTHO TRI-CYCLEN Lo

##### 2.3 Missed Tablets

##### 2.4 Advice in Case of Gastrointestinal Disturbances

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Thromboembolic Disorders and Other Vascular Problems

##### 5.2 Liver Disease

##### 5.3 High Blood Pressure

##### 5.4 Gallbladder Disease

##### 5.5 Carbohydrate and Lipid Metabolic Effects

##### 5.6 Headache

##### 5.7 Bleeding Irregularities

##### 5.8 COC Use Before or During Early Pregnancy

##### 5.9 Depression

##### 5.10 Carcinoma of the Breasts and Cervix

##### 5.11 Effect on Binding Globulins

##### 5.12 Monitoring

##### 5.13 Hereditary Angioedema

##### 5.14 Chloasma

#### 6 ADVERSE REACTIONS

##### 6.1 Clinical Trial Experience

##### 6.2 Postmarketing Experience

#### 7 DRUG INTERACTIONS

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

##### 7.2 Effects of Combined Hormonal Contraceptives on Other Drugs

##### 7.3 Interference with Laboratory Tests

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

##### 8.3 Nursing Mothers

##### 8.4 Pediatric Use

##### 8.5 Geriatric Use

##### 8.6 Hepatic Impairment

##### 8.7 Renal Impairment

#### 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, and 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.

## FULL PRESCRIBING INFORMATION

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

### 1 INDICATIONS AND USAGE

#### 1.1 Oral Contraception

ORTHO TRI-CYCLEN Lo Tablets are indicated for use by females of reproductive potential to prevent pregnancy [see *Clinical Studies (14)*].

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 How to Start ORTHO TRI-CYCLEN Lo

ORTHO TRI-CYCLEN Lo is dispensed in either a DIALPAK Tablet dispenser or a VERIDATE Tablet Dispenser [see *How Supplied/Storage and Handling (16)*]. ORTHO TRI-CYCLEN Lo 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 ORTHO TRI-CYCLEN Lo

Table 1: Instructions for Administration of ORTHO TRI-CYCLEN Lo	
<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>ORTHO TRI-CYCLEN Lo active tablets are white (Day 1 to Day 7), light blue (Day 8 to Day 15), and dark blue (Day 16 to Day 21).</li></ul>	<p><b>Day 1 Start:</b></p> <ul style="list-style-type: none"><li>Take first active tablet without regard to meals on the first day of menses.</li><li>Take subsequent active tablets once daily at the same time each day for a total of 21 days.</li><li>Take one <b>dark green</b> inactive 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 inactive tablet)</li></ul>

	<p><b>Sunday Start:</b></p> <ul style="list-style-type: none"> <li>Take first active tablet without regard to meals 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 and spermicide) for the first seven days of the patient's first cycle pack of ORTHO TRI-CYCLEN Lo.</b></li> <li>Take subsequent active tablets once daily at the same time each day for a total of 21 days.</li> <li>Take one <b>dark green</b> inactive 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 inactive tablet) and additional non-hormonal contraceptive is not needed.</li> </ul>
<b>Switching to ORTHO TRI-CYCLEN Lo from another oral contraceptive</b>	Start on the same day that a new pack of the previous oral contraceptive would have started.
<b>Switching from another contraceptive method to ORTHO TRI-CYCLEN Lo</b>	<b>Start ORTHO TRI-CYCLEN Lo:</b>
<ul style="list-style-type: none"> <li><b>Transdermal patch</b></li> </ul>	<ul style="list-style-type: none"> <li>On the day when next application would have been scheduled</li> </ul>
<ul style="list-style-type: none"> <li><b>Vaginal ring</b></li> </ul>	<ul style="list-style-type: none"> <li>On the day when next insertion would have been scheduled</li> </ul>
<ul style="list-style-type: none"> <li><b>Injection</b></li> </ul>	<ul style="list-style-type: none"> <li>On the day when next injection would have been scheduled</li> </ul>
<ul style="list-style-type: none"> <li><b>Intrauterine contraceptive</b></li> </ul>	<ul style="list-style-type: none"> <li>On the day of removal</li> <li>If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraceptive (such as condoms and spermicide) is needed for the first seven days of the first cycle pack.</li> </ul>
<ul style="list-style-type: none"> <li><b>Implant</b></li> </ul>	<ul style="list-style-type: none"> <li>On the day of removal</li> </ul>
<b>Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-Approved Patient Labeling.</b>	

### Starting ORTHO TRI-CYCLEN Lo after Abortion or Miscarriage

#### *First-trimester*

- After a first-trimester abortion or miscarriage, ORTHO TRI-CYCLEN Lo may be started immediately. An additional method of contraception is not needed if ORTHO TRI-CYCLEN Lo is started immediately.
- If ORTHO TRI-CYCLEN Lo is not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of her first cycle pack of ORTHO TRI-CYCLEN Lo.

