QUARTETE® (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets

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**WARNINGS AND PRECAUTIONS**

- **Vascular risks:** Stop if a thrombotic or thromboembolic 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. Consider cardiovascular risk factors before initiating in all females, particularly those over 35 years. (5.1, 5.5)
- **Liver disease:** Discontinue if jaundice occurs. (5.2)
- **Hypertension:** If used in females with well-controlled hypertension, monitor blood pressure and stop use if blood pressure rises significantly. (5.3)
- **Gallbladder disease:** May cause or worsen gallbladder disease. (5.6)
- **Carbohydrate and lipid metabolic effects:** Monitor glucose in prediabetic and diabetic women taking QUARTETE. Consider an alternate contraceptive method for women with uncompensated dyslipidemias. (5.6)
- **Headache:** Evaluate significant change in headaches and discontinue if indicated. (5.7)
- **Uterine bleeding:** May cause irregular bleeding or amenorrhea. Evaluate for other causes if symptoms persist. (5.8)

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**ADVERSE REACTIONS**

The most common adverse reactions (>2%) in clinical trials for QUARTETE were headaches, heavy/irregular vaginal bleeding, nausea/vomiting, acne, dysmenorrhea, weight increased, mood changes, anxiety/panic attack, breast pain and migraines. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-463-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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**DRUG INTERACTIONS**

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

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: Discontinue use if pregnancy occurs. (8.1)
- Lactation: Advise use of another method. QUARTETE is not recommended for nursing mothers; may decrease milk production. (8.2)

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

**REFERENCES**

Revised: 08/2022
QUARTETTE® (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets

Switching to QUARTETTE from another oral hormonal contraceptive or from another contraceptive method (transdermal patch, vaginal ring, injection, intrauterine contraceptive, implant)

Start on the Sunday after the patient’s next period starts. Use additional non-hormonal contraceptive (such as condoms and spermicide) until the patient has taken 7 light pink pills (7 days).

Starting QUARTETTE after Abortion or Miscarriage

First-trimester

QUARTETTE may be started on the Sunday after an abortion or miscarriage. The patient must use additional non-hormonal contraceptive (such as condoms and spermicide) until the patient has taken a light pink tablet for 7 days.

Second-trimester

Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start contraceptive therapy with QUARTETTE following the instructions for women not currently using hormonal contraception. Use additional non-hormonal contraception (such as condoms and spermicide) until the patient has taken a light pink tablet for 7 days [see Contraindications (4) and Warnings and Precautions (5.5)].

Starting QUARTETTE after Childbirth

Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with QUARTETTE following the instructions for women not currently using hormonal contraception. Use additional non-hormonal contraception (such as condoms and spermicide) until the patient has taken a light pink tablet for 7 days (see Contraindications (4) and Warnings and Precautions (5.5)).

QUARTETTE is not recommended for use in lactating women [see Use in Specific Populations (8.2)]. If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of QUARTETTE [see Warnings and Precautions (5.5)]. Use in Specific Populations (8.1).

2.2 Dosing QUARTETTE

Take one tablet by mouth at the same time every day. The dosage of QUARTETTE is one light pink tablet once daily for 42 days, one pink tablet once daily for 21 days, one purple tablet once daily for 21 days, and one yellow tablet once daily for 7 days.

To achieve maximum contraceptive effectiveness, take QUARTETTE exactly as directed, in the order directed, and at intervals not exceeding 24 hours. The failure rate may increase when pills are missed or taken incorrectly.

2.3 Missed Doses

Table 1. Instructions for Missed QUARTETTE Tablets

| If one light pink, pink or purple tablet is missed | Take the missed tablet as soon as possible. Take the next tablet at the regular time. Continue taking one tablet a day until the pack is finished. A back-up birth control method is not required if the patient has sex. |
| If two light pink, pink or purple tablets in a row are missed | Take the two missed tablets as soon as possible, and the next two tablets the next day. Continue taking one tablet a day until the pack is finished. Use additional nonhormonal contraception (such as condoms and spermicide) until tablets have been taken for 7 days after missing tablets. |
| If three or more light pink, pink or purple tablets in a row are missed | Throw away the missed tablets. Continue taking one tablet every day as indicated on the pack until the pack is finished. Bleeding may occur during the week following the missed tablets. Use additional nonhormonal contraception (such as condom and spermicide) until tablets have been taken for 7 days after missing tablets. |
| If any of the seven yellow tablets are missed | Throw away the missed tablets. Continue taking the remaining tablets until the pack is finished. A backup birth control method is not needed. |

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 3-4 hours after taking a light pink, pink or purple tablet, handle this as a missed tablet [see Dosage and Administration (2.3)].

