TRI-LO-MARZIA - norgestimate and ethinyl estradiol
LUPIN LIMITED

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRI-LO-MARZIA safely and effectively. See full prescribing information for TRI-LO-MARZIA

TRI-LO-MARZIA™ (norgestimate and ethinyl estradiol tablets USP), for oral use
Initial U.S. Approval: 1989

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS
See full prescribing information for complete boxed warning.
- **Tri-Lo-Marzia is contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. (4)**

INDICATIONS AND USAGE
Tri-Lo-Marzia is an estrogen/progestin COC, indicated for use by women to prevent pregnancy. (1.1)

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

DOSAGE FORMS AND STRENGTHS
Tri-Lo-Marzia consists of 28 round, film-coated tablets in the following order (3):
- 7 white to off white tablets each containing 0.18 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 light blue tablets each containing 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 blue tablets each containing 0.25 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 green tablets (inert)

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

WARNINGS AND PRECAUTIONS
- Thromboembolic Disorders and Other Vascular Problems: Stop Tri-Lo-Marzia if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver Disease: Discontinue Tri-Lo-Marzia if jaundice occurs. (5.2)
- High Blood Pressure: Control in women with well-controlled hypertension, monitor blood pressure and stop Tri-Lo-Marzia if blood pressure rises significantly. (5.3)
- Carbohydrate and Lipid Metabolic Effects: Monitor prediabetic and diabetic women taking Tri-Lo-Marzia. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.5)
- Headaches: Evaluate significant change in headaches and discontinue Tri-Lo-Marzia if indicated. (5.6)
- Bleeding Irregularities and Amenorrhea: Evaluate irregular bleeding or amenorrhea. (5.7)

ADVERSE REACTIONS
The most common adverse reactions reported during clinical trials (>2%) were: headache/migraine, nausea/vomiting, breast issues, abdominal pain, menstrual disorders, mood disorders, acne, vulvovaginal infection, abdominal distension, weight increased, fatigue. (6.1)
To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Drugs or herbal products that induce certain enzymes including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

USE IN SPECIFIC POPULATIONS
Nursing mothers: Not recommended; can decrease milk production. (8.3)
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

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

1 INDICATIONS AND USAGE

1.1 Oral Contraception

Tri-Lo-Marzia™ Tablets are indicated for use by females of reproductive potential to prevent pregnancy *[see CLINICAL STUDIES (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 How to Start Tri-Lo-Marzia

Tri-Lo-Marzia is dispensed in a wallet *[see HOW SUPPLIED/STORAGE AND HANDLING (16)]*. Tri-Lo-Marzia 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 Tri-Lo-Marzia

Table 1: Instructions for Administration of Tri-Lo-Marzia

Starting COCs in women not currently using hormonal contraception (Day 1 Start or Sunday Start) **Important:** Consider the possibility of ovulation and conception prior to initiation of this product. **Tablet Color:** Tri-Lo-Marzia 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)	**Day 1 Start:** Take first active tablet without regard to meals on the first day of menses. Take subsequent active tablets once daily at the same time each day for a total of 21 days. Take one **green** inactive tablet daily for 7 days and at the same time of day that active tablets were taken. Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last inactive tablet)
	Sunday Start: Take first active tablet without regard to meals on the first Sunday after the onset of menses. **Due to the potential risk of becoming pregnant, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of Tri-Lo-Marzia.** 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 contraceptive is not needed.
Switching to Tri-Lo-Marzia from another oral contraceptive	Start on the same day that a new pack of the previous oral contraceptive would have started.
Switching from another contraceptive method to Tri-Lo-Marzia	**Start Tri-Lo-Marzia:**
Transdermal patch	On the day when next application would have been scheduled
Vaginal ring	On the day when next insertion would have been scheduled
Injection	On the day when next injection would have been scheduled
Intrauterine contraceptive	On the day of removal If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraceptive (such as condoms and spermicide) is needed for the first seven days of the first cycle pack.
Implant	On the day of removal
Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-Approved Patient Labeling.	

