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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ORTHO-CYCLEN or ORTHO TRI-CYCLEN safely and effectively. See full prescribing information for ORTHO-CYCLEN and ORTHO TRI-CYCLEN.

ORTHO-CYCLEN® and ORTHO TRI-CYCLEN® (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-CYCLEN or ORTHO TRI-CYCLEN 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 (5.11) 04/2022

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

ORTHO-CYCLEN and ORTHO TRI-CYCLEN are estrogen/progestin COCs, indicated for use by women to prevent pregnancy. (1.1)

ORTHO TRI-CYCLEN is also indicated for the treatment of moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche.

ORTHO TRI-CYCLEN should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control. (1.2)

----------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-CYCLEN consists of 28 round, biconvex, coated tablets in the following order (3):
- 21 blue tablets each containing 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark green tablets (inert)

ORTHO TRI-CYCLEN consists of 28 round, biconvex, coated tablets in the following order (3):
- 7 white tablets each containing 0.180 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 light blue tablets each containing 0.215 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 blue tablets each containing 0.250 mg norgestimate and 0.035 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 (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

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

- Thromboembolic Disorders and Other Vascular Problems: Stop ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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-CYCLEN or ORTHO TRI-CYCLEN if jaundice occurs. (5.2)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop ORTHO-CYCLEN or ORTHO TRI-CYCLEN if blood pressure rises significantly. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue ORTHO-CYCLEN or ORTHO TRI-CYCLEN if indicated. (5.7)
- Bleeding Irregularities and Amenorrhea: Evaluate irregular bleeding or amenorrhea. (5.8)

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

The most common adverse reactions reported during clinical trials (≥2%) were:
ORTHO-CYCLEN: headache/migraine, abdominal/gastrointestinal pain, vaginal infection, genital discharge, breast issues (including breast pain, discharge, and enlargement), mood disorders (including depression and mood altered), flatulence, nervousness, rash. (6.1)
ORTHO TRI-CYCLEN: headache/migraine, breast issues (including breast pain, enlargement, and discharge), vaginal infection, abdominal/gastrointestinal pain, mood disorders (including mood alteration and depression), genital discharge, changes in weight (including weight increased or decreased). (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*.

----------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: 04/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 are contraindicated in women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

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

1.2 Acne

ORTHO TRI-CYCLEN is indicated for the treatment of moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. ORTHO TRI-CYCLEN should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 How to Start ORTHO-CYCLEN or ORTHO TRI-CYCLEN

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

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2.2 How to Take ORTHO-CYCLEN or ORTHO TRI-CYCLEN

Table 1: Instructions for Administration of ORTHO-CYCLEN or ORTHO TRI-CYCLEN

Starting COCs in women not currently using hormonal contraception (Day 1 Start or Sunday Start) **Important:** Consider the possibility of ovulation and conception prior to initiation of this product. **Tablet Color:** • ORTHO-CYCLEN active tablets are blue (Day 1 to Day 21). • ORTHO TRI-CYCLEN active tablets are white (Day 1 to Day 7), light blue (Day 8 to Day 14) and blue (Day 15 to Day 21). • ORTHO-CYCLEN and ORTHO TRI-CYCLEN both have dark green inactive tablets (Day 22 to Day 28).	**Day 1 Start:** • Take first active tablet without regard to meals on the first day of menses. • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one **dark green** inactive tablet daily for 7 days and at the same time of day that active tablets were taken. • 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)
	Sunday Start: • Take first active tablet without regard to meals on the first Sunday after the onset of menses. **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-CYCLEN or ORTHO TRI-CYCLEN.** • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one **dark green** inactive tablet daily for the following 7 days and at the same time of day that active tablets were taken. • 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.
Switching to ORTHO-CYCLEN or ORTHO TRI-CYCLEN from another oral contraceptive	Start on the same day that a new pack of the previous oral contraceptive would have started.
Switching from another contraceptive method to ORTHO-CYCLEN or ORTHO TRI-CYCLEN	**Start ORTHO-CYCLEN or ORTHO TRI-CYCLEN:**
• **Transdermal patch**	• On the day when next application would have been scheduled
• **Vaginal ring**	• On the day when next insertion would have been scheduled
• **Injection**	• On the day when next injection would have been scheduled
• **Intrauterine contraceptive**	• On the day of removal • If the IUD is not removed on first day of the

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	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.
• **Implant**	• On the day of removal
Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-Approved Patient Labeling.	

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

First-trimester

- After a first-trimester abortion or miscarriage, ORTHO-CYCLEN or ORTHO TRI-CYCLEN may be started immediately. An additional method of contraception is not needed if ORTHO-CYCLEN or ORTHO TRI-CYCLEN is started immediately.

- If ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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-CYCLEN or ORTHO TRI-CYCLEN.

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-CYCLEN or ORTHO TRI-CYCLEN, 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-CYCLEN or ORTHO TRI-CYCLEN. *[see Contraindications (4), Warnings and Precautions (5.1), and FDA-Approved Patient Labeling.]*

Starting ORTHO-CYCLEN or ORTHO TRI-CYCLEN after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with ORTHO-CYCLEN or ORTHO TRI-CYCLEN following the instructions in Table 1 for women not currently using hormonal contraception.

- ORTHO-CYCLEN or ORTHO TRI-CYCLEN are 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-CYCLEN or ORTHO TRI-CYCLEN. *[See Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1 and 8.3), and FDA-Approved Patient Labeling]*.

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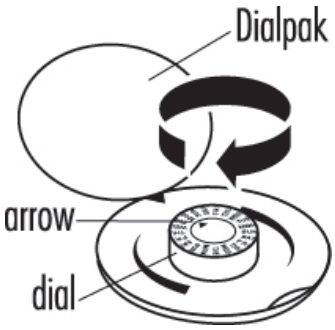
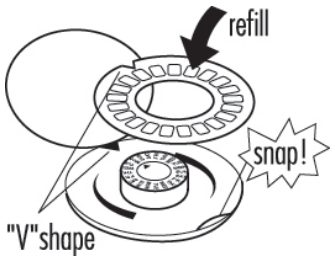
DIALPAK® Tablet Dispenser:



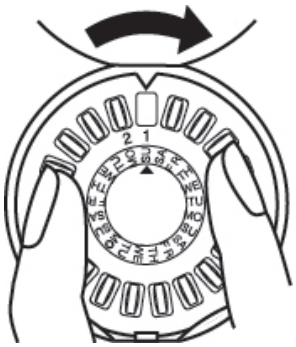
SET THE DAY:

- □ **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).

