

**TRILo-MARZA, norgestimate and ethinyl estradiol
Lipix Pharmaceuticals, Inc.**

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRILo-MARZA safely and effectively. See full prescribing information for TRILo-MARZA, TRILo-MARZA norgestimate and ethinyl estradiol tablets USP, for use in the U.S. Approved 1288

WARNING: CIGARETTE SMOKING and SERIOUS CARDIOVASCULAR EVENTS

- Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. The 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)).

RECENT MAJOR CHANGES

- Warnings and Precautions (5.1) 1/2021
- Contraindications (4) 1/2021
- Indications and Usage (2.1) 1/2021
- Warnings and Precautions (5.1) 1/2021
- Warnings and Precautions (5.1) 1/2021

INDICATIONS AND USAGE

- TRILo-MARZA is indicated for the prevention of pregnancy in women who desire to avoid pregnancy. (2.1)
- Use one tablet daily for 21 days of the 28-day cycle (see 2.1).
- Use tablets in the order directed on the label (2.2).
- Do not skip or delay tablet intake (2.2).

DOSE FORMS AND STRENGTHS

- TRILo-MARZA consists of 28 tablets. The tablets contain the following active ingredients: ethinyl estradiol 0.01 mg, norgestimate 0.01 mg, and norgestimate 0.01 mg and ethinyl estradiol 0.01 mg.
- 28 light blue tablets each containing 0.01 mg norgestimate and 0.01 mg ethinyl estradiol.
- 28 green tablets each containing 0.01 mg norgestimate and 0.01 mg ethinyl estradiol.
- 7 green tablets (inert).

CONTRAINDICATIONS

- A high risk of arterial or venous thrombotic disease (4)
- Current or past history of stroke (4)
- Current or past history of myocardial infarction (4)
- Current or past history of deep vein thromboses (4)
- Current or past history of pulmonary embolism (4)
- Current or past history of acute or chronic liver disease, which may be hormone-sensitive (4)
- Current or past history of hypertension (4)
- Current or past history of diabetes mellitus (4)
- Current or past history of hypercholesterolemia (4)
- Current or past history of severe renal impairment (4)
- Current or past history of severe allergic reaction to any of the components of TRILo-MARZA (4)

WARNINGS AND PRECAUTIONS

- **Thrombotic and Thromboembolic Disorders and Other Vascular Problems:** See full prescribing information for TRILo-MARZA for a thorough discussion. The risk of thrombotic and thromboembolic disorders, which may be hormone-related, increases with age and with increasing duration of use. The risk of thrombotic and thromboembolic disorders, which may be hormone-related, increases with age and with increasing duration of use. The risk of thrombotic and thromboembolic disorders, which may be hormone-related, increases with age and with increasing duration of use.
- **Cardiovascular Disease:** See full prescribing information for TRILo-MARZA for a thorough discussion. The risk of cardiovascular disease, which may be hormone-related, increases with age and with increasing duration of use.
- **Diabetes Mellitus and Impaired Glucose Tolerance:** See full prescribing information for TRILo-MARZA for a thorough discussion. The risk of diabetes mellitus and impaired glucose tolerance, which may be hormone-related, increases with age and with increasing duration of use.
- **Hypertension:** See full prescribing information for TRILo-MARZA for a thorough discussion. The risk of hypertension, which may be hormone-related, increases with age and with increasing duration of use.
- **Hypertriglyceridemia and Pancreatic Disease:** See full prescribing information for TRILo-MARZA for a thorough discussion. The risk of hypertriglyceridemia and pancreatic disease, which may be hormone-related, increases with age and with increasing duration of use.
- **Acute or Chronic Liver Disease:** See full prescribing information for TRILo-MARZA for a thorough discussion. The risk of acute or chronic liver disease, which may be hormone-related, increases with age and with increasing duration of use.

ADVERSE REACTIONS

- See full prescribing information for TRILo-MARZA for a thorough discussion of adverse reactions.

DRUG INTERACTIONS

- See full prescribing information for TRILo-MARZA for a thorough discussion of drug interactions.

USE IN SPECIFIC POPULATIONS

- See full prescribing information for TRILo-MARZA for a thorough discussion of use in specific populations.

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

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FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING and SERIOUS CARDIOVASCULAR EVENTS

INDICATIONS AND USAGE

1.1 Oral Contraception

TRILo-MARZA Tablets are indicated for use by females of reproductive potential to prevent pregnancy (see CLINICAL STUDIES (14)).

DOSE AND ADMINISTRATION

2.1 How to Start TRILo-MARZA

TRILo-MARZA is dispensed in a blister (see HOW SUPPLIED/STORAGE AND HANDLING (16)). TRILo-MARZA may be started using either a Day 1 start or a Sunday Start (see Table 1). For the first cycle of a Sunday Start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

2.2 How to Take TRILo-MARZA

TRILo-MARZA active tablets are white to off-white (Day 1 to Day 7), light blue (Day 8 to Day 15) and blue (Day 16 to Day 21) and has green inactive tablets (Day 22 to Day 28).

Table 1: Instructions for Administration of TRILo-MARZA

Starting COCs in women not currently using hormonal contraception (Day 1 Start or Sunday Start)

Day 1 Start:

- Take first active tablet without regard to menses 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 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).

Sunday Start:

- Take first active tablet without regard to menses 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 TRILo-MARZA.
- Take subsequent active tablets once daily at the same time each day for a total of 21 days.
- Take one 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 contraception is not needed).

Start on TRILo-MARZA:

- Start on the same day that a new pack of the previous oral contraceptive would have started.