Starting Tri-Lo-Marzia after Abortion or Miscarriage

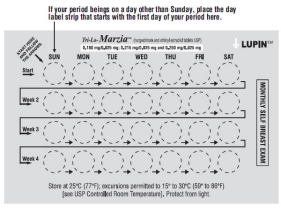
First-trimester:
- After a first-trimester abortion or miscarriage, Tri-Lo-Marzia may be started immediately. An additional method of contraception is not needed if Tri-Lo-Marzia is started immediately.
- If Tri-Lo-Marzia is not started within 5 days after termination of the pregnancy, the patient should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

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

Starting Tri-Lo-Marzia after Childbirth
- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with Tri-Lo-Marzia following the instructions in Table 1 for women not currently using hormonal contraception.
- Tri-Lo-Marzia is not recommended for use in lactating women *[see USE IN SPECIFIC POPULATIONS (8.3)]*.
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of Tri-Lo-Marzia. *[see CONTRAINDICATIONS (4), WARNINGS AND PRECAUTIONS (5.1), USE IN SPECIFIC POPULATIONS AND (8.1 AND 8.3), and FDA-APPROVED PATIENT LABELING]*.

Wallet Pack:

SET THE DAY
- **Sunday Start:** Each wallet 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 wallet (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 all the pills have been taken.
- When your wallet is empty, you will start a new wallet on the day after pill "28." The first pill in every refill will always be taken on the same day of the week, no matter when the patient's next period starts.

2.3 Missed Tablets

Table 2: Instructions for Missed Tri-Lo-Marzia Tablets	
If one active tablet is missed in Weeks 1, 2, or 3	Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.
If two active tablets are missed in Week 1 or Week 2	Take the two missed tablets as soon as possible and the next two active tablets the next day. Continue taking one tablet a day until the pack is finished. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as backup if the patient has sex within 7 days after missing tablets.**
If two active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	Day 1 start: Throw out the rest of the pack and start a new pack that same day. Sunday start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**

2.4 Advice in Case of Gastrointestinal Disturbances

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

3 DOSAGE FORMS AND STRENGTHS

Tri-Lo-Marzia Tablets are available in a wallet. Each wallet contains 28 tablets in the following order:
- 7 white to off white, round, film-coated tablets debossed with 'LU' 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 'LU' 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 'LU' on one side and "E23" on the other side of the tablet contains 0.25 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 green, round, biconvex, film-coated, tablets debossed with 'LU' on one side and "E24" on the other side of the tablet contains inert ingredients

4 CONTRAINDICATIONS

Do not prescribe Tri-Lo-Marzia to women who are known to have the following conditions:
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see WARNINGS AND PRECAUTIONS (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see WARNINGS AND PRECAUTIONS (5.1)]*
  - Have cerebrovascular disease *[see WARNINGS AND PRECAUTIONS (5.1)]*
  - Have coronary artery disease *[see WARNINGS AND PRECAUTIONS (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see WARNINGS AND PRECAUTIONS (5.1)]*
  - Have uncontrolled hypertension *[see WARNINGS AND PRECAUTIONS (5.3)]*
  - Have diabetes mellitus with vascular disease *[see WARNINGS AND PRECAUTIONS (5.5)]*
  - Have headaches with focal neurological symptoms or migraine headaches with aura *[see WARNINGS AND PRECAUTIONS (5.6)]*
  - Women over age 35 with any migraine headaches *[see WARNINGS AND PRECAUTIONS (5.6)]*
- Liver tumors, benign or malignant, or liver disease *[see WARNINGS AND PRECAUTIONS (5.2)]*
- Undiagnosed abnormal uterine bleeding *[see WARNINGS AND PRECAUTIONS (5.7)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see WARNINGS AND PRECAUTIONS (5.8) and USE IN SPECIFIC POPULATIONS (8.1)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see WARNINGS AND PRECAUTIONS (5.10)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems
- Stop Tri-Lo-Marzia if an arterial thrombotic event or venous thrombotic (VTE) event occurs.
- Stop Tri-Lo-Marzia if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately *[see ADVERSE REACTIONS (6.2)]*.
- If feasible, stop Tri-Lo-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 and following prolonged immobilization.
- Start Tri-Lo-Marzia no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued.
- Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.
- Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function

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

Liver Tumors

Tri-Lo-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 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the risk of liver cancers in COC users is less than one case per million users.

5.3 High Blood Pressure

Tri-Lo-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 Tri-Lo-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.

5.4 Gallbladder Disease

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

5.5 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who take Tri-Lo-Marzia. COCs may decrease glucose tolerance.