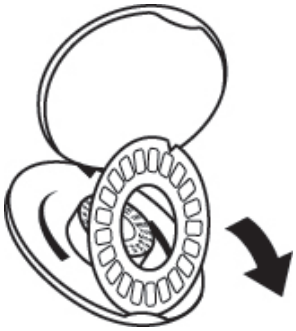


Insert the new refill by lining up the "**V**" shape on the refill with the "**V**" shape at the top of the DIALPAK. Snap the refill in place. Pill "**1**" is ready to be taken. Always begin the pill cycle with pill "**1**," as shown on the inner part of the refill ring.

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.

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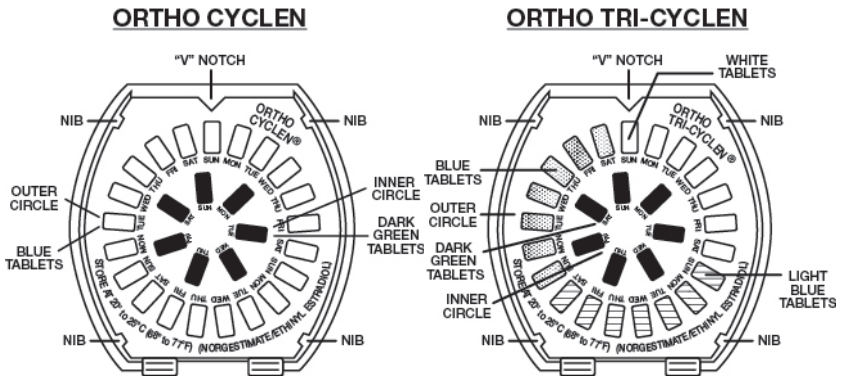
VERIDATE® Tablet Dispenser

- 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.



ORTHO-CYCLEN:

- If the patient will start pill-taking on "Day 1," choose a blue pill that corresponds with the day of the week the patient will take the first pill. Remove that blue pill by pressing the pill through the hole in the bottom of the dispenser.

ORTHO TRI-CYCLEN:

- 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 (ORTHO-CYCLEN or ORTHO TRI-CYCLEN):

- 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.

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2.3 Missed Tablets

Table 2: Instructions for Missed ORTHO-CYCLEN or ORTHO TRI-CYCLEN Tablets	
• 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. **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.**
• If two active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	Day 1 start: Throw out the rest of the pack and start a new pack that same day. Sunday start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. **Additional 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.**

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]*.

2.5 ORTHO-TRICYCLEN Use for Acne

The timing of initiation of dosing with ORTHO TRI-CYCLEN for acne should follow the guidelines for use of ORTHO TRI-CYCLEN as an oral contraceptive. Consult the DOSAGE AND ADMINISTRATION section (2.1) for instructions.

3 DOSAGE FORMS AND STRENGTHS

ORTHO-CYCLEN:

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

- 21 blue, round, biconvex, coated tablet imprinted "O 250" on one side and "35" on the other side of the tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark green round, biconvex, coated tablet (non-hormonal placebo) imprinted "O-M" on one side and "P" on the other side contains inert ingredients

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ORTHO TRI-CYCLEN:

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

- 7 white, round, biconvex, coated tablet imprinted "O 180" on one side and "35" on the other side of the tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 light blue, round, biconvex, coated tablet imprinted "O 215" on one side and "35" on the other side of the tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 blue, round, biconvex, coated tablet imprinted "O 250" on one side and "35" on the other side of the tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark green round, biconvex, coated tablet (non-hormonal placebo) imprinted "O-M" on one side and "P" on the other side contains inert ingredients

4 CONTRAINDICATIONS

ORTHO-CYCLEN and ORTHO TRI-CYCLEN are contraindicated in females who are known to have or develop the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or 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 Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*

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- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive *[see Warnings and Precautions (5.11)]*
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

- Stop ORTHO-CYCLEN or ORTHO TRI-CYCLEN if an arterial thrombotic event or venous thromboembolic (VTE) event occurs.

- Stop ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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-CYCLEN or ORTHO TRI-CYCLEN 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-CYCLEN or ORTHO TRI-CYCLEN 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-CYCLEN or ORTHO TRI-CYCLEN in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver *[see Contraindications (4)]*.

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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-CYCLEN or ORTHO TRI-CYCLEN if jaundice develops.

Liver Tumors

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

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the 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 women using ethinyl estradiol-containing medications, such as COCs. Discontinue ORTHO-CYCLEN or ORTHO TRI-CYCLEN prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. ORTHO-CYCLEN or ORTHO TRI-CYCLEN can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.4 High Blood Pressure

ORTHO-CYCLEN and ORTHO TRI-CYCLEN are contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop ORTHO-CYCLEN and ORTHO TRI-CYCLEN 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.

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5.6 Carbohydrate and Lipid Metabolic Effects

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

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

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

5.7 Headache

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

Consider discontinuation of ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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.

In clinical trials of ORTHO-CYCLEN and ORTHO TRI-CYCLEN, the frequency and duration of breakthrough bleeding and/or spotting was assessed in 1,647 patients (21,275 evaluable cycles) and 4,826 patients (35,546 evaluable cycles), respectively. A total of 100 (7.5%) women discontinued ORTHO-CYCLEN and 231 (4.8%) women discontinued ORTHO TRI-CYCLEN, at least in part, due to bleeding or spotting. Based on data from the clinical trials, 14-34% of women using ORTHO-CYCLEN experienced unscheduled bleeding per cycle in the first year; for ORTHO TRI-CYCLEN, the respective numbers were 13-38%. The percent of women who experienced breakthrough/unscheduled bleeding tended to decrease over time.

Amenorrhea and Oligomenorrhea

Women who use ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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

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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 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-CYCLEN or ORTHO TRI-CYCLEN 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)]*.

5.10 Depression

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

5.11 Malignant Neoplasms

Breast Cancer

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

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

Cervical Cancer

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

5.12 Effect on Binding Globulins

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

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5.13 Monitoring

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

5.14 Hereditary Angioedema

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

5.15 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking ORTHO TRI-CYCLEN or ORTHO-CYCLEN.

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.

ORTHO-CYCLEN

The safety of ORTHO-CYCLEN was evaluated in 1,647 healthy women of child-bearing potential who participated in 3 clinical trials and received at least 1 dose of ORTHO-CYCLEN for contraception. Two trials were randomized active-controlled trials and 1 was an uncontrolled open-label trial. In all 3 trials, subjects were followed for up to 24 cycles.

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Common Adverse Reactions (≥ 2% of subjects): The most common adverse reactions reported by at least 2% of the 1,647 women were the following in order of decreasing incidence: headache/migraine (32.9%), abdominal/gastrointestinal pain (7.8%), vaginal infection (8.4%), genital discharge (6.8%), breast issues (including breast pain, discharge, and enlargement) (6.3%), mood disorders (including depression and mood altered) (5.0%), flatulence (3.2%), nervousness (2.9%), and rash (2.6%).