Missing Tablets:

- On the day when next ingestion would have been scheduled.
- On the day when next ingestion would have been scheduled.
- On the day when next ingestion would have been scheduled.
- On the day of menses.
- On the day when next ingestion would have been scheduled.
- On the day when next ingestion would have been scheduled.
- On the day of menses.
- On the day of menses.

Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-Approved Patient Labeling.

Starting TRILo-MARZA after Abortion or Miscarriage

First trimester:

- After a first-trimester abortion or miscarriage, TRILo-MARZA may be started immediately. An additional method of contraception is not needed if TRILo-MARZA is started immediately.
- If TRILo-MARZA 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 TRILo-MARZA.

Second trimester:

- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thrombotic disease. Start TRILo-MARZA following the instructions in Table 1 for Day 1 or Sunday Start, as desired. If a Sunday Start regimen is used, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of TRILo-MARZA (see CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1), and FDA-APPROVED PATIENT LABELING).

Starting TRILo-MARZA after Childbirth

Do not start until 4 weeks after delivery, due to the increased risk of thrombotic disease. Start TRILo-MARZA following the instructions in Table 1 for Day 1 or Sunday Start, as desired. If a Sunday Start regimen is used, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of TRILo-MARZA (see CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1), USE IN SPECIFIC POPULATIONS (8.1), and FDA-APPROVED PATIENT LABELING).

Bliстер Pack:

SET THE DAY

- **Sunday Start:** Each blister has been preprinted with the days of the week, starting with Sunday, to facilitate a Sunday-Start regimen.
- **Day 1 Start:**
 - Six different day label strips of the week have been provided with this pack in order to accommodate a Day 1 Start regimen.
 - Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the blister (Refer Figure below).

Remove pill "1" by pushing down on the pill. The pill will come out through a hole in the back of the strip. The patient should wait 24 hours to take the next pill. Continue to take one pill each day until the pack has been taken. When your blister is empty, you will start a new blister on the day after pill 28. The first pill in every blister will always be taken on the same day of the week, no matter when the patient's next period starts.

2.3 Missed Tablets

Table 2: Instructions for Missed TRILo-MARZA Tablets

If one active tablet is missed in the first week or three or more active tablets are missed in a row in Weeks 1, 2, or 3:

- Skip the missed tablet(s) as soon as possible and take the next day active tablet 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 backup if the patient has sex within 7 days after missing tablet(s).
- Skip the missed tablet(s) as soon as possible and take the next day active tablet the next day. 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 backup if the patient has sex within 7 days after missing tablet(s).

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 DOSAGE FORMS AND STRENGTHS

TriLo-Marzia Tablets are available in 3 boxes. Each blister contains 28 tablets in the following order:

- 7 white, flat, round, film-coated tablets debossed with 'L1' on one side and 'E21' on the other side of the tablet contains 0.18 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 light blue, round, film-coated tablets debossed with 'L1' on one side and 'E22' on the other side of the tablet contains 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 blue, round, film-coated tablets debossed with 'L1' on one side and 'E23' on the other side of the tablet contains 0.23 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 green, round, scoreless, film-coated tablets debossed with 'L1' on one side and 'E24' on the other side of the tablet contains inert ingredients

4 CONTRAINDICATIONS

TriLo-Marzia is contraindicated in females who are known to have or develop the following conditions:

- A high risk of arterial or venous thrombotic disease. Examples include women who are known to:
 - Smoke, if over age 35 [see **BOXED WARNING** and **WARNINGS AND PRECAUTIONS** (5.3)]
 - Have deep vein thrombosis or pulmonary embolism, now or in the past [see **WARNINGS AND PRECAUTIONS** (5.1)]
 - Have an inherited or acquired hypercoagulopathy [see **WARNINGS AND PRECAUTIONS** (5.1)]
 - Have cardiovascular disease [see **WARNINGS AND PRECAUTIONS** (5.1)]
 - Have coronary artery disease [see **WARNINGS AND PRECAUTIONS** (5.1)]
 - Have thrombotic valvular or thrombotic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see **WARNINGS AND PRECAUTIONS** (5.1)]
 - Have 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)]
- Unexplained abnormal uterine bleeding [see **WARNINGS AND PRECAUTIONS** (5.8)]
- Pregnancy, because there is no reason to use COCs during pregnancy [see **WARNINGS AND PRECAUTIONS** (4.0) and **USE IN SPECIFIC POPULATIONS** (6.1)]
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive [see **WARNINGS AND PRECAUTIONS** (5.1)]
- Use of Hepatitis C drug combinations containing ombitasvir/paritapavir/sofosbuvir, with or without daclatasvir, due to the potential for ALT elevations [see **WARNINGS AND PRECAUTIONS** (5.3)]

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic Disorders and Other Vascular Problems

- Stop TriLo-Marzia if an arterial thrombotic event or venous thrombotic (VTE) event occurs.
- Stop TriLo-Marzia if there is unexplained loss of vision, proptosis, diplopia, papilloedema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately [see **ADVERSE REACTIONS** (6.2)].
- If feasible, stop TriLo-Marzia 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 the period of immobilization.
- Start TriLo-Marzia no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of pulmonary VTE decreases after the third postpartum week, whereas the risk of venous thrombosis 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 thrombotic disease due to COCs gradually disappears after use is discontinued.
- Use of COCs also increases the risk of arterial thrombooses 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 absolute risk of stroke and myocardial events (myocardial infarction and hemorrhagic stroke). 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 TriLo-Marzia in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver [see **CONTRAINDICATIONS** (4)]. Acute or chronic disturbance of liver function may necessitate the discontinuation of COC use and return of liver function returns to normal and COC cessation has been evaluated [discontinue TriLo-Marzia if jaundice develops].