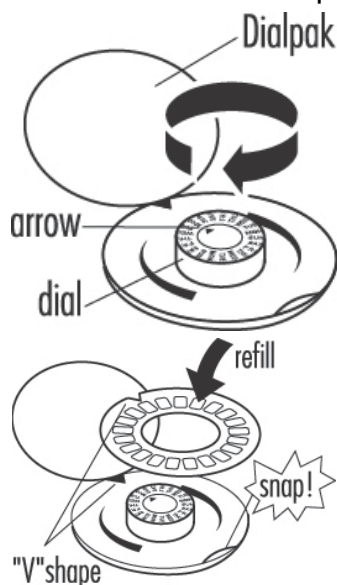
## Second-trimester

- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start ORTHO TRI-CYCLEN Lo, following the instructions in Table 1 for Day 1 or Sunday start, as desired. If using Sunday start, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of ORTHO TRI-CYCLEN Lo. [See Contraindications (4), Warnings and Precautions (5.1), and FDA-Approved Patient Labeling.]

## Starting ORTHO TRI-CYCLEN Lo after Childbirth

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

## DIALPAK<sup>®</sup> Tablet Dispenser:



### SET THE DAY:

- **Day 1 Start:** turn the dial on the *empty* DIALPAK until the arrow points to the first day of the patient's period.
- **Sunday Start:** the arrow on the *empty* DIALPAK should point to SU (Sunday).

Insert the new refill by lining up the “V” shape on the refill with the “V” shape at the top of the DIALPAK. Snap the refill in place. Pill “1” is ready to be taken. Always begin the pill cycle with pill “1,” as shown on the inner part of the refill ring.



Remove pill “1” by pushing down on the pill. The pill will come out through a hole in the back of the DIALPAK.

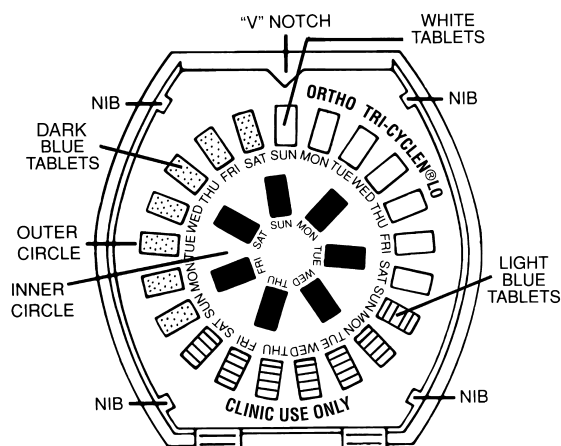
The patient should wait 24 hours to take the next pill. To take pill “2,” turn the dial on the DIALPAK in a clockwise direction to the next day. Continue to take one pill each day until all the pills have been taken.

Turn the dial to the pill “1” position to remove the empty refill and insert a new refill. The first pill in every refill will always be taken on the same day of the week, no matter when the patient’s next period starts.

### VERIDATE® Tablet Dispenser

- Place the refill in the VERIDATE Tablet Dispenser so that the **V** notch in the refill is at the top of the dispenser. Press the refill down so that it fits firmly under all the nibs (see illustration below).

- If the patient starts pill-taking on Sunday, the first active pill should be taken on the first Sunday after the patient’s menstrual period begins. Remove the first active pill at the top of the dispenser (Sunday) by pressing the pill through the hole in the bottom of the dispenser.



- If the patient will start pill-taking on a day other than Sunday, a calendar label has been provided and should be placed over the calendar in the center of the VERIDATE. To place the label correctly, identify the correct starting day, locate that day printed in blue on the label, and line that day up with the first white pill directly under the V notch at the top of the dispenser. Remove the label from the backing. Press the center of the label down onto the center of the printed calendar. Remove that white pill by pressing the pill through the hole in the bottom of the dispenser.
- After all the dark green pills have been taken, insert a new refill into the VERIDATE. The patient should take the first pill on the next day, even if the patient’s period is not over yet.

### To Insert New Refill:

- Lift the empty refill out of the VERIDATE Tablet Dispenser.
- Insert the new refill so that the V notch in the refill is at the top of the dispenser. Press the refill down so that it fits firmly under the nibs.

### 2.3 Missed Tablets

<b>Table 2: Instructions for Missed ORTHO TRI-CYCLEN Lo Tablets</b>	
• If one active tablet is missed in Weeks 1, 2, or 3	Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.
• If two active tablets are missed in Week 1 or Week 2	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 and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.</b>
• If two active tablets are missed in the third	<u>Day 1 start:</u> Throw out the rest of the pack and start a

week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	new pack that same day. <u>Sunday start:</u> Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. <b>Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.</b>
--	--

## 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 an active tablet, handle this as a missed tablet [see FDA-Approved Patient Labeling].