Adverse Reactions Leading to Study Discontinuation: Over the three trials, between 11 to 21% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions (≥1%) leading to discontinuation were: metrorrhagia (6.9%), nausea/vomiting (5.0%), headache (4.1%), mood disorders (including depression and mood altered) (2.4%), premenstrual syndrome (1.7%), hypertension (1.4%), breast pain (1.4%), nervousness (1.3%), amenorrhea (1.1%), dysmenorrhea (1.1%), weight increased (1.1%), and flatulence (1.1%).

Serious Adverse Reactions: breast cancer (1 subject), mood disorders including depression, irritability, and mood swings (1 subject), myocardial infarction (1 subject), and venous thromboembolic events including pulmonary embolism (1 subject) and deep vein thrombosis (DVT) (1 subject).

ORTHO TRI-CYCLEN

The safety of ORTHO TRI-CYCLEN was evaluated in 4,826 healthy women of child-bearing potential who participated in 6 clinical trials and received at least 1 dose of ORTHO TRI-CYCLEN for contraception. Two trials were randomized active-controlled trials and 4 were uncontrolled open-label trials. In 3 trials, subjects were followed for up to 24 cycles; in 2 trials, subjects were followed for up to 12 cycles; and in 1 trial, subjects were followed for up to 6 cycles.

Common Adverse Reactions (≥ 2% of subjects): The most common adverse reactions reported by at least 2% of the 4,826 women were the following in order of decreasing incidence: headache/migraine (33.6%), breast issues (including breast pain, enlargement, and discharge) (8.0%), vaginal infection (7.1%), abdominal/gastrointestinal pain (5.6%), mood disorders (including mood alteration and depression) (3.8%), genital discharge (3.2%), and changes in weight (including weight fluctuation, increased or decreased) (2.5%).

Adverse Reactions Leading to Study Discontinuation: Over the trials, between 9 to 27% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions (≥1%) leading to discontinuation were: metrorrhagia (4.3%), nausea/vomiting (2.8%), headache/migraine (2.4%), mood disorders (including depression and mood altered) (1.1%), and weight increased (1.1%).

Serious Adverse Reactions: breast cancer (1 subject), carcinoma of the cervix *in situ* (1 subject), hypertension (1 subject), and migraine (2 subjects).

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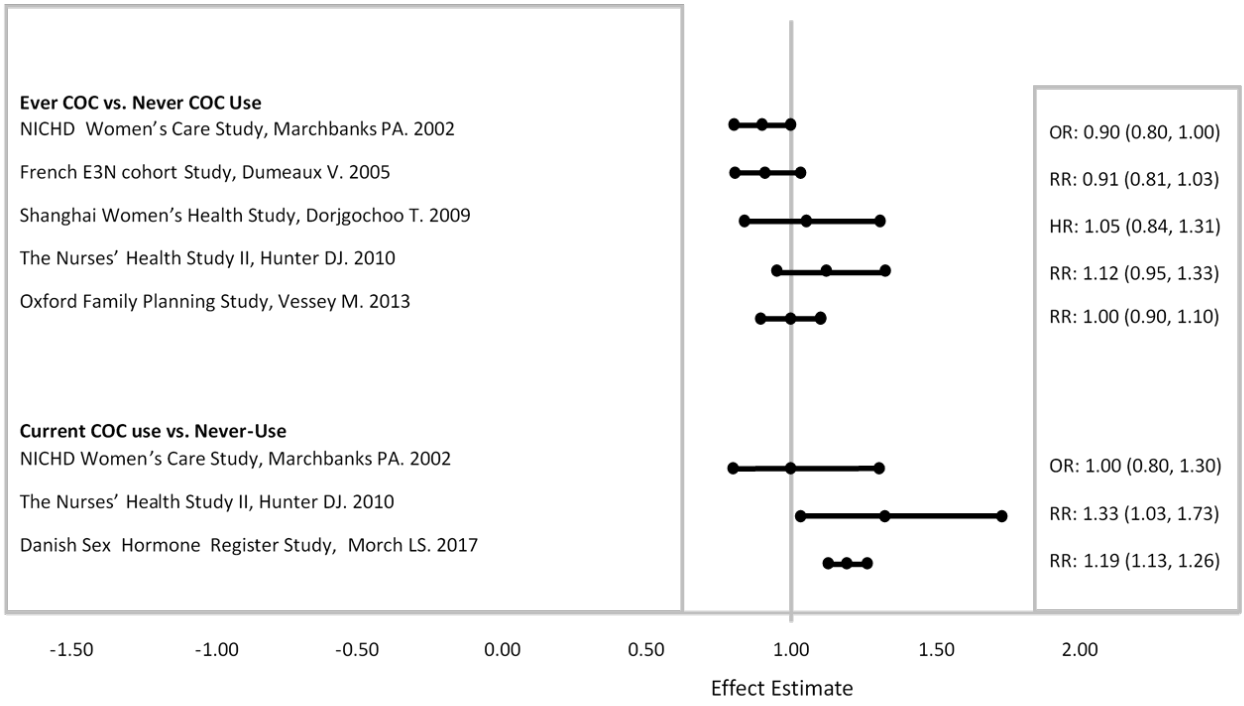
6.2 Postmarketing Experience

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 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 (Incl. Cysts and Polyps): Breast cancer, benign breast neoplasm, hepatic adenoma, focal nodular hyperplasia, breast cyst;

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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, venous thrombosis (including Budd Chiari Syndrome and hepatic vein thrombosis);

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-CYCLEN or ORTHO TRI-CYCLEN.

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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 hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between hormonal contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

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

Substances increasing the plasma concentrations of COCs

Co-administration of atorvastatin or rosuvastatin and certain COCs containing ethinyl estradiol (EE) increase AUC values for EE by approximately 20-25%. 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, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of

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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.

7.4 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

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

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-CYCLEN Tablets and ORTHO TRI-CYCLEN 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.

There was no significant difference between ORTHO TRI-CYCLEN Tablets and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineral density between baseline and Cycle 13 in 123 adolescent females with anorexia nervosa in a double-blind,

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placebo-controlled, multicenter, one-year treatment duration clinical trial for the Intent To Treat (ITT) population.

8.5 Geriatric Use

ORTHO-CYCLEN and ORTHO TRI-CYCLEN have not been studied in postmenopausal women and are not indicated in this population.

8.6 Hepatic Impairment

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

8.7 Renal Impairment

The pharmacokinetics of ORTHO-CYCLEN and ORTHO TRI-CYCLEN have 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

Each of the following products 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,(17α)-(+)-) and ethinyl estradiol is designated as (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol).

ORTHO-CYCLEN®

- Each active blue tablet contains 0.250 mg of norgestimate and 0.035 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, and titanium dioxide.
- Each dark green placebo tablet containing 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.