3 DOSAGE FORMS AND STRENGTHS

QUARTETTE (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets are available as round, film-coated, biconvex tablets debossed with TV on one side, packaged in Extended-Cycle Tablet Dispensers, each containing a 13-week supply of tablets in the following order:

- 42 light pink tablets, each containing 0.15 mg of levonorgestrel and 0.02 mg ethinyl estradiol: debossed with 076 on the other side
- 21 pink tablets containing 0.15 mg of levonorgestrel and 0.025 mg ethinyl estradiol: debossed with 075 on the other side
- 21 purple tablets containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol: debossed with 074 on the other side and
- 7 yellow tablets containing 0.01 mg of ethinyl estradiol: debossed with 077 on the other side

4 CONTRAINDICATIONS

QUARTETTE is contraindicated in females who are known to have or develop the following conditions:
- A history of arterial or venous thrombotic diseases. Examples include females who are known to:
  - Smoke, if over age 35 [see Boxed Warning and Warnings and Precautions (5.5)].
  - Have current or history of deep vein thrombosis or pulmonary embolism [see Warnings and Precautions (5.5)].
- Liver tumors, acute viral hepatitis, or severe (decompensated) cirrhosis [see Warnings and Precautions (5.5)].
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations [see Warnings and Precautions (5.4)].

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Conditions

- Stop QUARTETTE if an arterial or deep venous thromboembolic event occurs.
- Stop QUARTETTE if there is unexplained loss of vision, prosptosis, diplapia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.
- Discontinue QUARTETTE during prolonged immobilization. If feasible, stop QUARTETTE at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.
- Start QUARTETTE no earlier than 4 weeks after delivery, in females who are not breastfeeding.
- The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- Before starting QUARTETTE evaluate any past medical history or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy. QUARTETTE is contraindicated in females with a high risk of arterial or venous/thrombembolic diseases [see Contraindications (4)].

Arterial Events

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

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

Venous Events

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

The risk of VTE is highest during the first year of use of a COC and when restarting hormonal contraception after a break of four weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after COCe use is discontinued. Figure 1 shows the risk of developing a VTE for females who are not pregnant and do not use oral contraceptives, for females who use oral contraceptives, and for females in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 females who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these females will develop a VTE.

Figure 1:     Likelihood of Developing a VTE

Non-Pregnant Non-COC user

COC-User

Pregnancy *

Postpartum (12 weeks only)

Ranges from 1 to 5

Ranges from 2 to 9

Ranges from 40 to 65

Ranges from 5 to 20

Ranges from 40 to 65

Ranges from 5 to 20

Ranges from 40 to 65

Ranges from 5 to 20

Ranges from 40 to 65

Ranges from 5 to 20

Ranges from 40 to 65

Ranges from 5 to 20

0 10 20 30 40 50 60 70

Number of Women with a Blood Clot out of 10,000 Women Years (WY)

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

Elevated Liver Enzymes

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

Liver Tumors

QUARTETTE is contraindicated in females with benign or malignant liver tumors [see Contraindications (4)].

5.3 Hypertension

QUARTETTE is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease (see Contraindications (4)). For all females, including those with well-controlled hypertension, monitor blood pressure at routine visits and stop QUARTETTE 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 and with extended duration of use. The effect of COCs on blood pressure may vary according to the progestin in the COC.

5.4 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as QUARTETTE. Discontinue QUARTETTE prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir [see Contraindications (4)]. QUARTETTE can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.5 Age-related Considerations

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

- Hypertension
- Diabetes
- Dyslipidemia
- Obesity

5.6 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs, including QUARTETTE, may also 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.

5.7 Adverse Carbohydrate and Lipid Metabolic Effects

Hyperglycemia

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

Dyslipidemia

Consider alternative contraception for females with uncontrolled dyslipidemias. QUARTETTE may cause adverse lipid changes.