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

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

5.6 Headache

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

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

5.7 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different contraceptive product.

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

Amenorrhea and Oligomenorrhea

Women who use Tri-Lo-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 active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.8 COC Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue Tri-Lo-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 (8.1)]*.

5.9 Depression

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

5.10 Carcinoma of Breast and Cervix
- Tri-Lo-Marzia is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see CONTRAINDICATIONS (4)]*.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.
- Some studies suggest that COC use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

5.11 Effect on Binding Globulins

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

5.12 Monitoring

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

5.13 Hereditary Angioedema

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

5.14 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Tri-Lo-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 Tri-Lo-Marzia was evaluated in 1,723 subjects who participated in a randomized, partially blinded, multicenter, active-controlled clinical trial of Tri-Lo-Marzia for contraception. This trial examined healthy, nonpregnant, volunteers aged 18 to 45 (nonsmoker if 35 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/migraine (30.5%), nausea/vomiting (16.3%); breast issues (including tenderness, pain, enlargement, swelling, discharge, discomfort, cyst, and nipple pain) (10.3%), abdominal pain (9.2%), menstrual disorders (including dysmenorrhea, menstrual discomfort, menstrual disorder) (9.2%), mood disorders (including depression, mood altered, mood swings and depressed mood) (7.6%); acne (5.1%), vulvovaginal infection (3.5%), abdominal distension (2.8%), weight increased (2.4%), fatigue (2.1%).

Adverse Reactions Leading to Study Discontinuation

In the clinical trial of Tri-Lo-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%), nausea/vomiting (0.7%), cervical dysplasia (0.7%), abdominal pain (0.4%), ovarian cyst (0.3%), acne (0.2%), flatulence (0.2%) and depression (0.2%).

Serious Adverse Reactions

Carcinoma of the cervix *in situ* (1 subject) and cervical dysplasia (1 subject).

6.2 Postmarketing Experience

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

Infections and Infestations

Urinary tract infection

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)

Breast cancer, benign breast neoplasm, hepatic adenoma, focal nodular hyperplasia, breast cyst

Immune System Disorders

Hypersensitivity

Metabolism and Nutrition Disorders

Dyslipidemia

Psychiatric Disorders

Anxiety, insomnia

Nervous System Disorders

Syncope, convulsion, paresthesia, dizziness

Eye Disorders

Visual impairment, dry eye, contact lens intolerance

Ear and Labyrinth Disorders

Vertigo

Cardiac Disorders

Tachycardia, palpitations

Vascular Events

Deep vein thrombosis, pulmonary embolism, retinal vascular thrombosis, hot flush

Arterial Events

Arterial thromboembolism, myocardial infarction, cerebrovascular accident

Respiratory, Thoracic and Mediastinal Disorders

Dyspnea

Gastrointestinal Disorders

Pancreatitis, abdominal distension, diarrhea, constipation

Hepatobiliary Disorders

Hepatitis

Skin and Subcutaneous Tissue Disorders

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

Musculoskeletal, Connective Tissue, and Bone Disorders

Muscle spasms, pain in extremity, myalgia, back pain

Reproductive System and Breast Disorders

Ovarian cyst, suppressed lactation, vulvovaginal dryness

General Disorders and Administration Site Conditions

Chest pain, asthenic conditions.

7 DRUG INTERACTIONS

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

No drug-drug interaction studies were conducted with Tri-Lo-Marzia.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances Decreasing the Plasma Concentrations of COCs

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

Colesevelam

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

Substances Increasing the Plasma Concentrations of COCs

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

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

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

7.2 Effects of Combined Oral Contraceptives on Other Drugs

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

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

7.3 Interference with Laboratory Tests

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

8.3 Nursing Mothers

Advise the nursing mother to use other forms of contraception, when possible, until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of Tri-Lo-Marzia 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

Tri-Lo-Marzia has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

The pharmacokinetics of Tri-Lo-Marzia has not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. *[see CONTRAINDICATIONS (4) and WARNINGS AND PRECAUTIONS (5.2).]*

8.7 Renal Impairment

The pharmacokinetics of Tri-Lo-Marzia has not been studied in women with renal impairment.