ORTHO TRI-CYCLEN®

- Each active white tablet contains 0.180 mg of norgestimate and 0.035 mg of ethinyl estradiol. Inactive ingredients include carnauba wax, croscarmellose sodium,

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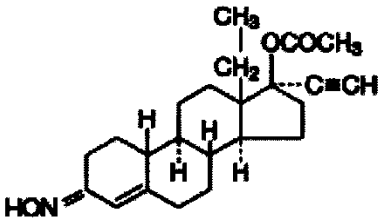
hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, purified water, and titanium dioxide.

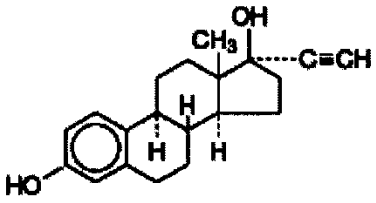
- Each active light blue tablet contains 0.215 mg of norgestimate and 0.035 mg of ethinyl estradiol. Inactive ingredients include carnauba wax, croscarmellose sodium, FD & C Blue No. 2 Aluminum Lake, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, purified water, and titanium dioxide.

- Each active blue tablet contains 0.250 mg of norgestimate and 0.035 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, 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

- Oral Contraception

  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.

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- Acne

  Acne is a skin condition with a multifactorial etiology, including androgen stimulation of sebum production. While the combination of ethinyl estradiol and norgestimate increases sex hormone-binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with ORTHO-CYCLEN or ORTHO TRI-CYCLEN.

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 norgestimate.

Peak serum concentrations of NGMN and EE are generally reached by 2 hours after administration of ORTHO-CYCLEN or ORTHO TRI-CYCLEN. Accumulation following multiple dosing of the 250 mcg NGM / 35 mcg EE dose is approximately 2-fold for NGMN and EE compared with single dose administration. The pharmacokinetics of NGMN is dose-proportional following NGM doses of 180 mcg to 250 mcg. Steady-state concentration of EE is achieved by Day 7 of each dosing cycle. Steady-state concentrations of NGMN and NG are achieved by Day 21. Non-linear accumulation (approximately 8 fold) of NG is observed as a result of high-affinity binding to SHBG, which limits its biological activity (Table 3).

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

Mean (SD) Pharmacokinetic Parameters of ORTHO TRI-CYCLEN During a Three Cycle Study						
Analyte	Cycle	Day	C_{max}	t_{max} (h)	AUC_{0-24h}	$t_{1/2}$ (h)
NGMN	3	7	1.80 (0.46)	1.42 (0.73)	15.0 (3.88)	NC
		14	2.12 (0.56)	1.21 (0.26)	16.1 (4.97)	NC
		21	2.66 (0.47)	1.29 (0.26)	21.4 (3.46)	22.3 (6.54)
NG	3	7	1.94 (0.82)	3.15 (4.05)	34.8 (16.5)	NC
		14	3.00 (1.04)	2.21 (2.03)	55.2 (23.5)	NC
		21	3.66 (1.15)	2.58 (2.97)	69.3 (23.8)	40.2 (15.4)
EE	3	7	124 (39.5)	1.27 (0.26)	1130 (420)	NC
		14	128 (38.4)	1.32 (0.25)	1130 (324)	NC
		21	126 (34.7)	1.31 (0.56)	1090 (359)	15.9 (4.39)
Mean (SD) Pharmacokinetic Parameters of ORTHO-CYCLEN During a Three Cycle Study						
Analyte	Cycle	Day	C_{max}	t_{max} (h)	AUC_{0-24h}	$t_{1/2}$ (h)
NGMN	1	1	1.78 (0.397)	1.19 (0.250)	9.90 (3.25)	18.4 (5.91)
	3	21	2.19 (0.655)	1.43 (0.680)	18.1 (5.53)	24.9 (9.04)
NG	1	1	0.649 (0.49)	1.42 (0.69)	6.22 (2.46)	37.8 (14.0)
	3	21	2.65 (1.11)	1.67 (1.32)	48.2 (20.5)	45.0 (20.4)
EE	1	1	92.2 (24.5)	1.2 (0.26)	629 (138)	10.1 (1.90)
	3	21	147 (41.5)	1.13 (0.23)	1210 (294)	15.0 (2.36)

C_{max} = peak serum concentration, t_{max} = time to reach peak serum concentration, AUC_{0-24h} = area under serum concentration vs time curve from 0 to 24 hours, $t_{1/2}$ = elimination half-life, NC = not calculated.
NGMN and NG: C_{max} = ng/mL, AUC_{0-24h} = h•ng/mL
EE: C_{max} = pg/mL, AUC_{0-24h} = h•pg/mL

Food Effect

The effect of food on the pharmacokinetics of ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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.

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Excretion

The metabolites of NGMN and EE are eliminated by renal and fecal pathways. Following administration of ^{14}C-norgestimate, 47% (45-49%) and 37% (16-49%) of the administered radioactivity was eliminated in the urine and feces, respectively. Unchanged NGM was not detected in the urine. In addition to 17-deacetyl norgestimate, a number of metabolites of NGM have been identified in human urine following administration of radiolabeled NGM. These include 18, 19-Dinor-17-pregn-4-en-20-yn-3-one,17-hydroxy-13-ethyl,(17α)-(-);18,19-Dinor-5β-17-pregnan-20-yn,3α,17β-dihydroxy-13-ethyl,(17α), various hydroxylated metabolites and conjugates of these metabolites.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.2, 5.11) and Use in Specific Populations (8.1).]

14 CLINICAL STUDIES

14.1 Contraception

In three US clinical trials with ORTHO-CYCLEN, 1,651 women aged 18 to 38 years were studied for up to 24 cycles, proving a total of 24,272 cycles of exposure. The racial demographic was about 73-86% Caucasian, 8-13% African-American, 6-14% Hispanic with the remainder Asian or Other (≤1%). There were no exclusions on the basis of weight; the weight range for women treated was 82-303 lbs, with a mean weight of about 135 lbs. The pregnancy rate was approximately 1 pregnancy per 100 women-years.

In four clinical trials with ORTHO TRI-CYCLEN, 4,756 women aged 15 to 41 years were studied for 24 cycles, providing a total of 45,244 cycles of exposure. The racial demographic was about 87-90% Caucasian, 6-10% African-American, with the remainder Asian (≤1%) or Other (2-5%). There were no exclusions on the basis of weight; the weight range for women treated was 80-310 lbs, with a mean weight of about 132 lbs. The pregnancy rate was approximately 1 pregnancy per 100 women-years.