Liver Tumors

TriLo-Marzia is contraindicated in women with benign and malignant liver tumors [see **CONTRAINDICATIONS** (4)]. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3 to 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/paritapavir/sofosbuvir, with or without daclatasvir, 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, than in women using TriLo-Marzia prior to starting therapy with the combination drug regimen ombitasvir/paritapavir/sofosbuvir, with or without daclatasvir [see **CONTRAINDICATIONS** (4)]. TriLo-Marzia can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.4 High Blood Pressure

TriLo-Marzia is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease [see **CONTRAINDICATIONS** (4)]. For women with well-controlled hypertension, monitor blood pressure and stop TriLo-Marzia 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 meta-analysis of COC-related cholelithiasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholelithiasis may be at an increased risk for COC related cholelithiasis.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor diabetic and diabetic women who take TriLo-Marzia. COCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled diabetes. 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

A woman taking TriLo-Marzia develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue TriLo-Marzia if indicated.

Consider discontinuation of TriLo-Marzia in the case of increased frequency or severity of migraines during COC use, which may be proportional to a cerebrovascular event.

5.8 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough or intermenstrual) 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 malabsorption of ethinyl estradiol and progestin. The following bleeding irregularities may resolve over time, or with a change to a different birth control product:

• the clinical trial of TriLo-Marzia, the frequency and duration of unscheduled bleeding and spotting was assessed in 1,673 women (11,015 evaluable cycles). A total of 3 malabsorption events were reported in women using TriLo-Marzia, as well as 12 bleeding irregularities based on data from the clinical trial. In 76.1% of women using TriLo-Marzia, experienced unscheduled bleeding per cycle in the first year. The percent of women who experience unscheduled bleeding tended to decrease over time.

Amenorrhea and Oligomenorrhea

Women who use TriLo-Marzia 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 tablets or started taking them on a day that 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 epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in the first trimester of pregnancy, and any reduction defects are concerned when oral contraceptives are taken inadvertently during early pregnancy. Discontinue TriLo-Marzia 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** (6.1)].

5.10 Depression

Carefully observe women with a history of depression and discontinue TriLo-Marzia if depression recurs to a serious degree.

5.11 Malignant Neoplasms

Breast Cancer

TriLo-Marzia is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormone 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 oral (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 and recent users 1-6 months since last usage 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.

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 using TriLo-Marzia.

6 ADVERSE REACTIONS

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

- Serious cardiovascular events and stroke [see **BOXED WARNING** and **WARNINGS AND PRECAUTIONS** (5.1)]
- Vascular events [see **WARNINGS AND PRECAUTIONS** (5.1)]
- Liver disease [see **WARNINGS AND PRECAUTIONS** (5.2)]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

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

The safety of TriLo-Marzia was evaluated in 1,723 subjects who participated in a randomized, partially blinded, multicenter, active-controlled clinical trial of TriLo-Marzia for contraception. This trial examined health, reproductive, and safety outcomes in 45 (100%) women 17 to 45 years of age, who were sexually active with regular coitus. Subjects were followed for up to 13 28-day cycles.

Common Adverse Reactions (≥ 2% of subjects)

The most common adverse reactions reported by at least 2% of the 1,723 women using the 28-day regimen were the following in order of decreasing incidence: headache (16.3%), malabsorption (15.3%), breast discomfort (including tenderness, pain, enlargement, swelling, discharge, discomfort, cyst, and nipple pain) (13.3%), abdominal pain (12.7%), menstrual disorder (including dysmenorrhea, menstrual discomfort, menstrual disorder) (9.2%), mood disorders (including depression, mood elevated, mood swings and depressed mood) (7.7%), acne (5.1%), vulvovaginal infection (3.5%), abdominal distention (2.8%), weight increased (2.4%), fatigue (2.3%).

Adverse Reactions Leading to Study Discontinuation

In the clinical trial of TriLo-Marzia 4% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions leading to discontinuation were

headache/migraine (1.2%), nasabronchitis (0.7%), cervical dysplasia (0.7%), abdominal pain (0.4%), ovarian cyst (0.3%), acne (0.2%), fatigue (0.2%) and depression (0.2%).

6.5 Adverse Reactions

Cancers of the cervix (n=46) (subject) and cervical dysplasia (1 subject).

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 0.99 - 1.12 (Figure 1).

Three studies compared breast cancer risk between current or recent COC users (< 65 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 or 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.

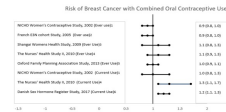


Figure 1: Risk of Breast Cancer with Combined Oral Contraceptive Use

RR = relative risk; OR = odds ratio; WH = hazard ratio. Ever COC User = females with current or past COC use; never COC User = females that never used COCs.

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

Infections and Infestations

Urinary tract infection

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

Immune System Disorders

Hypersensitivity

Metabolism and Nutrition Disorders

Dyslipidemia

Psychiatric Disorders

Anxiety, insomnia

Nervous System Disorders

Syncope, convulsion, paraesthesia, 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 flash

Arterial Events

Arterial thromboembolism, myocardial infarction, cerebrovascular accident

Respiratory, Thoracic and Mediastinal Disorders

Dyspnea

Gastrointestinal Disorders

Pain, flatulence, abdominal distension, diarrhea, constipation

Hepatoerythroid Disorders

Hepatitis

Skin and Subcutaneous Tissue Disorders

Angioedema, erythema nodosum, itchy rash, night sweats, hyperhidrosis, photosensitivity reaction, urticaria, pruritus, acne

Musculoskeletal, Connective Tissue, and Bone Disorders

Muscle spasms, pain in extremities, 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 TriLo-Maria.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances Decreasing the Plasma Concentrations of COCs

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

Coenzalim

Coenzalim, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of ethinyl estradiol (EE). The drug interaction between the contraceptive and coenzalim was decreased when the two drug products were given 4 hours apart.