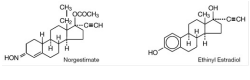
10 OVERDOSAGE

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

11 DESCRIPTION

Tri-Lo-Marzia is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. Norgestimate is designated as ((+)-13-Ethyl-17-hydroxy-18, 19-dinor-17α-pregn-4-en-20-yn-3-one oxime acetate (ester)) and ethinyl estradiol is designated as (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-,3,17-diol).

- 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, FD&C Blue No. 2 Aluminium 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, FD&C Blue No. 2 Aluminium 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, FD&C Blue No. 2 Aluminium Lake, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.



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 Tri-Lo-Marzia.

12.3 Pharmacokinetics

Absorption

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

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

Peak serum concentrations of NGMN and EE were generally reached by 2 hours after administration of Tri-Lo-Marzia. Accumulation following multiple dosing of the 0.18 mg NGM / 0.025 mg EE dose is approximately 1.5 to 2 fold for NGMN and approximately 1.5 fold for EE compared with single dose administration, in agreement with that predicted based on linear kinetics of NGMN and EE. The pharmacokinetics of NGMN is dose proportional following NGM doses of 0.18 to 0.25 mg. Steady-state conditions for NGMN following each NGM dose and for EE were achieved during the three cycle study. Non-linear accumulation (4.5 to 14.5 fold) of NG was observed as a result of high affinity binding to SHBG, which limits its biological activity.

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

Table 3: Mean (SD) Pharmacokinetic Parameters of Tri-Lo-Marzia During a Three Cycle Study

Analyte*	Cycle	Day	C_{max}	t_{max} (h)	$AUC_{0 \text{ to } 24h}$	$t_{1/2}$ (h)
NGMN[†† to ‡]	1	1	**0.91** (0.27)	**1.8** (1.0)	**5.86** (1.54)	NC
	3	7	**1.42** (0.43)	**1.8** (0.7)	**11.3** (3.2)	NC
		14	**1.57** (0.39)	**1.8** (0.7)	**13.9** (3.7)	NC
		21	**1.82** (0.54)	**1.5** (0.7)	**16.1** (4.8)	**28.1 (10.6)**
NG[† to ‡]	1	1	**0.32** (0.14)	**2.0** (1.1)	**2.44** (2.04)	NC
	3	7	**1.64** (0.89)	**1.9** (0.9)	**27.9** (18.1)	NC
		14	**2.11** (1.13)	**4.0** (6.3)	**40.7** (24.8)	NC
		21	**2.79** (1.42)	**1.7** (1.2)	**49.9** (27.6)	**36.4 (10.2)**
EE[†,§,¶]	1	1	**55.6** (18.1)	**1.7** (0.5)	**421** (118)	NC
	3	7	**91.1** (36.7)	**1.3** (0.3)	**782** (329)	NC
		14	**96.9** (38.5)	**1.3** (0.3)	**796** (273)	NC
		21	**95.9** (38.9)	**1.3** (0.6)	**771** (303)	**17.7 (4.4)**

NC = not calculated

* NGMN = Norelgestromin, NG = norgestrel, EE = ethinyl estradiol

† C_{max} = peak serum concentration, t_{max} = time to reach peak serum concentration, $AUC_{0 to 24h}$= area under serum concentration vs. time curve from 0 to 24 hours, $t_{1/2}$= elimination half-life.

‡ units for NGMN and NG - C_{max} = ng/mL, $AUC_{0 to 24h}$= h.ng/mL

§ units for all analytes; h = hours

¶ units for EE only - C_{max} = pg/mL, $AUC_{0 to 24h}$= h.pg/mL

Food Effect:

The effect of food on the pharmacokinetics of Tri-Lo-Marzia has not been studied.

Distribution

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

Metabolism

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

Excretion

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

Use in Specific Populations

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

The effects of body weight, body surface area, age and race on the pharmacokinetics of NGMN, NG and EE were evaluated in 79 healthy women using pooled data following single dose administration of NGM 0.18 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 $AUC_{0 to 24h}$ values for NGMN and EE and increases in CL/F (oral clearance) for EE. Increasing body weight by 10 kg is predicted to reduce the following parameters: NGMN C_{max} by 9% and $AUC_{0 to 24h}$ by 19%, NG C_{max} by 12% and $AUC_{0 to 24h}$ by 46%, EE C_{max} by 13% and $AUC_{0 to 24h}$ by 12%. These changes were statistically significant. Increasing age was associated with slight decreases (6% with increasing age by 5 years) in C_{max} and $AUC_{0 to 24h}$ for NGMN and were statistically significant, but there was no significant effect for NG or EE. Only a small to moderate fraction (5 to 40%) of the overall variability in the pharmacokinetics of NGMN and EE following Tri-Lo-Marzia Tablets may be explained by any or all of the above demographic parameters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[see WARNINGS AND PRECAUTIONS (5.2, 5.10) and USE IN SPECIFIC POPULATIONS (8.1).