14.2 Acne

ORTHO TRI-CYCLEN was evaluated for the treatment of acne vulgaris in two randomized, double-blind, placebo-controlled, multicenter, six- (28 day) cycle studies. Two hundred twenty-one patients received ORTHO TRI-CYCLEN and 234 patients received placebo. Mean age at enrollment for both groups was 28 years. At the end of 6 months, the mean total lesion count changed from 55 to 31 (42% reduction) in patients treated with ORTHO TRI-CYCLEN and from 54 to 38 (27% reduction) in patients similarly treated with placebo. Table 4 summarizes the changes in lesion count for each type of lesion. Based on the investigator's global assessment conducted at the final visit, patients treated with ORTHO TRI-CYCLEN showed a statistically significant improvement in total lesions compared to those treated with placebo.

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Table 4: Acne Vulgaris Indication. Combined Results: Two Multicenter, Placebo-Controlled Trials. Observed Means at Six Months (LOCF)* and at Baseline. Intent-to-Treat Population.

	ORTHO TRI-CYCLEN (N=221)		Placebo (N=234)		Difference in Counts between ORTHO TRI-CYCLEN and Placebo at 6 Months
# of Lesions	Counts	% Reduction	Counts	% Reduction	
INFLAMMATORY LESIONS					
Baseline Mean	19		19		
Sixth Month Mean	10	48%	13	30%	3 (95% CI: -1.2, 5.1)
NON-INFLAMMATORY LESIONS					
Baseline Mean	36		35		
Sixth Month Mean	22	34%	25	21%	3 (95% CI: -0.2, 7.8)
TOTAL LESIONS					
Baseline Mean	55		54		7 (95% CI: 2.0, 11.9)
Sixth Month Mean	31	42%	38	27%	

*LOCF: Last Observation Carried Forward

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ORTHO-CYCLEN

ORTHO-CYCLEN® Tablets are available in a single pouch containing a VERIDATE blister card (refill) of 28 tablets (NDC 50458-197-28). ORTHO-CYCLEN Tablets are packaged in a carton containing 6 pouches and 6 unfilled VERIDATE Tablet Dispensers (NDC 50458-197-06).

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

- 21 blue, round, biconvex, coated tablet imprinted "O 250" on one side and "35" on the other side of the tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark green round, biconvex, coated tablet (non-hormonal placebo) imprinted "O-M" on one side and "P" on the other side contains inert ingredients

ORTHO-CYCLEN Tablets are also available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE refills (NDC 50458-197-20 and NDC 50458-197-12).

ORTHO-CYCLEN Tablets are available in a DIALPAK Tablet Dispenser (unfilled) and DIALPAK refills (NDC 50458-197-00 and NDC 50458-197-15).

ORTHO TRI-CYCLEN

ORTHO TRI-CYCLEN® Tablets are available in a single pouch containing a VERIDATE blister card (refill) of 28 tablets (NDC 50458-191-28.) ORTHO TRI-CYCLEN Tablets are packaged in a carton containing 6 pouches and 6 unfilled VERIDATE Tablet dispensers (NDC 50458-191-06).

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

- 7 white, round, biconvex, coated tablet imprinted "O 180" on one side and "35" on the other side of the tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 light blue, round, biconvex, coated tablet imprinted "O 215" on one side and "35" on the other side of the tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 blue, round, biconvex, coated tablet imprinted "O 250" on one side and "35" on the other side of the tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark green round, biconvex, coated tablet (non-hormonal placebo) imprinted "O-M" on one side and "P" on the other side contains inert ingredients

ORTHO TRI-CYCLEN Tablets are also available for clinic usage in a VERIDATE Tablet Dispenser (unfilled) and VERIDATE refills (NDC 50458-191-20 and NDC 50458-191-12).

ORTHO TRI-CYCLEN Tablets are available in a DIALPAK Tablet Dispenser (unfilled) and DIALPAK refills (NDC 50458-191-00 and NDC 50458-191-15).

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.
- Keep 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)]*.
- ORTHO-CYCLEN and ORTHO TRI-CYCLEN do not protect against HIV infection (AIDS) and other sexually transmitted infections.
- ORTHO-CYCLEN and ORTHO TRI-CYCLEN are not to be used during pregnancy; if pregnancy occurs during use of ORTHO-CYCLEN or ORTHO TRI-CYCLEN instruct the patient to stop further use *[see Warnings and Precautions (5.9)]*.
- 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)]*.

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- Use a back-up or alternative method of contraception when enzyme inducers are used with ORTHO-CYCLEN or ORTHO TRI-CYCLEN *[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 an active 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 (5.8)]*.

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

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

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Patient Information

ORTHO-CYCLEN [OR-tho sī-klin]

ORTHO TRI-CYCLEN [OR-tho trī-sī-klin]

(norgestimate and ethinyl estradiol)

Tablets

What is the most important information I should know about ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

Do not use ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

ORTHO-CYCLEN or ORTHO TRI-CYCLEN is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

ORTHO TRI-CYCLEN is also used to treat moderate acne vulgaris in females 15 years of age and older, who have no known history of allergies or problems taking birth control pills, and have started their menstrual cycle ("period"). ORTHO TRI-CYCLEN should only be used to treat acne in women who want to take birth control pills to prevent pregnancy.

How does ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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 of clinical studies, about 1 out of 100 women may get pregnant during the first year they use ORTHO-CYCLEN or ORTHO TRI-CYCLEN.

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.