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

5.8 Headache

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

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

Consider discontinuation of QUARTETTE in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) [see Contraindications (4)].

5.9 Bleeding Irregularities and Amenorrhea

Bleeding and/or spotting that occurs at any time while taking the first 84 tablets (light pink, pink and purple) of each extended-cycle regimen is considered "unscheduled" bleeding/spotting. Unscheduled bleeding or spotting occurs during the time a woman takes the seven tablets (yellow) containing 10 mcg of ethinyl estradiol is considered "scheduled" bleeding.

 Unscheduled and Scheduled Bleeding and Spotting

Females using QUARTETTE may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first 3 months of use. Bleeding irregularities may resolve over time or by changing to a different contraceptive product. If unscheduled bleeding persists or occurs after previously regular cycles on QUARTETTE, evaluate for causes such as pregnancy or malignancy.

When prescribing QUARTETTE, consider the occurrence of fewer scheduled menses (4 per year instead of 13 per year) against the occurrence of increased unscheduled bleeding and/or spotting. A 12-month open-label study of the efficacy of QUARTETTE in preventing pregnancy assessed scheduled and unscheduled bleeding (see Clinical Studies (14)) in 3,597 women who completed 34,087 28-day cycles of exposure. A total of 178 (4.9%) of the women discontinued QUARTETTE, at least in part, due to bleeding and/or spotting.

Scheduled (withdrawal) bleeding and/or spotting remained fairly stable over time, with an average of 3 to 4 days of bleeding and/or spotting per each 91-day cycle. Unscheduled bleeding and unscheduled spotting decreased over successive 91-day cycles. Table 2 below presents the number of days with unscheduled bleeding, spotting, and unscheduled bleeding and/or spotting in Treatment Cycles 1-4.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Days of Unscheduled Bleeding per 84-Day Interval</th>
<th>Days of Unscheduled Spotting per 84-Day Interval</th>
<th>Days of Unscheduled Bleeding and/or Spotting per 84-Day Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Q1</td>
<td>Median</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>2.2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 2: Number of Unscheduled Bleeding, Spotting and Bleeding and/or Spotting Days per 91-day Cycle

5.10 Depression

Females who use QUARTETTE may experience absence of scheduled (withdrawal) bleeding, even if they are not pregnant. Based on data from the clinical trial, amenorrhea occurred in approximately 1.9% of women during Cycle 1, 7.7% during Cycle 2, 10.7% during Cycle 3, and 10.1% during Cycle 4 using QUARTETTE.

If unscheduled spotting or bleeding occurs, instruct the patient to continue on the same regimen. If the bleeding is persistent or prolonged, advise the patient to consult her healthcare provider.

Amenorrhea and Disamenorrhea

Disamenorrhea after stopping QUARTETTE, especially if these conditions were pre-existent.

5.11 Pregnancy

Females who use QUARTETTE may experience absence of scheduled and/or unscheduled bleeding, even if they are not pregnant. Based on data from the clinical trial, amenorrhea occurred in approximately 1.9% of women during Cycle 1, 7.7% during Cycle 2, 10.7% during Cycle 3, and 10.1% during Cycle 4 using QUARTETTE.

Rule out pregnancy in the event of amenorrhea. Some women may experience amenorrhea or oligomenorrhea after stopping QUARTETTE, especially if these conditions were pre-existent.

5.12 Asthma

Females with asthma who have had an increase in symptoms of asthma while taking COCs, including QUARTETTE, should discontinue the COC.

5.13 Migraine

Females with migraine headache without aura who experience increased frequency or severity of migraine while taking COCs, including QUARTETTE, may discontinue the drug.

5.14 Systemic Lupus Erythematosus

Females with systemic lupus erythematosus who develop a lupus flare or exacerbation of existing lupus should discontinue the COC.
QUARTETTE® (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets

5.11 Malignant Neoplasms

Breast Cancer
Quartetted is 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 COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

5.12 Effect on Binding Globulins

The estrogen component of QUARTETTE 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.