14 CLINICAL STUDIES

In an active controlled clinical trial lasting 12 months, 1,673 women, 18 to 45 years old completed 11,003 cycles of Tri-Lo-Marzia use and a total of 20 pregnancies were reported in Tri-Lo-Marzia users. The racial demographic of those treated with Tri-Lo-Marzia was: Caucasian (86%), African-American (6%), Asian (2%), and Other (6%). There were no exclusions on the basis of weight; the weight range for women treated was 90 to 240 lbs, with a mean weight of about 142 lbs. The pregnancy rate in women aged 18 to 35 years was approximately 2.6 pregnancies per 100 woman-years of use.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Tri-Lo-Marzia are available in a wallet (NDC 68180-837-11) containing 28 tablets packed in a pouch (NDC 68180-837-11). Such three pouches are packaged in a carton (NDC 68180-837-13).

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

- 7 white to off white, round, film-coated tablets debossed with 'LU' 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 'LU' on one side and "E22" on the other side contains 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 blue, round, film-coated tablets debossed with 'LU' 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 'LU' on one side and "E24" on the other side contains inert ingredients

16.2 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.

17 PATIENT COUNSELING INFORMATION

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

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs *[see BOXED WARNING]*.
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC *[see WARNINGS AND PRECAUTIONS (5.1)]*.
- Tri-Lo-Marzia does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- Tri-Lo-Marzia is not to be used during pregnancy; if pregnancy occurs during use of Tri-Lo-Marzia instruct the patient to stop further use *[see WARNINGS AND PRECAUTIONS (5.8)]*.
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed *[see DOSAGE AND ADMINISTRATION (2.2)]*.
- Use a back-up or alternative method of contraception when enzyme inducers are used with Tri-Lo-Marzia *[see DRUG INTERACTIONS (7.1)]*.
- COCs may reduce breast milk production, this is less likely to occur if breastfeeding is well established *[see USE IN SPECIFIC POPULATIONS (8.3)]*.
- Women who start COCs postpartum; and who have not yet had a period, should use an additional method of contraception until they have taken a white tablet for 7 consecutive days *[see DOSAGE AND ADMINISTRATION (2.2)]*.
- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea at the time of the first missed period. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles *[see WARNINGS AND PRECAUTIONS (5.7)]*.

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India

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PATIENT INFORMATION

Tri-Lo-Marzia™ [TRY-LOW-mar-ZEE-uh]

(norgestimate and ethinyl estradiol tablets USP)

What is the most important information I should know about Tri-Lo-Marzia?

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

What is Tri-Lo-Marzia?

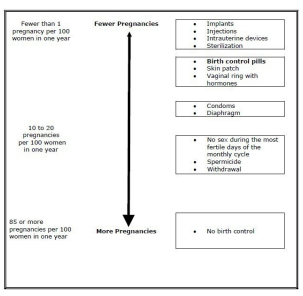
Tri-Lo-Marzia is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

How does Tri-Lo-Marzia work for contraception?

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

Based on the results from the clinical study, about 3 out of 100 women may get pregnant during the first year they use Tri-Lo-Marzia.

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 Tri-Lo-Marzia?

Do not take Tri-Lo-Marzia 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
- 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 Tri-Lo-Marzia, stop taking Tri-Lo-Marzia right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking Tri-Lo-Marzia.

What should I tell my healthcare provider before taking Tri-Lo-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 pregnancy)
- are breastfeeding or plan to breastfeed. Tri-Lo-Marzia may decrease the amount of breast milk you make. A small amount of the hormones in Tri-Lo-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.

Tri-Lo-Marzia may affect the way other medicines work, and other medicines may affect how well Tri-Lo-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 Tri-Lo-Marzia?