## 3 DOSAGE FORMS AND STRENGTHS

ORTHO TRI-CYCLEN Lo Tablets are available in a blister card. Each blister card contains 28 tablets in the following order:

- 7 white, round convex, coated tablet imprinted “O-M” on one side and “180” on the other side of the tablet contains 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 light blue, round convex, coated tablet imprinted “O-M” on one side and “215” on the other side of the tablet contains 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 dark blue, round convex, coated tablet imprinted “O-M” on one side and “250” on the other side of the tablet contains 0.250 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 dark green, round convex, coated tablet imprinted “O-M” on one side and “P” on the other side of the tablet contains inert ingredients

## 4 CONTRAINDICATIONS

Do not prescribe ORTHO TRI-CYCLEN Lo 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 inherited or acquired hypercoagulopathies [see Warnings and Precautions (5.1)]
  - Have cerebrovascular disease [see Warnings and Precautions (5.1)]
  - Have coronary artery disease [see Warnings and Precautions (5.1)]
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see Warnings and Precautions (5.1)]
  - Have uncontrolled hypertension [see Warnings and Precautions (5.3)]

- Have diabetes mellitus with vascular disease [*see Warnings and Precautions (5.5)*]
- Have headaches with focal neurological symptoms or migraine headaches with aura [*see Warnings and Precautions (5.6)*]
  - Women over age 35 with any migraine headaches [*see Warnings and Precautions (5.6)*]
- Liver tumors, benign or malignant, or liver disease [*see Warnings and Precautions (5.2)*]
- Undiagnosed abnormal uterine bleeding [*see Warnings and Precautions (5.7)*]
- Pregnancy, because there is no reason to use COCs during pregnancy [*see Warnings and Precautions (5.8)* and *Use in Specific Populations (8.1)*]
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past [*see Warnings and Precautions (5.10)*]

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Thromboembolic Disorders and Other Vascular Problems**

- Stop ORTHO TRI-CYCLEN Lo if an arterial thrombotic event or venous thrombotic (VTE) event occurs.
- Stop ORTHO TRI-CYCLEN Lo if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately [*see Adverse Reactions (6.2)*].
- If feasible, stop ORTHO TRI-CYCLEN Lo 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 ORTHO TRI-CYCLEN Lo no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued.
- Use of COCs also increases the risk of arterial thromboses such as 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 ORTHO TRI-CYCLEN Lo 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 ORTHO TRI-CYCLEN Lo if jaundice develops.

### **Liver Tumors**

ORTHO TRI-CYCLEN Lo 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/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 High Blood Pressure**

ORTHO TRI-CYCLEN Lo 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 ORTHO TRI-CYCLEN Lo 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.

## **5.4 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.

## **5.5 Carbohydrate and Lipid Metabolic Effects**

Carefully monitor prediabetic and diabetic women who take ORTHO TRI-CYCLEN Lo. COCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

## **5.6 Headache**

If a woman taking ORTHO TRI-CYCLEN Lo develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue ORTHO TRI-CYCLEN Lo if indicated.

Consider discontinuation of ORTHO TRI-CYCLEN Lo in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event).

## **5.7 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.

In the clinical trial of ORTHO TRI-CYCLEN Lo, the frequency and duration of unscheduled bleeding and/or spotting was assessed in 1,673 women (11,015 evaluable cycles). A total of 3 (0.2%) women discontinued ORTHO TRI-CYCLEN Lo, at least in part, due to bleeding or spotting. Based on data from the clinical trials, 7-17% of women using ORTHO TRI-CYCLEN Lo experienced unscheduled bleeding per cycle in the first year. The percent of women who experienced unscheduled bleeding tended to decrease over time.

### **Amenorrhea and Oligomenorrhea**

Women who use ORTHO TRI-CYCLEN Lo may experience amenorrhea. Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was pre-existent.

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.

## **5.8 COC Use Before or During Early Pregnancy**

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

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

## **5.9 Depression**

Carefully observe women with a history of depression and discontinue ORTHO TRI-CYCLEN Lo if depression recurs to a serious degree.

## **5.10 Carcinoma of Breast and Cervix**

- ORTHO TRI-CYCLEN Lo is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive [see *Contraindications (4)*].

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

## **5.11 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 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.

## **5.13 Hereditary Angioedema**

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

## **5.14 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 ORTHO TRI-CYCLEN Lo.

## 6 ADVERSE REACTIONS

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

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

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

### 6.1 Clinical Trial Experience

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

The safety of ORTHO TRI-CYCLEN Lo was evaluated in 1,723 subjects who participated in a randomized, partially blinded, multicenter, active-controlled clinical trial of ORTHO TRI-CYCLEN Lo for contraception. This trial examined healthy, nonpregnant, volunteers aged 18-45 (nonsmoker if 35-45 years of age), who were sexually active with regular coitus. Subjects were followed for up to 13 28-day cycles.