5.13 Hereditary Angioedema

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

5.14 Chloasma

Chloasma may occur with QUARTETTE use, especially in females with a history of chloasma gravidarum. Advise females with a history of chloasma to avoid exposure to the sun or ultraviolet radiation while taking QUARTETTE.

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trial Experience

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

The safety data described below are from a 12-month, US, open-label study, which enrolled women aged 18-40, of whom 3,597 took at least one dose of QUARTETTE (2,661 woman-years of exposure) [see Clinical Studies (4)].

Adverse Reactions Leading to Study Discontinuation: 13.3% of the women discontinued from the clinical trial due to an adverse reaction; the most common adverse reactions (≥1% of women) leading to discontinuation were heavy/irregular bleeding (5.0%), mood swings/alteration/affect (4.6%), headaches/migraines (3.3%), weight increased (3.3%) and acne (3.0%).

Common Adverse Reactions (≥2% of women): headaches (12.2%), heavy/irregular vaginal bleeding (9.7%), nausea/vomiting (8.8%), acne (5.4%), dysmenorrhea (5.4%), weight increased (4.6%), mood changes (depressed mood, crying, major depression, affective disorder, depression suicidal, dysthymic disorder) (2.9%), anxiety/panic attack (2.4%), breast tenderness/pain/discomfort (2.2%), migraine (2.0%).

Serious Adverse Reactions (≥2 women): Abortion Spontaneous, Suicide Attempt, Cholecystitis/Cholelithiasis, Deep Vein Thrombosis, Ectopic Pregnancy.

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 3).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure 2). 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 3: Relevant Studies of Risk of Breast Cancer with Combined Oral Contraceptives

6.3 Effects of Other Drugs on Combined Oral Contraceptives

Substances Decreasing the Plasma Concentrations of COCs and Potentially Diminishing the Efficacy of COCs:

Table 3 includes substances that demonstrated an important drug interaction with QUARTETTE.

7 DRUG INTERACTIONS

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

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

No drug-drug interaction studies were conducted with QUARTETTE.

51 Effects of Other Drugs on Combined Oral Contraceptives

- Metabolic Enzyme Inducers

<table>
<thead>
<tr>
<th>Metabolic Enzyme Inducers</th>
<th>Clinical effect</th>
<th>Concomitant use of COCs with metabolic enzyme inducers may decrease the plasma concentrations of the estrogen and/or progestin component of COCs.</th>
</tr>
</thead>
</table>

- Increased exposure of the estrogen and/or progestin component of COCs may potentially reduce contraceptive efficacy or result in an increase in breakthrough bleeding.

- Prevention or management

| Prevention or management | Counsel females to use an alternative method of contraception or a backup method when enzyme inducers are used with COCs. |

| Examples | Aprepitant, barbiturates, bosentan, carbamazepine, elavirenz, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, rifabutin, rufinamide, topiramate, products containing St. John’s wort, and certain protease inhibitors (see separate section on protease inhibitors below). |

- Coleselam

<table>
<thead>
<tr>
<th>Coleselam</th>
<th>Clinical effect</th>
</tr>
</thead>
</table>

| Concomitant use of COCs with coleselam significantly decreases systemic exposure of ethinyl estradiol. |

| Decreased exposure of the estrogen component of COCs may potentially reduce contraceptive efficacy or result in an increase in breakthrough bleeding, depending on the strength of ethinyl estradiol in the COC. |

| Prevention or management | Administer 4 or more hours apart to attenuate this drug interaction. |

Induction potency of St. John’s wort may vary widely based on preparation.

Substances increasing the systemic exposure of COCs:

- Co-administration of atorvastatin or rosuvastatin and COCs containing ethinyl estradiol increase systemic exposure of ethinyl estradiol by approximately 20 to 25 percent. Absorptive acid and acetaminophen may increase systemic exposure of ethinyl estradiol, possibly by inhibition of conjugation. CVSAA inhibitors such as icarazone, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase systemic exposure of the estrogen and/or progestin component of COCs. |

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

| Concomitant use of COCs with protease inhibitors significantly decreases systemic exposure of ethinyl estradiol. |

| Decreased exposure of the estrogen component of COCs may potentially reduce contraceptive efficacy or result in an increase in breakthrough bleeding, depending on the strength of ethinyl estradiol in the COC. |

| Prevention or management | Administer 4 or more hours apart to attenuate this drug interaction. |

* Induction potency of St. John’s wort may vary widely based on preparation.