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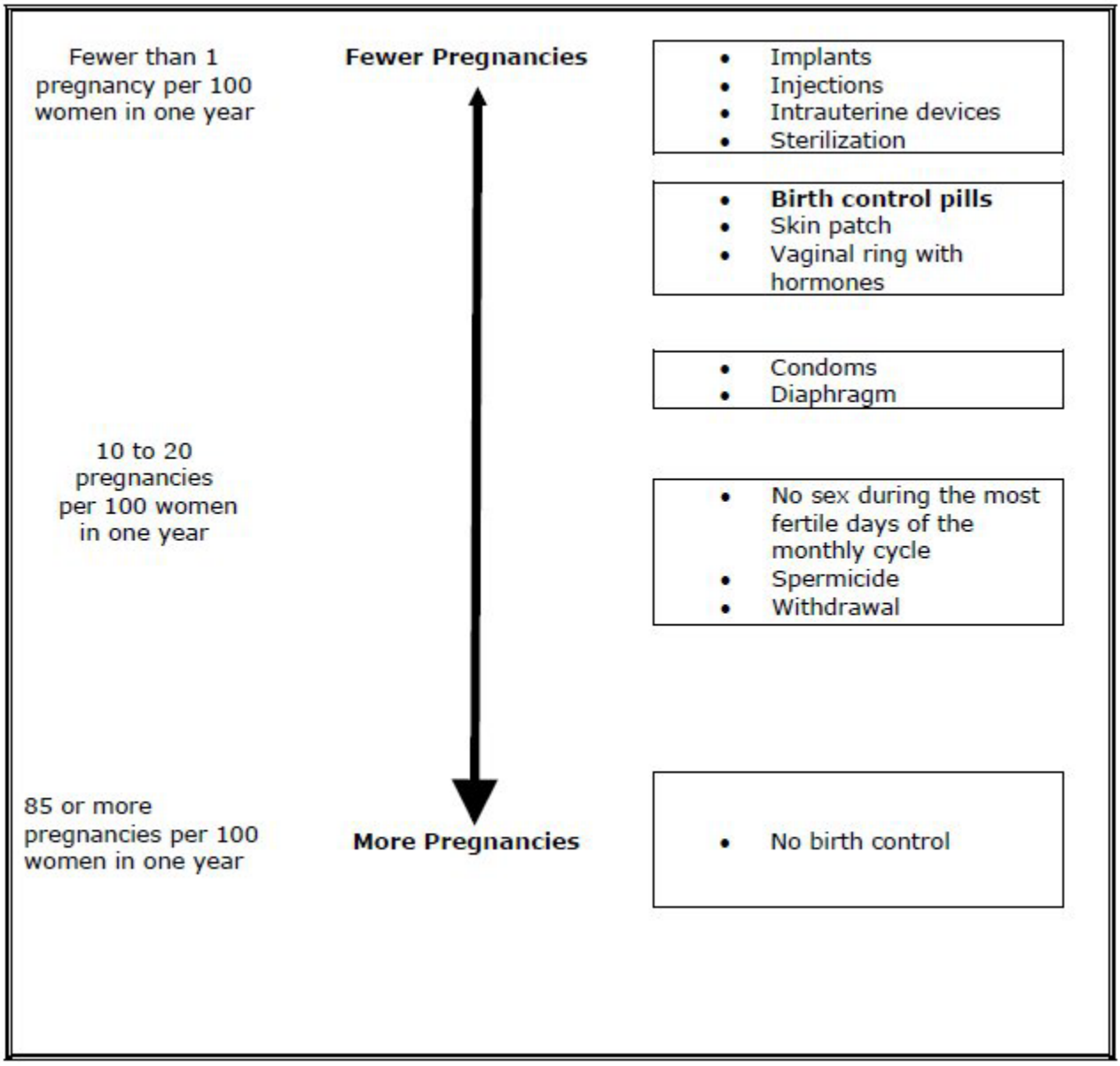

Who should not take ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

Do not take ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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

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- 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN, stop taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN.

What should I tell my healthcare provider before taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

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. ORTHO-CYCLEN or ORTHO TRI-CYCLEN may decrease the amount of breast milk you make. A small amount of the hormones in ORTHO-CYCLEN or ORTHO TRI-CYCLEN may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

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

ORTHO-CYCLEN or ORTHO TRI-CYCLEN may affect the way other medicines work, and other medicines may affect how well ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

Read the Instructions for Use at the end of this Patient Information**.**

What are the possible serious side effects of ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

- **Like pregnancy, ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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:

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- 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.** You should see your healthcare provider for a yearly check of your blood pressure.
- **gallbladder problems**
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood**
- **new or worsening headaches including migraine headaches**
- **irregular or unusual vaginal bleeding and spotting between your menstrual periods, especially during the first 3 months of taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN.**
- **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 is 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

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under sun lamps while taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

- headache (migraine)
- breast pain or tenderness, enlargement or discharge
- stomach pain, discomfort, and gas
- vaginal infections and discharge
- mood changes, including depression
- nervousness
- changes in weight
- skin rash

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These are not all the possible side effects of ORTHO-CYCLEN or ORTHO TRI-CYCLEN. 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

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

How should I store ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

- Store ORTHO-CYCLEN or ORTHO TRI-CYCLEN at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep ORTHO-CYCLEN or ORTHO TRI-CYCLEN and all medicines out of the reach of children.
- Store away from light.

General information about the safe and effective use of ORTHO-CYCLEN or ORTHO TRI-CYCLEN.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ORTHO-CYCLEN or ORTHO TRI-CYCLEN for a condition for which it was not prescribed. Do not give ORTHO-CYCLEN or ORTHO TRI-CYCLEN to other people, even if they have the same symptoms that you have.

This Patient Information summarizes the most important information about ORTHO-CYCLEN or ORTHO TRI-CYCLEN. You can ask your pharmacist or healthcare provider for information about ORTHO-CYCLEN or ORTHO TRI-CYCLEN that is written for health professionals.

For more information, call 1-800-JANSSEN (1-800-526-7736).

Do birth control pills cause cancer?

It is not known if hormonal birth control pills cause breast cancer. Some studies, but not all, suggest that there could be a slight increase in the risk of

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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.

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

What 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN, 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

ORTHO-CYCLEN:

Active ingredients: Each blue pill contains norgestimate and ethinyl estradiol.

Inactive ingredients:

Blue pills: carnauba wax, croscarmellose sodium, FD & C Blue No. 2 Aluminum Lake, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, purified water, and titanium dioxide.

Dark-green pills: 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.

ORTHO TRI-CYCLEN:

Active ingredients: Each white, light-blue, and blue pill contains norgestimate and ethinyl estradiol.

Inactive ingredients:

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White pills: carnauba wax, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, purified water, and titanium dioxide.

Light-blue pills: carnauba wax, croscarmellose sodium, FD & C Blue No. 2 Aluminum Lake, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, purified water, and titanium dioxide.

Blue pills: carnauba wax, croscarmellose sodium, FD & C Blue No. 2 Aluminum Lake, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, purified water, and titanium dioxide.

Dark-green pills: 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.

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Instructions For Use

ORTHO-CYCLEN [OR-tho sī-klin]

ORTHO TRI-CYCLEN [OR-tho trī-sī-klin]

(norgestimate and ethinyl estradiol)

Tablets

Important Information about taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN

- Take **1** pill every day at the same time. Take the pills in the order directed on your pill dispenser.
- 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN, talk to your healthcare provider. When you first start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN, 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN. 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 (see **What should I do if I miss any ORTHO-CYCLEN or ORTHO TRI-CYCLEN pills?** below), 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN.
- If you have vomiting or diarrhea within **3-4** hours of taking your pill, take another pill of the same color from your extra pill dispenser. If you do not

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have an extra pill dispenser, take the next pill in your pill dispenser. Continue taking all your remaining pills in order. Start the first pill of your next pill dispenser the day after finishing your current pill dispenser. 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 and a spermicide, until you check with your healthcare provider.
- Stop taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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 and spermicide) during this time period.

Before you start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN:

- 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 pill dispenser.
- Have backup contraception (condoms and spermicide) available and if possible, an extra full pack of pills as needed.

When should I start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN?

If you start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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 and spermicide for the first **7** days that you take ORTHO-CYCLEN or ORTHO TRI-CYCLEN. You do not need back-up contraception if you use the Day 1 Start.

If you start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN and you are switching from another birth control pill:

- Start your new ORTHO-CYCLEN or ORTHO TRI-CYCLEN pack on the same day that you would start the next pack of your previous birth control method.