Substances Increasing the Plasma Concentrations of COCs

Co-administration of atorvastatin or rosuvastatin and certain COCs containing EE increase AUC values for EE by approximately 20 to 25%. Acetaminophen, aspirin, and antiplatelet drugs may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as Erlofinic, voriconazole, itraconazole, 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 atazanavir and/or protease have been noted in some cases of co-administration with HIV protease inhibitors (lopinavir, nelfinavir, ritonavir, darunavir/Ritonavir, fosamprenavir, saquinavir, zalcitabine, and zalcitabine/Ritonavir) or increase (e.g., indinavir and atazanavir/Ritonavir/HCV protease inhibitors (boceprevir (e.g., boceprevir) and telaprevir) or with non-nucleoside reverse transcriptase inhibitors (lopinavir (e.g., lopinavir) or increase (e.g., efavirenz).

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds (e.g., prochlorperazine, promethazine, theophylline, theophylline, and terfenadine) to increase their plasma concentrations.

COCs have been shown to decrease plasma concentrations of acetaminophen, cefaclor, ace, morphine, salicylic acid, tramadol and lamotrigine. Significant decrease in plasma concentration of lamotrigine has been observed. Delay due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

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

7.3 Interference with Laboratory Tests

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

7.4 Concomitant Use with HCV Combination Therapy - Liver Enzyme Elevation

Do not co-administer TriLo-Maria Tablets with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without sofosbuvir, due to potential for ALT elevations (see WARNINGS AND PRECAUTIONS (3.3)).

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-analysis have not found an increased risk of genital or non-genital limb defects (including cleft lip and/or palate 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.

8.2 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 TriLo-Maria Tablets have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

TriLo-Maria has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

The pharmacokinetics of TriLo-Maria has not been studied in subjects with hepatic impairment. However, altered clearance may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbance of liver function may increase the distribution of COC, use until markers of liver function return to normal and COC clearance has been established. (see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (3.2))

8.7 Renal Impairment

The pharmacokinetics of TriLo-Maria has not been studied in women with renal impairment.

10 OVERDOSAGE

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

11 DESCRIPTION

TriLo-Maria is a combination oral contraceptive containing the progestational component norgestimate and the estrogenic component ethinyl estradiol. Norgestimate is designated as (1-[13-Ethinyl-17-methylene-18,19-dioxo-17a-pregn-4-en-20-yn-5-one carbonyl acetate]) ester) and ethinyl estradiol is designated as (13a-oxo-17a-pregn-4-en-20-yn-5-one).

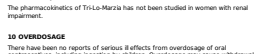
Each active white film-coated tablet contains 0.18 mg norgestimate and 0.025 mg ethinyl estradiol. Inactive ingredients include anhydrous lactose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide.

Each active light blue film-coated tablet contains 0.215 mg norgestimate and 0.025 mg ethinyl estradiol. Inactive ingredients include anhydrous lactose, croscarmellose sodium, FDC Blue No. 2 Aluminum Lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide.

Each active blue film-coated tablet contains 0.25 mg norgestimate and 0.025 mg ethinyl estradiol. Inactive ingredients include anhydrous lactose, croscarmellose sodium, FDC Blue No. 2 Aluminum Lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide.

Each green film-coated tablet contains only inert ingredients, as follows: croscarmellose sodium, FDC Blue No. 2 Aluminum Lake, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

TriLo-Maria



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with TriLo-Maria.

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 norgestrelone (NGN) and norgestrel (NG), which are the major active metabolites of NGM.

Mean pharmacokinetic parameters for NGM, NG and EE during three cycles of administration of TriLo-Maria are summarized in Table 3.

Peak serum concentrations of NGM and EE were generally reached by 2 hours after administration of TriLo-Maria. Accumulated plasma concentrations of the 0.18 mg EE and 0.25 mg NGM were approximately 1.5 to 2 times the mean plasma concentration of EE and NGM, respectively, following single-dose administration, in agreement with the predicted based on linear kinetics of NGM and EE. The pharmacokinetics of NGM at dose proportional following NGM doses of 0.18 to 0.25 mg. Steady-state conditions for NGM following each NGM dose and for EE were achieved during the three cycle study. Non-linear accumulation (1.5 to 1.4 fold) of NG was observed as a result of high affinity binding to SHBG, which limits its biological activity.

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

Table 3: Mean (SD) Pharmacokinetic Parameters of TriLo-Maria During a Three Cycle Study									
Study ^a	Cycle	Day	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₂₄ (ng·h/mL)	AUC ₀₋₂₄ (ng·h/mL)	t _{1/2} (h)	C _{min} (ng/mL)	IC ₅₀ (ng/mL)
NGM ^b (n=17)	1	1	0.93 (0.27)	1.8 (1.0)	5.88 (1.54)	NC			
	7	1	1.82 (0.43)	1.8 (0.7)	11.8 (3.7)	NC			
	14	1	1.57 (0.39)	1.8 (0.7)	11.9 (4.3)	NC			
NGM ^c (n=17)	1	1	0.52 (0.18)	2.0 (1.1)	2.44 (1.04)	NC			
	7	1	1.24 (0.30)	1.9 (0.9)	7.2 (3.1)	NC			
	14	1	1.11 (1.33)	4.0 (0.9)	46.7 (24.8)	NC			
EE ^b (n=17)	1	1	35.8 (10.1)	1.7 (0.5)	421 (138)	NC			
	7	1	62.1 (25.7)	1.8 (0.5)	752 (200)	NC			
	14	1	56.9 (28.3)	1.8 (0.5)	799 (233)	NC			
EE ^c (n=17)	1	1	15.9 (5.0)	1.8 (0.6)	171 (50)	NC			

NC = not calculated.