Substances increasing the systemic exposure of COCs:

**Table 3** includes substances that demonstrated an important drug interaction with QUARTETTE.

**Figure 3** includes a relevant studies of risk of breast cancer with combined oral contraceptives.
QUARTETTE® (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets

72 Effects of Combined Oral Contraceptives on Other Drugs

Table 4 provides significant drug interaction information for drugs co-administered with QUARTETTE.

Table 4: Significant Drug Interaction Information for Drugs Co-Administered With COCs

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drug Combination</th>
<th>Clinical effect</th>
<th>Prevention or Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>COCs with lamotrigine</td>
<td>Concomitant use of COCs may significantly decrease systemic exposure of lamotrigine due to induction of lamotrigine glucuronidation. Decreased systemic exposure of lamotrigine may reduce seizure control.</td>
<td>Dose adjustment may be necessary. Consult the approved product labeling for lamotrigine.</td>
</tr>
<tr>
<td>Thyroid Hormone Replacement Therapy or Corticosteroid Replacement Therapy</td>
<td>COCs with thyroid hormone replacement therapy or corticosteroid replacement therapy</td>
<td>Concomitant use of COCs may increase systemic exposure of thyroid-binding and cortisol-binding globulin.</td>
<td>The dose of replacement thyroid hormone or cortisol therapy may need to be increased. Consult the approved product labeling for the therapy in use.</td>
</tr>
<tr>
<td>Other Drugs</td>
<td>Concomitant use of COCs may decrease systemic exposure of acacetaminophen, morphine, salicylic acid, and temazepam. Concomitant use with ethinyl estradiol-containing COCs may increase systemic exposure of other drugs (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole).</td>
<td>The dosages of drugs that can be affected by this interaction may need to be increased. Consult the approved product labeling for the concomitantly used drug.</td>
<td></td>
</tr>
</tbody>
</table>

7.3 Concomitant Use with Hepatitis C Virus (HCV) Combination Therapy – Liver Enzyme Elevation

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

7.4 Effect on Laboratory Tests

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There is no use for contraception in pregnancy; therefore, QUARTETTE should be discontinued during 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 CHCs before conception or during early pregnancy.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

8.2 Lactation

Risk Summary

Contraceptive hormones and/or metabolites are present in human milk. CHCs can reduce milk production in breastfeeding females. This reduction can occur at any time but is less likely to occur once breastfeeding is well-established. When possible, advise the nursing female to use other methods of contraception until she discontinues breastfeeding (see Dosage and Administration (2.2)). The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for QUARTETTE and any potential adverse effects on the breastfeeding child from QUARTETTE or the underlying maternal condition.

8.4 Pediatric Use

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

8.6 Hepatic Impairment

No studies have been conducted to evaluate the effect of hepatic impairment on the disposition of QUARTETTE. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. QUARTETTE is contraindicated in females with acute hepatitis or severe decompensated cirrhosis. [see Contraindications (4) and Warnings and Precautions (5.2)]

10 OVERDOSAGE

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

II DESCRIPTION

QUARTETTE (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets is an extended-cycle oral contraceptive. QUARTETTE consists of 42 light pink tablets containing 0.15 mg levonorgestrel and 0.02 mg ethinyl estradiol, 21 pink tablets containing 0.05 mg levonorgestrel and 0.025 mg ethinyl estradiol, and 21 purple tablets containing 0.05 mg levonorgestrel and 0.03 mg ethinyl estradiol, and 7 yellow tablets containing 0.01 mg ethinyl estradiol. Levonorgestrel is a progestin and ethinyl estradiol is an estrogen.

The structural formulas, molecular formulas, molecular weights, and chemical names for the active components are shown below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Molecule</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levonorgestrel</td>
<td>C17H18O2</td>
<td>MW: 286.35</td>
<td></td>
</tr>
<tr>
<td>Ethinyl Estradiol</td>
<td>C18H20O2</td>
<td>MW: 286.35</td>
<td></td>
</tr>
</tbody>
</table>

Levonorgestrel is chemically 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-(17α)- (1α, 3a, 5α, 16α, 17α)-estratriene-3,17-diol, (17α, 3α, 5α, 16α, 17α)-estratriene-3,17-diol.