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

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

Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age. Serious blood clots are more likely to happen when you:
- first start taking birth control pills
- restart the same or different birth control pills after not using them for a month or more

Call your healthcare provider or go to a hospital emergency room right away if you have:
- leg pain that will not go away
- sudden severe shortness of breath
- sudden change in vision or blindness
- chest pain
- a sudden, severe headache unlike your usual headaches
- weakness or numbness in your arm or leg
- trouble speaking

Other serious side effects include:
- **liver problems, including:**
- rare liver tumors
- jaundice (cholestasis), especially if you previously had cholestasis of pregnancy. Call your healthcare provider if you have yellowing of your skin or eyes.

- **high blood pressure** . 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 Tri-Lo-Marzia.**
- **depression**
- **possible cancer in your breast and cervix**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider if you have a swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher is you have a history of angioedema.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Women who tend to get chloasma should avoid spending a long time in sunlight, tanning booths, and under sun lamps while taking Tri-Lo-Marzia. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of Tri-Lo-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
- acne
- vaginal infections
- bloating
- weight gain
- fatigue

These are not all the possible side effects of Tri-Lo-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 Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or you can visit the Lupin website at www.lupinpharmaceuticals.com.

What else should I know about taking Tri-Lo-Marzia?
- If you are scheduled for any lab tests, tell your healthcare provider you are taking Tri-Lo-Marzia. Certain blood tests may be affected by Tri-Lo-Marzia.
- Tri-Lo-Marzia does not protect against HIV infection (AIDS) and other sexually transmitted infections.

How should I store Tri-Lo-Marzia?
- Store Tri-Lo-Marzia at room temperature between 68° to 77°F (20° to 25°C).
- Keep Tri-Lo-Marzia and all medicines out of the reach of children.
- Store away from light.

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

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

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

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

Do birth control pills cause cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills 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 Tri-Lo-Marzia?

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

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

Inactive ingredients:

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

Light blue pills: anhydrous lactose, croscarmellose sodium, FD&C Blue No. 2 Aluminium Lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide.

Blue pills: anhydrous lactose, croscarmellose sodium, FD&C Blue No. 2 Aluminium Lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide.

Green pills: croscarmellose sodium, FD&C Blue No. 2 Aluminium Lake, hypromellose, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol and titanium dioxide.

INSTRUCTIONS OF USE

Tri-Lo-Marzia [TRY-LOW-mar-ZEE-uh]

(norgestimate and ethinyl estradiol tablets USP)

Important Information about taking Tri-Lo-Marzia
- Take **1** pill every day at the same time. Take the pills in the order directed on your wallet.
- Do not skip your pills, even if you do not have sex often. If you miss pills (including starting the pack late) **you could get pregnant** . The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take Tri-Lo-Marzia, talk to your healthcare provider. When you first start taking Tri-Lo-Marzia, spotting or light bleeding in between your periods may occur. Contact your healthcare provider if this does not go away after a few months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking Tri-Lo-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 later. On the days you take **2** pills to make up for missed pills (see **What should I do if I miss any Tri-Lo-Marzia pills?** below), you could also feel a little sick to your stomach.
- It is not uncommon to miss a period. However, if you miss a period and have not taken Tri-Lo-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 Tri-Lo-Marzia.
- If you have vomiting or diarrhea within **3 to 4** hours of taking your pill, take another pill of the same color from your extra wallet. If you do not have an extra wallet, take the next pill in your wallet. Continue taking all your remaining pills in order. Start the first pill of your next wallet the day after finishing your current wallet. This will be 1 day earlier than originally scheduled. Continue on your new schedule.
- If you have vomiting or diarrhea for more than 1 day, your birth control pills may not work as well. Use an additional birth control method, like condoms and a spermicide, until you check with your healthcare provider.
- Stop taking Tri-Lo-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 Tri-Lo-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 wallet.
- Have backup contraception (condoms and spermicide) available and if possible, an extra full pack of pills as needed.

When should I start taking Tri-Lo-Marzia?

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

If you start taking Tri-Lo-Marzia and you are switching from another birth control pill:
- Start your new Tri-Lo-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 Tri-Lo-Marzia and previously used a vaginal ring or transdermal patch:
- Start using Tri-Lo-Marzia on the day you would have reapplied the next ring or patch.

If you start taking Tri-Lo-Marzia and you are switching from a progestin-only method such as an implant or injection:
- Start taking Tri-Lo-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 Tri-Lo-Marzia and you are switching from an intrauterine device or system (IUD or IUS):
- Start taking Tri-Lo-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 Tri-Lo-Marzia.