^a NGM = norgestimate, NG = norgestrel, EE = ethinyl estradiol.
^b NGM = norgestimate, NG = norgestrel, EE = ethinyl estradiol. AUC₀₋₂₄ = area under serum concentration vs. time curve from 0 to 24 hours, t_{1/2} = elimination half-life, C_{min} for EE and NG = 0.05 ng/mL, AUC₀₋₂₄ = ng·h/mL.
^c Units for EE analyses: n = 16 only.
Units for EE C_{max}, C_{min}, AUC₀₋₂₄ = ng·h/mL, AUC₀₋₂₄ = h·ng/mL.

Food Effect:

The effect of food on the pharmacokinetics of TriLo-Maria has not been studied.

Distribution

NGM and NG are highly bound (>97%) to serum proteins. NGM is bound to albumin and not to SHBG, while NG is bound primarily to SHBG. EE is extensively bound (>97%) to serum albumin and its binding increases as the serum concentration of SHBG increases.

Metabolism

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

Excretion

Following 3 cycles of administration of TriLo-Maria, the mean (± SD) elimination half-life values, at steady-state, for NGM, NG and EE were 28.1 (± 10.4) hours, 30.4 (± 10.2) hours and 17.7 (± 4.6) hours, respectively (Table 2). The metabolites of NGM and EE are eliminated by renal and fecal pathways.

Use in Specific Populations

Effects of Body Weight, Body Surface Area, and Age:

The effects of body weight, body surface area, age and race on the pharmacokinetics of NGM, NG and EE were evaluated in 19 healthy women using pooled data following single-dose administration of NGM 0.18 or 0.25 mg/EE 0.025 mg tablets in four pharmacokinetic studies. Increasing body weight and body surface area were each associated with decreases in C_{max} and AUC₀₋₂₄ values for NGM and EE and increases in C_{min} for EE. Increasing body weight by 15 kg is predicted to reduce the following parameters: NGM C_{max} by 9% and AUC₀₋₂₄ by 17%, NG C_{max} by 17% and AUC₀₋₂₄ by 40%, EE C_{min} by 15% and AUC₀₋₂₄ by 12%. These changes were statistically significant. Increasing age was associated with an increase in C_{max} and AUC₀₋₂₄ values for NGM and EE and with a decrease in C_{min} for EE. These changes were statistically significant, but trends were not significant for NGM or EE. Overall, age and weight had little to no effect on the pharmacokinetics of NGM and EE following TriLo-Maria tablets may be explained by any or all of the above demographic parameters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(see WARNINGS AND PRECAUTIONS (5.2, 5.11) and USE IN SPECIFIC POPULATIONS (6.8))

14 CLINICAL STUDIES

In an active controlled clinical trial lasting 12 months, 1,673 women, 18 to 45 years old completed 11,203 cycles of TriLo-Maria use and a total of 20 pregnancies were reported as TriLo-Maria users. The racial demographics of those treated with TriLo-Maria was: Caucasian (86%), African-American (6%), Asian (2%), and Other (6%). There were no exclusions on the basis of weight, the weight gain for women treated was 10 to 240 lbs, with a mean weight of about 142 lbs. The pregnancy rate in women aged 18 to 35 years was approximately 2.5 pregnancies per 100 women years of use.

15 HOW SUPPLIED/STORAGE AND HANDLING

15.1 How Supplied

TriLo-Maria are available in a blister (NDC 68180-837-71) containing 28 tablets packed in a pouch (NDC 68180-837-71). Such three pouches are packaged in a carton (NDC 68180-837-73).

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

- 1 white to off white, round, film-coated tablet, debossed with "L1" on one side and "E21" on the other side contains 0.18 mg norgestimate and 0.025 mg ethinyl estradiol.
- 7 light blue, round, film-coated tablets, debossed with "L1" on one side and "E23" on the other side contains 0.215 mg norgestimate and 0.025 mg ethinyl estradiol.
- 7 blue, round, film-coated tablets, debossed with "L1" on one side and "E23" on the other side contains 0.25 mg norgestimate and 0.025 mg ethinyl estradiol.
- 7 green, round, biconvex, film-coated tablets (non-hormonal placebo) debossed with "L1" on one side and "E24" on the other side contains inert ingredients.

15.2 Storage Conditions

- Store at 25°C (77°F), excursions permitted to 15° to 30°C (59° to 86°F). (see USP Controlled Room Temperature).
- Protect from light.
- Keep this and all medication out of reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-APPROVED PATIENT LABELING (PATIENT INFORMATION AND INSTRUCTION FOR USE).