Common Adverse Reactions ( $\geq 2\%$  of subjects): The most common adverse reactions reported by at least 2% of the 1,723 women using the 28-day regimen were the following in order of decreasing incidence: headache/migraine (30.5%), nausea/vomiting (16.3%); breast issues (including tenderness, pain, enlargement, swelling, discharge, discomfort, cyst, and nipple pain) (10.3%), abdominal pain (9.2%), menstrual disorders (including dysmenorrhea, menstrual discomfort, menstrual disorder) (9.2%), mood disorders (including depression, mood altered, mood swings and depressed mood) (7.6%); acne (5.1%), vulvovaginal infection (3.5%), abdominal distension (2.8%), weight increased (2.4%), fatigue (2.1%).

Adverse Reactions Leading to Study Discontinuation: In the clinical trial of ORTHO TRI-CYCLEN Lo 4% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions leading to discontinuation were headache/migraine (1.2%), nausea/vomiting (0.7%), **cervical dysplasia (0.7%)**, abdominal pain (0.4%), ovarian cyst (0.3%), acne (0.2%), **flatulence (0.2%)** and depression (0.2%).

Serious Adverse Reactions: carcinoma of the cervix *in situ* (1 subject) and cervical dysplasia (1 subject).

## **6.2 Postmarketing Experience**

The following additional adverse drug reactions have been reported from worldwide postmarketing experience with norgestimate/ethinyl estradiol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Infections and Infestations:* Urinary tract infection

*Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps):* Breast cancer, benign breast neoplasm, hepatic adenoma, focal nodular hyperplasia, breast cyst

*Immune System Disorders:* Hypersensitivity

*Metabolism and Nutrition Disorders:* Dyslipidemia

*Psychiatric Disorders:* Anxiety, insomnia

*Nervous System Disorders:* Syncope, convulsion, paresthesia, dizziness

*Eye Disorders:* Visual impairment, dry eye, contact lens intolerance

*Ear and Labyrinth Disorders:* Vertigo

*Cardiac Disorders:* Tachycardia, palpitations

*Vascular Events:* Deep vein thrombosis, pulmonary embolism, retinal vascular thrombosis, hot flush

*Arterial Events:* Arterial thromboembolism, myocardial infarction, cerebrovascular accident

*Respiratory, Thoracic and Mediastinal Disorders:* Dyspnea

*Gastrointestinal Disorders:* Pancreatitis, abdominal distension, diarrhea, constipation

*Hepatobiliary Disorders:* Hepatitis

*Skin and Subcutaneous Tissue Disorders:* Angioedema, erythema nodosum, hirsutism, night sweats, hyperhidrosis, photosensitivity reaction, urticaria, pruritus, acne

*Musculoskeletal, Connective Tissue, and Bone Disorders:* Muscle spasms, pain in extremity, myalgia, back pain

*Reproductive System and Breast Disorders:* Ovarian cyst, suppressed lactation, vulvovaginal dryness

*General Disorders and Administration Site Conditions:* Chest pain, asthenic conditions.

## **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.

No drug-drug interaction studies were conducted with ORTHO TRI-CYCLEN Lo.

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

#### **Substances Decreasing the Plasma Concentrations 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 COCs include 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 method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

**Colesevelam:** Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of ethinyl estradiol (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 EE increase AUC values for EE by approximately 20-25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

## Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors

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

### **7.2 Effects of Combined Oral Contraceptives on Other Drugs**

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

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs.

### **7.3 Interference with Laboratory Tests**

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

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

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

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

### **8.3 Nursing Mothers**

Advise the nursing mother to use other forms of contraception, when possible, until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some

women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

#### **8.4 Pediatric Use**

Safety and efficacy of ORTHO TRI-CYCLEN Lo Tablets have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

#### **8.5 Geriatric Use**

ORTHO TRI-CYCLEN Lo has not been studied in postmenopausal women and is not indicated in this population.

#### **8.6 Hepatic Impairment**

The pharmacokinetics of ORTHO TRI-CYCLEN Lo 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 ORTHO TRI-CYCLEN Lo has not been studied in women with renal impairment.

### **10 OVERDOSAGE**

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

### **11 DESCRIPTION**

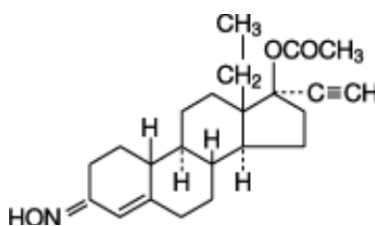
ORTHO TRI-CYCLEN Lo is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. Norgestimate is designated as (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime,(17 $\alpha$ )-(+)-) and ethinyl estradiol is designated as (19-nor-17 $\alpha$ -pregna,1,3,5(10)-trien-20-yne-3,17-diol).