Each light pink tablet contains the following inactive ingredients:

- anhydrous lactose, D&C Red no. 27/phloxine aluminum lake, FD&C Blue no. 1/Indigo Carmine aluminum lake, FD&C Yellow no. 6/Sunset Yellow FCF aluminum lake, hylpromellose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, polyethylene glycol/macrogl, titanium dioxide and triacetin. Each yellow tablet contains the following inactive ingredients:

- anhydrous lactose, D&C Red no. 27/phloxine aluminum lake, FD&C Blue no. 1/Indigo Carmine aluminum lake, hylpromellose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, polyethylene glycol/macrogl, titanium dioxide and triacetin.

Each purple tablet contains the following inactive ingredients:

- anhydrous lactose, D&C Red no. 27/phloxine aluminum lake, FD&C Blue no. 2/Brilliant blue FCF aluminum lake, hylpromellose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, polyethylene glycol/macrogl, titanium dioxide and triacetin. Each pink tablet contains the following inactive ingredients:

- anhydrous lactose, D&C Yellow no. 10 aluminum lake, FD&C Yellow no. 6/Sunset Yellow FCF aluminum lake, hylpromellose, magnesium stearate, microcrystalline cellulose, polacriline potassium, polyethylene glycol/macrogl, polysorbate 80 and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CHCs prevent pregnancy primarily by suppressing ovulation.

12.2 Pharmacodynamics

No pharmacodynamic studies were conducted with QUARTETTE.

12.3 Pharmacokinetics

Absorption

Ethinyl estradiol and levonorgestrel are absorbed with maximum plasma concentrations occurring within 2 hours after QUARTETTE administration. Levonorgestrel is completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism.

Ethinyl estradiol is absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is approximately 40%. The effect of food on the rate and extent of levonorgestrel and ethinyl estradiol absorption following oral administration of QUARTETTE has not been evaluated.

The mean plasma pharmacokinetic parameters of levonorgestrel following administration of another levonorgestrel/ethinyl estradiol combination tablet with an equal dose of levonorgestrel for 84 days, in healthy women are reported in Table 5.

Table 5: Mean Pharmacokinetic Parameters for 150 mcg Levonorgestrel Following Administration of a Levonorgestrel/ Ethinyl Estradiol Combination Tablet Once Daily for 84 Days

<table>
<thead>
<tr>
<th>Dose</th>
<th>AUC last (mean ± SD)</th>
<th>Cmax (mean ± SD)</th>
<th>Tmax (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>18.2 ± 0.9 ng·hr/mL</td>
<td>3.1 ± 1.0 ng/mL</td>
<td>1.3 ± 0.4 hours</td>
</tr>
<tr>
<td>Day 21</td>
<td>64.2 ± 2.5 ng·hr/mL</td>
<td>6.2 ± 1.6 ng/mL</td>
<td>1.3 ± 0.4 hours</td>
</tr>
<tr>
<td>Day 84</td>
<td>60.2 ± 2.4 ng·hr/mL</td>
<td>5.5 ± 1.6 ng/mL</td>
<td>1.3 ± 0.3 hours</td>
</tr>
</tbody>
</table>

Following repeated daily dosing of levonorgestrel/ethinyl estradiol oral contraceptives, levonorgestrel plasma concentrations accumulate more than predicted based on single-dose pharmacokinetics, and in part, to increased sex hormone binding globulin (SHBG) levels that are induced by ethinyl estradiol, and a possible reduction in hepatic metabolic capacity.