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should use COCs (see BOXED WARNING).
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC, and reducing following a week of use. The risk of VTE is increased in a different COC (see WARNINGS AND PRECAUTIONS (5.1)).
- TriLo-Maria does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- TriLo-Maria is not to be used during pregnancy. If pregnancy occurs during use of TriLo-Maria instruct the patient to stop further COC use (WARNINGS AND PRECAUTIONS (5.8)).
- Take one tablet daily by mouth, at the same time every day. Instruct patients what to do in the event tablets are missed (see DOSAGE AND ADMINISTRATION (2.2)).
- Use a backup or alternative method of contraception when excursions are used with TriLo-Maria (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 (6.3)).
- Women who start COC postpartum, and who have not yet had a period, should use an additional method of contraception until they have had a white tablet for 7 consecutive days (see CONTRAINDICATIONS (4.2)).
- 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)).

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United States

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India

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PATIENT INFORMATION

TriLo-Maria® (E21-L0W-mar-ZEE-uh)

(norgestimate and ethinyl estradiol tablets USP)

What is the most important information I should know about TriLo-Maria?

Do not use TriLo-Maria 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. The risk increases with age and the number of cigarettes you smoke.

What is TriLo-Maria?

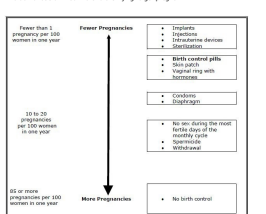
TriLo-Maria is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

How does TriLo-Maria work for contraception?

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

Based on this results from the clinical study, about 3 out of 100 women may get pregnant during the first year you use TriLo-Maria.

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



Who should not take TriLo-Maria?

Do not take TriLo-Maria if you:

- smoke and are over 35 years of age
- had blood clots in your arms, legs, lungs, or eyes
- had a problem with your blood that makes it clot more than normal
- have certain heart valve problems or irregular heart beat that increases your risk of having blood clots
- had a stroke
- had a heart attack
- have high blood pressure that cannot be controlled by medicine
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or any migraine headaches if you are over 35 years of age
- have liver problems, including liver tumors
- take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme 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 TriLo-Maria, stop taking TriLo-Maria right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking TriLo-Maria.

What should I tell my healthcare provider before taking TriLo-Marzia?

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 the liver
- are breastfeeding or plan to breastfeed. TriLo-Marzia may decrease the amount of breast milk you make. A small amount of the hormones in TriLo-Marzia may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. TriLo-Marzia may affect the way other medicines work, and other medicines may affect how well TriLo-Marzia 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 TriLo-Marzia?

Read the instructions for use at the end of this Patient Information.

What are the possible serious side effects of TriLo-Marzia?

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

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

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

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

- leg pain that will not go away
- sudden severe shortness of breath
- sudden change in vision or blindness
- chest pain
- 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 failure
 - 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 TriLo-Marzia.**
- **depression**
- **possible cancer in your breast and cervix**
- **darkening of your skin especially around your mouth, eyes, and in your hands (acanthosis).** Call your healthcare provider if you have a certain face, lip, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your blood or urine sometimes is higher than normal from a history of acanthosis.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Women who use birth control pills should avoid spending a long time in sunlight, tanning booths, and under a tanning bed while taking TriLo-Marzia. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of TriLo-Marzia?

- headache (including migraine)
- nausea and vomiting
- breast problems
- tenderness, pain and discomfort
- enlargement and swelling
- discharge
- nipple pain
- stomach pain
- pain with your periods (menstrual cycle)
- mood changes, including depression
- vaginal infections
- chloasma
- weight gain
- fatigue

These are not all the possible side effects of TriLo-Marzia. For more information, ask your healthcare provider or pharmacist.

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

You may also report side effects to Lupton Pharmaceuticals, Inc. at 1-800-399-2561 or you can visit the Lupton website at www.luptonpharmaceutical.com.

What else should I know about taking TriLo-Marzia?

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

How should I store TriLo-Marzia?

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

General information about the safe and effective use of TriLo-Marzia.

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

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

For more information, call Lupton Pharmaceuticals, Inc. at 1-800-399-2561 or you can visit the Lupton website at www.luptonpharmaceutical.com.

Does hormonal birth control 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 TriLo-Marzia?

Your periods may be lighter and shorter than usual. Some women may miss a period. Irregular vaginal bleeding or spotting may happen when you are taking TriLo-Marzia, 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 TriLo-Marzia?

Active Ingredients: Each white to off white, light blue, and blue pill contains norgestrel and ethinyl estradiol.

Inactive Ingredients

White to off white pill: anhydrous lactose, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol and titanium dioxide.

Light blue pill: anhydrous lactose, croscarmellose sodium, FDSC Blue No. 2, aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

Blue pill: anhydrous lactose, croscarmellose sodium, FDSC Blue No. 2, aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, and titanium dioxide.

Green pill: croscarmellose sodium, FDSC Blue No. 2, aluminum lake, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

INSTRUCTIONS FOR USE

TriLo-Marzia (TRY-LOW-mar-ZEE-uh)

(norgestrel and ethinyl estradiol tablets USP)

Important information about taking TriLo-Marzia

- Take 1 pill every day at the same time. Take the pills in the order directed on your blister.
- Do not stop 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 TriLo-Marzia, talk to your healthcare provider. When you first start taking TriLo-Marzia, spotting or light bleeding in between your periods may occur. Contact your healthcare provider if this does not go away after 4 free months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking TriLo-Marzia. 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. Do not change your take 28 pill pack for missed pills. See **What Should I Do if I Miss Any TriLo-Marzia Pills?** below. If you find out that you do not have your stomach.
- If you do not want to miss a period, however, if you miss a period and have not taken TriLo-Marzia 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 TriLo-Marzia.
- If you have vomiting or diarrhea within 1 to 4 hours of taking your pill, take another pill of the same color from your extra blister. If you do not have an extra blister, take the next pill in your blister. Continue taking any remaining pills in the order. Start the first pill of your next blister the day after finishing your current blister. 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, when you use TriLo-Marzia with your healthcare provider.
- Stop taking TriLo-Marzia 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 TriLo-Marzia

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

When should I start taking TriLo-Marzia?