- Each active white tablet contains 0.180 mg of norgestimate and 0.025 mg of ethinyl estradiol. Inactive ingredients include carnauba wax, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, purified water (removed during processing), and titanium dioxide.
- Each active light blue tablet contains 0.215 mg of norgestimate and 0.025 mg of ethinyl estradiol. Inactive ingredients include carnauba wax, croscarmellose sodium, FD & C Blue No. 2 Aluminum Lake, hypromellose, lactose, magnesium stearate, microcrystalline

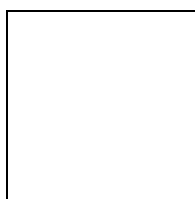


cellulose, polyethylene glycol, purified water (removed during processing), and titanium dioxide.

- Each active dark blue tablet contains 0.250 mg of norgestimate and 0.025 mg of ethinyl estradiol. Inactive ingredients include carnauba wax, croscarmellose sodium, FD & C Blue No. 2 Aluminum Lake, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, purified water (removed during processing), and titanium dioxide.
- Each dark green placebo tablet contains only inert ingredients, as follows: FD & C Blue No. 2 Aluminum Lake, ferric oxide, lactose, magnesium stearate, polyethylene glycol, pregelatinized corn starch, purified water, polyvinyl alcohol, talc, and titanium dioxide.



Norgestimate



Ethinyl Estradiol

## 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 ORTHO TRI-CYCLEN Lo.

### 12.3 Pharmacokinetics

#### Absorption

Norgestimate (NGM) and EE are rapidly absorbed following oral administration. NGM is rapidly and completely metabolized by first pass (intestinal and/or hepatic) mechanisms to norelgestromin (NGMN) and norgestrel (NG), which are the major active metabolites of NGM.

Mean pharmacokinetic parameters for NGMN, NG and EE during three cycles of administration of ORTHO TRI-CYCLEN Lo are summarized in Table 3.

Peak serum concentrations of NGMN and EE were generally reached by 2 hours after administration of ORTHO TRI-CYCLEN Lo. Accumulation following multiple dosing of the 0.180 mg NGM / 0.025 mg EE dose is approximately 1.5 to 2 fold for NGMN and approximately 1.5 fold for EE compared with single dose administration, in agreement with that predicted based on linear kinetics of NGMN and EE. The pharmacokinetics of NGMN is dose proportional following NGM doses of 0.180 to 0.250 mg. Steady-state conditions for NGMN following each NGM dose and for EE were achieved during the three cycle study. Non-linear accumulation (4.5-14.5 fold) of NG was observed as a result of high affinity binding to SHBG, which limits its biological activity.

Table 3 Summary of NGMN, NG and EE pharmacokinetic parameters.

**Table 3: Mean (SD) Pharmacokinetic Parameters of ORTHO TRI-CYCLEN Lo During a Three Cycle Study**

Analyte <sup>1</sup>	Cycle	Day	C <sub>max</sub>	t <sub>max</sub> (h)	AUC <sub>0-24h</sub>	t <sub>1/2</sub> (h)
<b>NGMN</b> <sup>(2-4)</sup>	<b>1</b>	<b>1</b>	<b>0.91</b> (0.27)	<b>1.8</b> (1.0)	<b>5.86</b> (1.54)	<b>NC</b>
	<b>3</b>	<b>7</b>	<b>1.42</b> (0.43)	<b>1.8</b> (0.7)	<b>11.3</b> (3.2)	<b>NC</b>
		<b>14</b>	<b>1.57</b> (0.39)	<b>1.8</b> (0.7)	<b>13.9</b> (3.7)	<b>NC</b>
		<b>21</b>	<b>1.82</b> (0.54)	<b>1.5</b> (0.7)	<b>16.1</b> (4.8)	<b>28.1</b> (10.6)
<b>NG</b> <sup>(2-4)</sup>	<b>1</b>	<b>1</b>	<b>0.32</b> (0.14)	<b>2.0</b> (1.1)	<b>2.44</b> (2.04)	<b>NC</b>
	<b>3</b>	<b>7</b>	<b>1.64</b> (0.89)	<b>1.9</b> (0.9)	<b>27.9</b> (18.1)	<b>NC</b>
		<b>14</b>	<b>2.11</b> (1.13)	<b>4.0</b> (6.3)	<b>40.7</b> (24.8)	<b>NC</b>
		<b>21</b>	<b>2.79</b> (1.42)	<b>1.7</b> (1.2)	<b>49.9</b> (27.6)	<b>36.4</b> (10.2)
<b>EE</b> <sup>(2,3,5)</sup>	<b>1</b>	<b>1</b>	<b>55.6</b> (18.1)	<b>1.7</b> (0.5)	<b>421</b> (118)	<b>NC</b>
	<b>3</b>	<b>7</b>	<b>91.1</b> (36.7)	<b>1.3</b> (0.3)	<b>782</b> (329)	<b>NC</b>
		<b>14</b>	<b>96.9</b> (38.5)	<b>1.3</b> (0.3)	<b>796</b> (273)	<b>NC</b>
		<b>21</b>	<b>95.9</b> (38.9)	<b>1.3</b> (0.6)	<b>771</b> (303)	<b>17.7</b> (4.4)