Systemic exposure to ethinyl estradiol following administration of a levonorgestrel/ethinyl estradiol combination tablet increases linearly in an approximate dose-proportional manner over the range of doses of 20 mcg to 30 mcg within this product. Systemic exposure to ethinyl estradiol (as assessed by AUC at steady state following administration of levonorgestrel/ethinyl estradiol oral contraceptives is approximately 20% higher than expected based on single-dose data for the dose range of 20-30 mcg.
Quartette® (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets

Dosing and Missed Pill Instructions

Instruct females to stop Quartette if pregnancy is confirmed during treatment. If women are restarting (following a 4-week or greater pill-free interval) the same or a different COC cycle, counseling should be provided to ensure that the woman understands that a period may occur with the first dose. Counsel women that Quartette should be taken daily without regard to menses or food. Counseling should include the risk of pregnancy if Quartette is not taken as directed. The following chart shows the chance of getting pregnant for women who do not use birth control and the chance of getting pregnant for women who use birth control methods that are similar in effectiveness. The most effective methods of birth control include the pill, patch, shot, implant and intrauterine device (IUD). The next most effective method is the condom. Additional methods include spermicides, diaphragm or cervical cap, withdrawal, or no birth control.

FDA-approved Patient Labeling

PATIENT INFORMATION

QUARTETTE® (kwor-tet) (levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets)

What is the most important information I should know about QUARTETTE?

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

What is QUARTETTE?

QUARTETTE is a birth control pill (hormonal contraceptive) used by women to prevent pregnancy. It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called levonorgestrel.

How does QUARTETTE work for contraception?

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

Based on the results of a single clinical study lasting 12 months, 2 to 4 women out of 100 women may get pregnant during the first year they use QUARTETTE. 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.

What do I do if I miss pills?

See "What to do if you miss pills" section of the FDA-approved Instructions for Use.
QUARTETTE® (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets

Who should not take QUARTETTE?
Do not take QUARTETTE if you:
• smoke and are over 35 years of age
• had blood clots in your arms, legs, eyes, or lungs
• have certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
• had a stroke
• had a heart attack
• have an inherited problem with your blood that makes it clot more than normal
• have liver disease, including liver tumors
• have high blood pressure that medicine can’t control
• 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 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 have any migraine headaches if you are over age 35
• have any unexplained bleeding from the vagina
• had breast cancer which may be sensitive to female hormones

If any of these conditions happens to you while you are taking QUARTETTE, stop taking QUARTETTE right away and talk to your healthcare provider. Use non-hormonal contraception (such as condoms and spermicide) when you stop taking QUARTETTE.

What should I tell my healthcare provider before taking QUARTETTE?
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. QUARTETTE may decrease the amount of breast milk you make. A small amount of the hormones in QUARTETTE may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

Tell your healthcare provider if you have ever had any of the conditions listed in, “Who should not take QUARTETTE” above. Your healthcare provider may recommend another method of birth control.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. QUARTETTE may affect the way other medicines work, and other medicines may affect how well QUARTETTE 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 QUARTETTE?
Read the Instructions for Use at the end of this Patient Information.

What are the most serious risks of taking birth control pills?
Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start taking birth control pills and when you restart the same or different birth control pills after not using them for a month or more.

It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious blood clots are blood clots in the:
• Legs (deep vein thrombosis)
• Lungs (pulmonary embolus)
• Eyes (loss of eyesight)
• Heart (heart attack)
• Brain (stroke)

Women who take birth control pills may get:
• High blood pressure
• Gallbladder problems
• Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

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

Use a back-up or alternative birth control method when you take medicines that may make birth control pills less effective, including:
• barbiturates
• bosentan
• carbamazepine
• felbamate
• griseofulvin
• oxcarbazepine
• phenytoin
• rifampin
• St. John's wort
• topiramate

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

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.
**QUARTETTE®** (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone.

**How should I store Quartette?**
- Store QUARTETTE at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep QUARTETTE and all medicines out of the reach of children.

**General information about QUARTETTE**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use QUARTETTE for a condition for which it was not prescribed. Do not give QUARTETTE to anyone else.

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

**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 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 QUARTETTE?**

When you take QUARTETTE, which has a 91-day extended dosing cycle, you should expect to have 4 scheduled periods per year (bleeding when you are taking the 7 yellow pills). Each period is likely to last about 3-4 days. However, you will probably have more bleeding or spotting between your scheduled periods than if you were using a birth control pill with a 28-day dosing cycle. This bleeding or spotting tends to decrease with each additional cycle. Do not stop taking QUARTETTE because of this bleeding or spotting. If the spotting continues for more than 7 consecutive days or if the bleeding is heavy, call your healthcare provider.