If you start taking TriLo-Marzia 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 TriLo-Marzia. You do not need back-up contraception if you use the Day 1 Start.

If you start taking TriLo-Marzia and you are switching from another birth control pill:

- Start your new TriLo-Marzia pack on the same day that you would start the next pack of your previous birth control method.
- Do not continue taking the pills from your previous birth control pack.

If you start taking TriLo-Marzia and previously used a vaginal ring or transdermal patch:

- Start using TriLo-Marzia on the day you would have replaced the next ring or patch.

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

- Start taking TriLo-Marzia on the day of removal of your implant or on the day when you would have had your next injection.

If you start taking TriLo-Marzia and you are switching from an intravaginal device or system (IUD or IUS):

- Start taking TriLo-Marzia 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 TriLo-Marzia.

Keep a calendar to track your period:

It is the first time you are taking birth control pills, read "When Should I Start Taking TriLo-Marzia?" 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 Sunday.

- Take pill 1 on the **Sunday after your period starts.**
- If your period starts on a Sunday, take pill 1 the day and refer to Day 1 Start instructions below.
- Take 1 pill every day in the order on the blister at the same time each day for **28** days.
- After taking the last pill on **Day 28** from the blister, 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 spermicide for the first 7 days of the first cycle that you take TriLo-Marzia.

Day 1 Start:

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

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

Instructions for using your blister:

Each new blister has 28 pills:

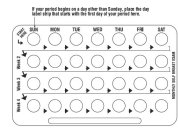
- 7 white to off-white pills with hormone, for **Days 1 to 7**
- 7 light blue pills with hormone, for **Days 8 to 14**
- 7 blue pills with hormone, for **Days 15 to 21**
- 7 green pills (without hormone), for **Days 22 to 28**

Step 1. SET THE DAY on your Blister

Sunday Start: Each blister has been preprinted with the days of the week, starting with Sunday to facilitate a Sunday-Start regimen.

Day 1 Start:

- On different day label (top) of the week have been provided with this pack in order to accommodate a Day 1 Start regimen.
- Put the day label (top) that starts with the first day of your period. Place this day label so it is over the area that has the days of the week (starting with Sunday) pre-printed on the blister (after figure below).



Step 2. Remove pill "1" by pushing down on the pill. The pill will come out through a hole in the back of the strip.

Step 3. Swallow the pill. You will take 1 pill every day, at the same time each day.

Step 4. Wait 24 hours to take your next pill. Continue to take 1 pill each day until all the pills have been taken.

Step 5. 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 brushing off your alarm clock or brushing your teeth.

Step 6. When your blister is empty, you will start a new blister on the day after pill "28." Remember to take your first pill in every row on the same day of the week, no matter when your next period starts.

What should I do if I miss any Tri-Le-Marzia pills?

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

- Take the 2 missed pills as soon as possible and the next 2 pills the next day.
- Then continue taking 1 pill every day until you finish the pack.
- You do not need to use a back-up birth control method if you have sex.

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

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

If you miss 2 pills in a row in Week 3, or you miss 3 or more pills in a row during Weeks 1, 2, or 3 of the pack, follow these steps:

- If you are a Day 1 Starter:
 - Throw out the rest of the 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 3 months in a row, call your healthcare provider because you might be pregnant.
 - The child becomes pregnant if you have sex during the first 7 days after you restart your pill. 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 pill.

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 pill.

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

PACKAGE LABEL PRINCIPAL DISPLAY PANEL

Tri-Lo-Marzia™ (norgestimate and ethinyl estradiol) tablets USP

0.18 mg 0.025 mg, 0.215 mg 0.025 mg, 7.0 25 mg 0.025 mg

28 Day Regimen
Blister Pack
NDC 68180-837-71
28 Tablets

Distributed by:
Lupin Pharmaceuticals, Inc.
Baltimore, Maryland 21202
United States
Manufactured by:
Lupin Limited
Pimpri (M.P.) - 454 775
India
This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.
Revised: July 2022 ID#: 270926

PACKAGE LABEL PRINCIPAL DISPLAY PANEL
Tri-Lo-Marzia™ (norgestimate and ethinyl estradiol) tablets USP
0.18 mg 0.025 mg, 0.215 mg 0.025 mg, 7.0 25 mg 0.025 mg
28 Day Regimen
Blister Pack
NDC 68180-837-71
28 Tablets



Tri-Lo-Marzia™ (norgestimate and ethinyl estradiol) tablets USP
0.18 mg 0.025 mg, 0.215 mg 0.025 mg, 7.0 25 mg 0.025 mg
28 Day Regimen
Blister Pack
NDC 68180-837-71
28 Tablets



Tri-Lo-Marzia™ (norgestimate and ethinyl estradiol) tablets USP
0.18 mg 0.025 mg, 0.215 mg 0.025 mg, 7.0 25 mg 0.025 mg
28 Day Regimen
Carton Pack
NDC 68180-837-73
3 Blisters of 28 Tablets Each