<sup>1</sup> NGMN = Norelgestromin, NG = norgestrel, EE = ethinyl estradiol

<sup>2</sup> C<sub>max</sub> = peak serum concentration, t<sub>max</sub> = time to reach peak serum concentration, AUC<sub>0-24h</sub> = area under serum concentration vs. time curve from 0 to 24 hours, t<sub>1/2</sub> = elimination half-life.

<sup>3</sup> units for all analytes; h = hours

<sup>4</sup> units for NGMN and NG – C<sub>max</sub> = ng/mL, AUC<sub>0-24h</sub> = h•ng/mL

<sup>5</sup> units for EE only – C<sub>max</sub> = pg/mL, AUC<sub>0-24h</sub> = h•pg/mL

NC = not calculated

### *Food Effect*

The effect of food on the pharmacokinetics of ORTHO TRI-CYCLEN Lo has not been studied.

### Distribution

NGMN and NG are highly bound (>97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while NG is bound primarily to SHBG. EE is extensively bound (>97%) to serum albumin and induces an increase in the serum concentrations of SHBG.

## Metabolism

NGM is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. NGM's primary active metabolite is NGMN. Subsequent hepatic metabolism of NGMN occurs and metabolites include NG, which is also active and various hydroxylated and conjugated metabolites. Although NGMN and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, under the recommended dosing regimen, the *in vivo* concentrations of NGMN and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant ( $K_i$ ). EE is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

## Excretion

Following 3 cycles of administration of ORTHO TRI-CYCLEN Lo, the mean ( $\pm$  SD) elimination half-life values, at steady-state, for NGMN, NG and EE were 28.1 ( $\pm$  10.6) hours, 36.4 ( $\pm$  10.2) hours and 17.7 ( $\pm$  4.4) hours, respectively (Table 2). The metabolites of NGMN and EE are eliminated by renal and fecal pathways.

## Use in Specific Populations

### *Effects of Body Weight, Body Surface Area, and Age*

The effects of body weight, body surface area, age and race on the pharmacokinetics of NGMN, NG and EE were evaluated in 79 healthy women using pooled data following single dose administration of NGM 0.180 or 0.250 mg / EE 0.025 mg tablets in four pharmacokinetic studies. Increasing body weight and body surface area were each associated with decreases in  $C_{max}$  and  $AUC_{0-24h}$  values for NGMN and EE and increases in CL/F (oral clearance) for EE. Increasing body weight by 10 kg is predicted to reduce the following parameters: NGMN  $C_{max}$  by 9% and  $AUC_{0-24h}$  by 19%, NG  $C_{max}$  by 12% and  $AUC_{0-24h}$  by 46%, EE  $C_{max}$  by 13% and  $AUC_{0-24h}$  by 12%. These changes were statistically significant. Increasing age was associated with slight decreases (6% with increasing age by 5 years) in  $C_{max}$  and  $AUC_{0-24h}$  for NGMN and were statistically significant, but there was no significant effect for NG or EE. Only a small to moderate fraction (5-40%) of the overall variability in the pharmacokinetics of NGMN and EE following ORTHO TRI-CYCLEN Lo Tablets may be explained by any or all of the above demographic parameters.

## **13 NONCLINICAL TOXICOLOGY**

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

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

## **14 CLINICAL STUDIES**

In an active controlled clinical trial lasting 12 months, 1,673 women, 18 to 45 years old completed 11,003 cycles of ORTHO TRI-CYCLEN Lo use and a total of 20 pregnancies were reported in ORTHO TRI-CYCLEN Lo users. The racial demographic of those treated with ORTHO TRI-CYCLEN Lo was: Caucasian (86%), African-American (6%), Asian (2%), and Other (6%). There were no exclusions on the basis of weight; the weight range for women

treated was 90-240 lbs, with a mean weight of about 142 lbs. The pregnancy rate in women aged 18 to 35 years was approximately 2.6 pregnancies per 100 woman-years of use.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**

ORTHO TRI-CYCLEN Lo Tablets are available in a blister card with a DIALPAK Tablet Dispenser (unfilled): NDC 50458-251-00