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- Do not continue taking the pills from your previous birth control pack.

If you start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN and previously used a vaginal ring or transdermal patch:

- Start using ORTHO-CYCLEN or ORTHO TRI-CYCLEN on the day you would have reapplied the next ring or patch.

If you start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN and you are switching from a progestin-only method such as an implant or injection:

- Start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN on the day of removal of your implant or on the day when you would have had your next injection.

If you start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN and you are switching from an intrauterine device or system (IUD or IUS):

- Start taking ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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 and spermicide for the first **7** days that you take ORTHO-CYCLEN or ORTHO TRI-CYCLEN.

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 ORTHO-CYCLEN or ORTHO TRI-CYCLEN?**" 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 pill dispenser at the same time each day for **28** days.
- After taking the last pill on **Day 28** from the pill dispenser, 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 and

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spermicide for the first **7** days of the first cycle that you take ORTHO-CYCLEN or ORTHO TRI-CYCLEN.

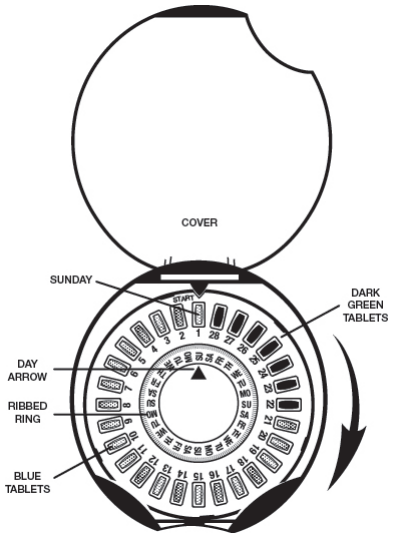
Day 1 Start:
You will use a **Day 1 Start** if your doctor told you to take your first pill (Day 1) on the **first day of your period**.

- Take **1** pill every day in the order of the pill dispenser dial pack, at the same time each day, for **28** days.
- After taking the last pill on **Day 28** from the pill dispenser, 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.

ORTHO-CYCLEN or ORTHO TRI-CYCLEN comes in either a DIALPAK pill dispenser or a VERIDATE pill dispenser. Read the instructions below for using your DIALPAK pill dispenser or your VERIDATE pill dispenser.

Instructions for using your DIALPAK pill dispenser:

ORTHO-CYCLEN



- **Each DIALPAK pill dispenser has 28 pills.**
  - **ORTHO-CYCLEN**
    - **21** blue pills with hormones, for **Days 1 to 21**.
    - **7** dark green pills (without hormones), for **Days 22 to 28**.

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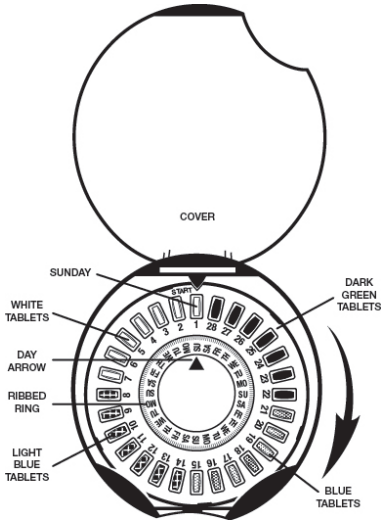
ORTHO TRI-CYCLEN



- **ORTHO TRI-CYCLEN**
  - **7** white pills with hormone, for **Days 1 to 7**
  - **7** light-blue pills with hormone, for **Days 8 to 14**
  - **7** blue pills with hormones, for **Days 15 to 21**
  - **7** dark green pills (without hormones), for **Days 22 to 28**.

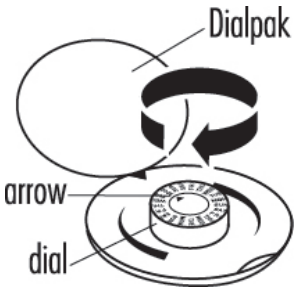


Figure A

Step 1. SET THE DAY on your DIALPAK
Sunday Start: The arrow on your *empty* DIALPAK should point to **SU** (Sunday).
Day 1 Start: Turn the dial on your *empty* DIALPAK in a clockwise direction until the arrow points to the first day of your period (if your period starts on Tuesday, the arrow will point to **TU**). **See Figure A.**

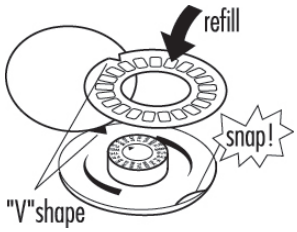


Figure B

Step 2. Insert the new refill by lining up the "V" shape on the refill with the "V" shape at the top of your DIALPAK.
Press the refill down so that it fits firmly. **See Figure B.** Snap the refill in place. You are ready to take pill "**1**". You should always begin your pill cycle with pill "**1**", as shown on the inner part of the refill ring.

Figure C

Step 3. Remove pill "1" by pushing down on the pill. The pill will come out through a hole in the back of the DIALPAK. **See Figure C.**

Step 4. Swallow the pill. You will take **1** pill

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every day, at the same time each day.

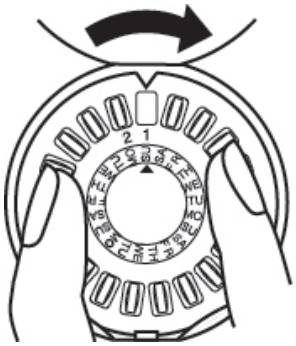

Figure D

Step 5. Wait 24 hours to take your next pill.
To take pill "**2**," turn the dial on your DIALPAK in a clockwise direction to the next day. **See Figure D.** Continue to take **1** pill each day until all the pills have been taken.

Step 6. Take your pill at the same time every day. It is important to take the correct pill each day and not miss any pills.

To help you remember, take your pill at the same time as another daily activity, like turning off your alarm clock or brushing your teeth.

Figure E

Step 7. Remove your empty pack. See Figure E. You will start a new refill on the first day after pill "**28**". Turn the dial to the pill "**1**" position to remove the empty refill pack. **When your refill is empty, keep your DIALPAK case.**

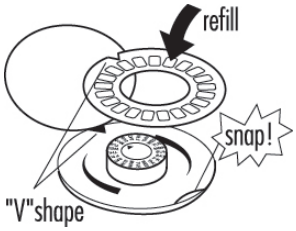

Figure F

Step 8. Insert a new refill pack. See Figure F. Insert a new refill pack. Remember to take your first pill in every refill on the same day of the week, no matter when your next period starts.

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Instructions for using your VERIDATE pill dispenser:

- Each VERIDATE pill dispenser has **28** pills. **See Figure A**.