**What if I miss my scheduled period when taking QUARTETTE?**

If you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider evaluates you to determine if you are pregnant. Stop taking QUARTETTE if it is determined that you are pregnant.

**What are the ingredients in QUARTETTE?**

**Active ingredients:**
- Light pink tablets: levonorgestrel acetate and ethinyl estradiol
- Yellow tablets: ethinyl estradiol

**Inactive ingredients:**
- Light pink tablets: anhydrous lactose, D&C Red no. 27/phloxine aluminum lake, FD&C Blue no. 2/Indigo Carmine aluminum lake, FD&C Yellow no. 6/Sunset Yellow FCF aluminum lake, hypromellose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, polyethylene glycol/macrogol, titanium dioxide, and triacetin.
- Pink tablets: anhydrous lactose, D&C Red no. 27/phloxine aluminum lake, FD&C Blue no. 2/Indigo Carmine aluminum lake, hypromellose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, polyethylene glycol/macrogol, titanium dioxide and triacetin.
- Purple tablets: anhydrous lactose, D&C Red no. 27/phloxine aluminum lake, FD&C Blue no. 1/Brilliant blue FCF aluminum lake, hypromellose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, polyethylene glycol/macrogol, titanium dioxide and triacetin.
- Blue no. 2/Indigo Carmine aluminum lake, hypromellose, lactose monohydrate, microcrystalline cellulose, magnesium stearate, polyethylene glycol/macrogol, polysorbate 80 and titanium dioxide.

**INSTRUCTIONS FOR USE QUARTETTE® (kwor-tet)**

**Yellow tablets:** anhydrous lactose, D&C yellow no. 10 aluminum lake, FD&C Yellow no. 6/Sunset Yellow FCF aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polacrill potassium, polyethylene glycol/macrogol, polysorbate 80 and titanium dioxide.

**Important information about taking QUARTETTE**

1. Take one pill every day at the same time. Take pills in the order directed on the Extended-Cycle Tablet Dispenser.
2. Do not skip pills or delay taking your pills. 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.
3. You may have spotting or light bleeding or feel sick to your stomach during the first few months of taking QUARTETTE. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn’t go away, check with your healthcare provider.
4. If you vomit or have diarrhea within 4 hours after taking your pill, follow the instructions in, “What to do if you miss pills.”
5. Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
6. If you have trouble remembering to take QUARTETTE, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

**Before you start taking QUARTETTE**

1. Decide what time of day you want to take your pill. It is important to take it at about the same time every day.
2. Look at your Extended-Cycle Tablet Dispenser. Your Extended-Cycle Tablet Dispenser consists of 3 trays with cards that hold 91 individually sealed pills (a 13-week or 91-day cycle). The 91 pills consist of 42 light pink tablets, each containing 0.15 mg of levonorgestrel and 0.02 mg ethinyl estradiol, 21 pink tablets containing 0.15 mg of levonorgestrel and 0.025 mg ethinyl estradiol, 21 purple tablets containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol, and 7 yellow tablets containing 0.01 mg of ethinyl estradiol.

Tray 1 contains 4 rows of 7 light pink pills.
If you **MISS 3 OR MORE** light pink, pink or purple pills in a row:
1. Do not take the missed pills. Keep taking 1 pill every day as indicated on the pack until you have completed all of the remaining pills in the pack. For example: If you resume taking the pill on Thursday, take the pill under “Thursday” and do not take the missed pills. You may experience bleeding during the week following the missed pills.
2. You could become pregnant if you have sex during the days of missed pills or during the first 7 days after restarting your pills.
3. You MUST use a non-hormonal birth control method (such as condoms and spermicide) as a back-up when you miss pills and for the first 7 days after you restart your pills. If you do not have your period when you are taking the yellow pills, call your healthcare provider because you may be pregnant.

If you **MISS ANY** of the 7 yellow pills:
1. Throw away the missed pills.
2. Take the next scheduled pill at the scheduled time.
3. You do not need a back-up method of birth control.

**Finally, if you are still not sure what to do about the pills you have missed**
1. Use a back-up method anytime you have sex.
2. Keep taking one pill each day until you contact your healthcare provider.

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

Manufactured for:
Teva Pharmaceuticals
Parsippany, NJ 07054

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.
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QRTPL-001
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