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

- 7 white, round, convex, coated tablets (active) imprinted “O-M” on one side and “180” on the other side contains 0.180 mg, norgestimate and 0.025 mg ethinyl estradiol
- 7 light blue, round, convex, coated tablets (active) imprinted “O-M” on one side and “215” on the other side contains 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 dark blue, round, convex, coated tablets (active) imprinted “O-M” on one side and “250” on the other side contains 0.250 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 dark green, round, convex, coated tablets (non-hormonal placebo) imprinted “O-M” on one side and “P” on the other side contains inert ingredients

ORTHO TRI-CYCLEN Lo Tablets are packaged in a carton containing 6 blister cards and 6 unfilled DIALPAK Tablet Dispensers: NDC 50458-251-15

ORTHO TRI-CYCLEN Lo Tablets are available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE refills: NDC 50458-251-20

### **16.2 Storage Conditions**

- Store at 20-25°C (68-77°F); excursions permitted to 15° to 30°C (59° to 86°F).
- Protect from light.

## **17 PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Patient Information and Instruction 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)*].
- ORTHO TRI-CYCLEN Lo does not protect against HIV infection (AIDS) and other sexually transmitted infections.

- ORTHO TRI-CYCLEN Lo is not to be used during pregnancy; if pregnancy occurs during use of ORTHO TRI-CYCLEN Lo instruct the patient to stop further use [*see Warnings and Precautions (5.8)*].
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed [*see Dosage and Administration (2.2)*].
- Use a back-up or alternative method of contraception when enzyme inducers are used with ORTHO TRI-CYCLEN Lo [*see Drug Interactions (7.1)*].
- COCs may reduce breast milk production, this is less likely to occur if breastfeeding is well established [*see Use in Specific Populations (8.3)*].
- Women who start COCs postpartum; and who have not yet had a period, should use an additional method of contraception until they have 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 in the event of amenorrhea in two or more consecutive cycles [*see Warnings and Precautions (5.7)*].

Mfd. by:

Janssen Ortho, LLC

Manati, Puerto Rico 00674

Mfd. for:

Janssen Pharmaceuticals, Inc.

Titusville, New Jersey 08560

© Janssen Pharmaceuticals, Inc. 1998

Revised July 2015





























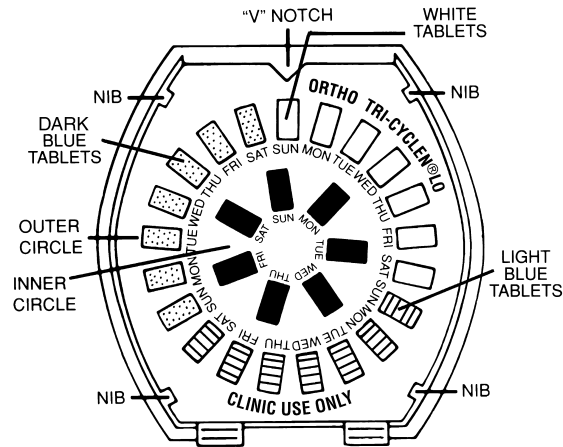




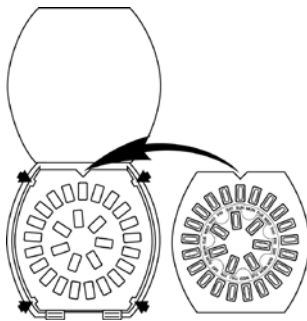


**Instructions for using your VERIDATE pill dispenser:**

- Each VERIDATE pill dispenser has 28 pills. See Figure A.  
**ORTHO TRI-CYCLEN Lo**
  - 7 white pills with hormone, for **Days 1 to 7**
  - 7 light blue pills with hormone, for **Days 8 to 14**
  - 7 dark blue pills with hormones, for **Days 15 to 21**
  - 7 dark green pills (without hormones), for **Days 22 to 28**



**Figure A**



**Figure B**

**Step 1.** Place the refill in the VERIDATE Pill Dispenser so that the "V" notch in the refill is at the top of the dispenser. Press the refill down so that it fits firmly under all the nibs. See Figure B.

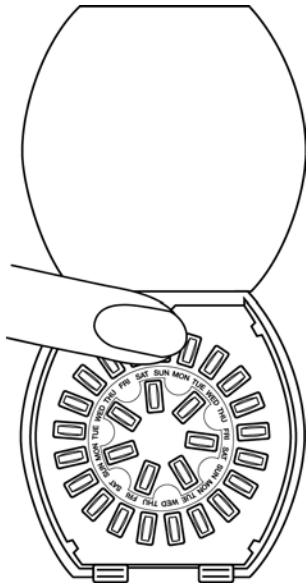


Figure C

## Step 2. Starting your pills.

**Sunday Start:** Remove the first pill at the top of the dispenser (**Sunday**) by pressing the pill through the hole in the bottom of the dispenser. **See Figure C.**

- If your healthcare provider tells you to start taking your pill on Sunday, take your first pill on the first Sunday after your period begins.
- If your period begins on Sunday, take your first pill that day.