  ORTHO-CYCLEN
  - **21** blue pills with hormones, for **Days 1 to 21**
  - **7** dark green pills (without hormones), for **Days 22 to 28**

  ORTHO TRI-CYCLEN
  - **7** white pills with hormone, for **Days 1 to 7**
  - **7** light-blue pills with hormone, for **Days 8 to 14**
  - **7** blue pills with hormones, for **Days 15 to 21**
  - **7** dark green pills (without hormones), for **Days 22 to 28**

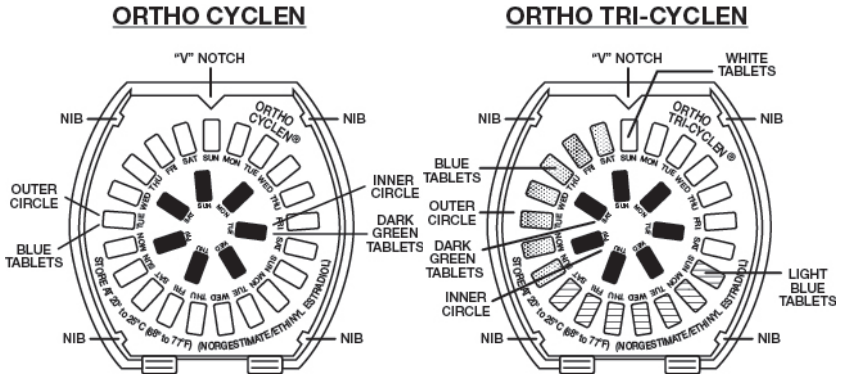

Figure A

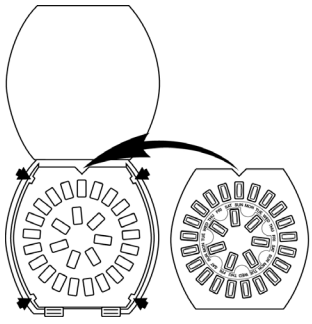

Figure B

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**.

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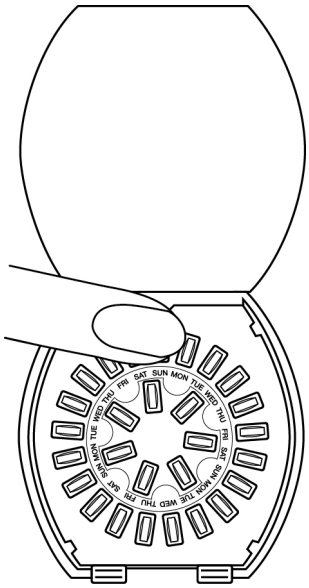

Figure C

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.

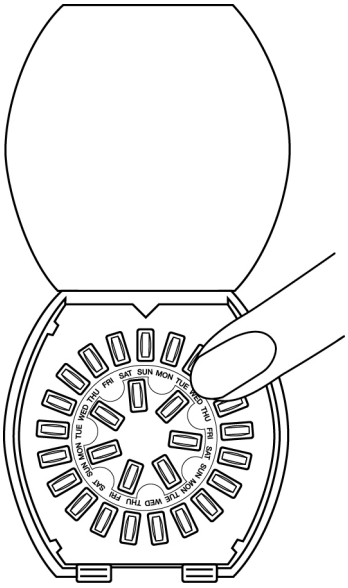

Figure D

Day 1 Start:
If you take ORTHO-CYCLEN:

- If your healthcare provider tells you to start taking your pill on "**Day 1**," choose a blue pill that corresponds with the day of the week on which you are taking the first pill.
- Remove that blue pill by pressing the pill through the hole in the bottom of the dispenser. **See Figure D**.

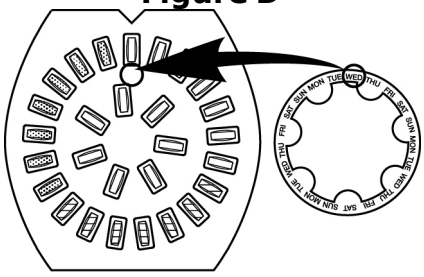

Figure E

If you take ORTHO TRI-CYCLEN:

- 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 E**.

- 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

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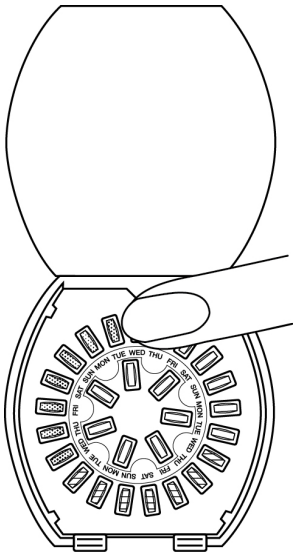

Figure F

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 F**.

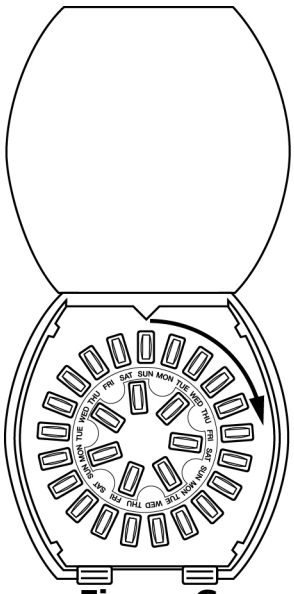

Figure G

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 G.

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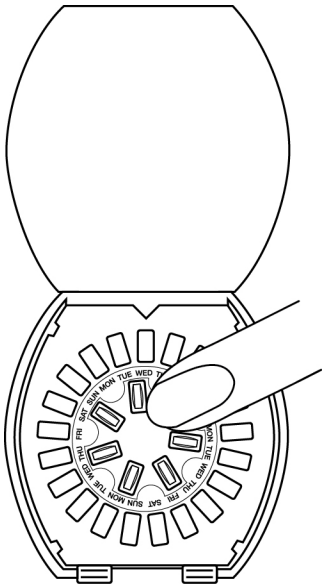

Figure H

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

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

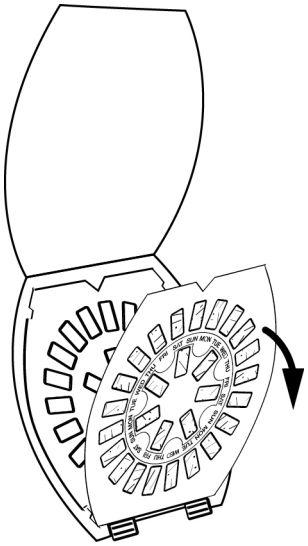

Figure I

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 I.**
- Follow the instructions in **Step 1** to replace the new refill.

What should I do if I miss any ORTHO-CYCLEN or ORTHO TRI-CYCLEN 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.

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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

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Mfd. for:

Janssen Pharmaceuticals, Inc.

Titusville, New Jersey 08560

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