TRI-LO-MARZIA			
(norgestimate and ethinyl estradiol) tablets USP			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC 68180-837
Packaging			
#	Item Code	Package Description	Marketing Start Date
1	NDC 68180-837	3.0 U.S. CARTRON	04/06/2020
2		0.18 mg 0.025 mg	
3		0.215 mg 0.025 mg	
4		7.0 25 mg 0.025 mg	
Quantity of Parts			
Part #	Package Quantity	Total Product Quantity	
Part 1	1	1	
Part 2	1	1	
Part 3	1	1	
Part 4	1	1	
Part 1 of 4			
TRI-LO-MARZIA			
(norgestimate and ethinyl estradiol) tablets, film coated			
Product Information			
Route of Administration: Oral			
Active Ingredient/Active Moiety			
Strength	Ingredient Name	Route of Strength	Strength
0.18 mg/0.025 mg	NORGESTIMATE, ETHINYL ESTRADIOL	ORAL	0.18 mg/0.025 mg

Inactive Ingredients	Ingredient Name	Strength
	ALUMINUM LACTATE (US: 10114990)	
	CELLULOSE, MICROCRYSTALLINE (US: 07143161)	
	ETHANOLAMINE SOLUTION (US: 06211462)	
	HYDROXYCELLULOSE (US: 06000000)	
	LACTOSE MONOHYDRATE (US: 10117000)	
	MAGNESIUM STEARATE (US: 10117000)	
	POLYETHYLENE GLYCOL 400 (US: 06014552)	
	POTASSIUM (US: 01100000)	
	TITANIUM DIOXIDE (US: 10117000)	

Product Characteristics	Color	Shape	Size	Strength
	White Round	Round	12mm	10.00mg
				10.00mg
				10.00mg
				10.00mg

Marketing Information	Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
	ANDA	ANDA080441	10/18/2005	

Part 2 of 4
TRIL-D-MARZIA
hydroxyzine and ethyl loxapine tablet, film coated

Product Information	Route of Administration
	Oral

Active Ingredient/Active Moiety	Ingredient Name	Basis of Strength	Strength
	ETHYL LOXAPINE, (US: 06017212) ETHYL LOXAPINE, (US: 06017212)	ETHYL LOXAPINE, (US: 06017212)	10.00mg
	HYDROXYZINE, (US: 06017212) HYDROXYZINE, (US: 06017212)	HYDROXYZINE, (US: 06017212)	10.00mg

Inactive Ingredients	Ingredient Name	Strength
	ALUMINUM OXIDE (US: 10117000)	
	ALUMINUM LACTATE (US: 10114990)	
	CELLULOSE, MICROCRYSTALLINE (US: 07143161)	
	ETHANOLAMINE SOLUTION (US: 06211462)	
	HYDROXYCELLULOSE (US: 06000000)	
	LACTOSE MONOHYDRATE (US: 10117000)	
	MAGNESIUM STEARATE (US: 10117000)	
	POLYETHYLENE GLYCOL 400 (US: 06014552)	
	POTASSIUM (US: 01100000)	
	TITANIUM DIOXIDE (US: 10117000)	

Product Characteristics	Color	Shape	Size	Strength
	White Round	Round	12mm	10.00mg
				10.00mg
				10.00mg
				10.00mg

Marketing Information	Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
	ANDA	ANDA080441	10/18/2005	

Part 3 of 4
TRIL-D-MARZIA
hydroxyzine and ethyl loxapine tablet, film coated

Product Information	Route of Administration
	Oral

Active Ingredient/Active Moiety	Ingredient Name	Basis of Strength	Strength
	ETHYL LOXAPINE, (US: 06017212) ETHYL LOXAPINE, (US: 06017212)	ETHYL LOXAPINE, (US: 06017212)	10.00mg
	HYDROXYZINE, (US: 06017212) HYDROXYZINE, (US: 06017212)	HYDROXYZINE, (US: 06017212)	10.00mg

Inactive Ingredients	Ingredient Name	Strength
	ALUMINUM OXIDE (US: 10117000)	
	ALUMINUM LACTATE (US: 10114990)	
	CELLULOSE, MICROCRYSTALLINE (US: 07143161)	
	ETHANOLAMINE SOLUTION (US: 06211462)	
	HYDROXYCELLULOSE (US: 06000000)	
	LACTOSE MONOHYDRATE (US: 10117000)	
	MAGNESIUM STEARATE (US: 10117000)	
	POLYETHYLENE GLYCOL 400 (US: 06014552)	
	POTASSIUM (US: 01100000)	
	TITANIUM DIOXIDE (US: 10117000)	

Product Characteristics	Color	Shape	Size	Strength
	White Round	Round	12mm	10.00mg
				10.00mg
				10.00mg
				10.00mg

Marketing Information	Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
	ANDA	ANDA080441	10/18/2005	

Part 4 of 4
INERT
film coated, film coated

Product Information	Route of Administration
	Oral

Inactive Ingredients	Ingredient Name	Strength
	ETHANOLAMINE SOLUTION (US: 06211462)	
	HYDROXYCELLULOSE (US: 06000000)	
	LACTOSE MONOHYDRATE (US: 10117000)	
	MAGNESIUM STEARATE (US: 10117000)	
	TITANIUM DIOXIDE (US: 10117000)	

Product Characteristics	Color	Shape	Size	Strength
	White Round	Round	12mm	10.00mg
				10.00mg
				10.00mg
				10.00mg

Marketing Information	Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
	ANDA	ANDA080441	10/18/2005	

Marketing Information	Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
	ANDA	ANDA080441	10/18/2005	

Labeler - LUPIN PHARMACEUTICALS, INC. (08815371)

Registrant - LUPIN LIMITED (07902351)

Establishment

Name	Address	RFPL	Business Operations
LUPIN LIMITED	30300110	(MANUFACTURING-001)	(MANUFACTURING-001)