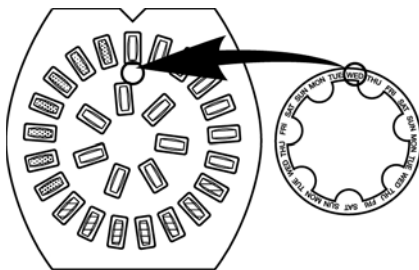


Figure D

## Day 1 Start:

• If your healthcare provider tells you to start taking your pill on a day other than Sunday, you will need the calendar label found in your pill package and place it over the calendar in the center of the VERIDATE. **See Figure D.**

- To correctly place the calendar label on the VERIDATE:
  - find your correct starting day
  - find that day printed in blue on the label
  - line your blue starting day up with the first white pill which is directly under the V notch at the top of the dispenser.
- Remove the label from the backing. Press the center of the label down onto the center of the printed calendar.
- Remove that white pill by pressing the pill through the hole in the bottom of the dispenser. **See Figure E.**

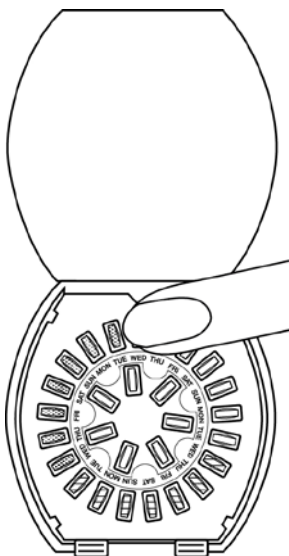
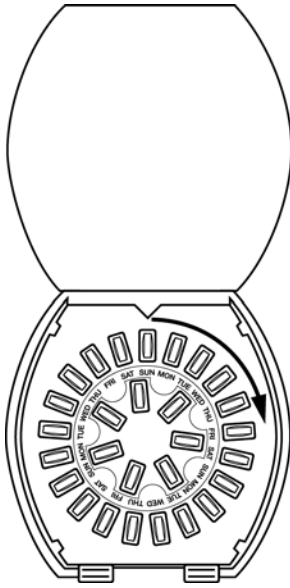
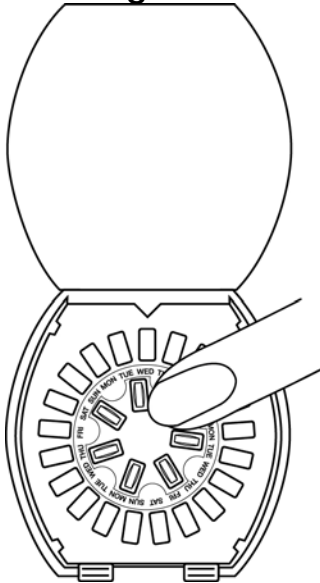


Figure E



**Figure F**

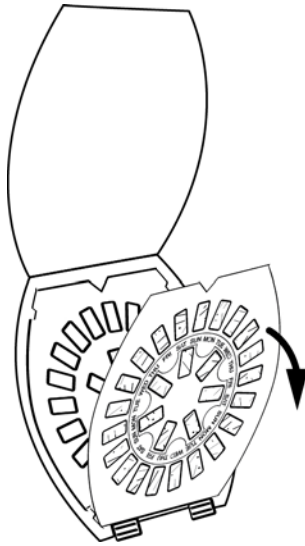
**Step 3. Continue taking 1 pill every day from the VERIDATE in a clockwise direction until no pills remain in the outer ring. See Figure F.**



**Figure G**

**Step 4. The next day take a dark green pill from the inner ring. See Figure G.**

- Continue to take a dark green pill each day until all 7 pills are taken.
- During this time your period should begin.



**Figure H**

**Step 5. Insert a new refill:**

- After you have taken all the dark green pills, insert a new refill into the VERIDATE and take the first pill on the next day, even if your period is not yet over.
- Lift the empty refill out of the VERIDATE Pill Dispenser. **See Figure H.**
- Follow the instructions in **Step 1** to replace the new refill.

**What should I do if I miss any ORTHO TRI-CYCLLEN Lo 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 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 and 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 during Weeks 1, 2, or 3 of the pack, 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.
- 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 if you have sex during the first **7** days after you restart your pills.

- **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.
- Use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7** days after you restart your pills.

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

Mfd. by:  
Janssen Ortho, LLC  
Manati, Puerto Rico 00674

Mfd. for:  
Janssen Pharmaceuticals, Inc.  
Titusville, New Jersey 08560

© Janssen Pharmaceuticals, Inc. 1998

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised July 2015