Keep a calendar to track your period:

If this is the first time you are taking birth control pills, read, **"When should I start taking Tri-Lo-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 a Sunday.

- Take pill **1** on the Sunday **after your period s tarts** .
- If your period starts on a Sunday, take pill **"1 "** that day and refer to Day 1 Start instructions below.
- Take **1** pill every day in the order on the wallet at the same time each day for **28** days.
- After taking the last pill on **Day 28** from the wallet, 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 Tri-Lo-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 wallet, at the same time each day, for **28** days.
- After taking the last pill on **Day 28** from the wallet, 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 wallet:

Each new wallet has 28 pills

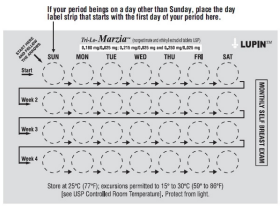
- **7** white to off white pills with hormone, for **Days 1 to 7**
- **7** light blue pills with hormone, for **Days 8 to 14**
- **7** blue pills with hormones, for **Days 15 to 21**
- **7** green pills (without hormones), for **Days 22 to 28** .

Step 1. SET THE DAY on your Wallet

Sunday Start: Each wallet 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 wallet (Refer 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 turning off your alarm clock or brushing your teeth.

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

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

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

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

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

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

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

- **If you are a Day 1 Starter:**
- Throw out the rest of the pill pack and start a new pack that same day.
- You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your healthcare provider because you might be pregnant.
- You could become pregnant if you have sex during the first 7 days after you restart your pills. You MUST use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first 7 days after you restart your pills.

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

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

Distributed by:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Pithampur (M.P.) - 454 775

India

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

October 2015 **ID#: 243295**

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

TRI-LO-MARZIA™ (norgestimate and ethinyl estradiol tablets USP)

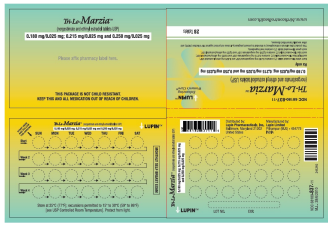
0.18 mg 0.025 mg, 0.215 mg 0.025 mg, 7 0.25 mg 0.025 mg

28 Day Regimen

Wallet Pack

NDC: 68180-837-11

28 Tablets



TRI-LO-MARZIA™ (norgestimate and ethinyl estradiol tablets USP)

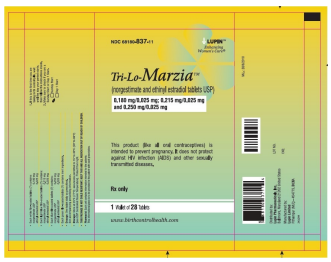
0.18 mg 0.025 mg, 0.215 mg 0.025 mg, 7 0.25 mg 0.025 mg

28 Day Regimen

Pouch:

NDC: 68180-837-11

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: 68180-837-13

3 Pouches of 28 Tablets Each

TRI-LO-MARZIA

norgestimate and ethinyl estradiol kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:57297-837

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:57297-837-11	3 in 1 CARTON	01/08/2016	
1	NDC:57297-837-21	1 in 1 POUCH		
1		1 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1		7
Part 2		7
Part 3		7
Part 4		7

Part 1 of 4

TRI-LO-MARZIA

norgestimate and ethinyl estradiol tablet, film coated

Product Information	
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.025 mg
NORGESTIMATE (UNII: C2168FXJDV) (NORGESTIMATE - UNII:C2168FXJDV)	NORGESTIMATE	0.18 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D6 1U)	
CROSCARMELLOSE SODIUM (UNII: M28 OL1HH48)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POVIDONE (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	WHITE (White to off white)	**Score**	no score
Shape	ROUND (Round)	**Size**	5mm
Flavor		**Imprint Code**	LU;E21
Contains			

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA201641	01/08/2016	

Part 2 of 4

TRI-LO-MARZIA

norgestimate and ethinyl estradiol tablet, film coated

Product Information	
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.025 mg
NORGESTIMATE (UNII: C2168FXJDV) (NORGESTIMATE - UNII:C2168FXJDV)	NORGESTIMATE	0.215 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ALUMINUM OXIDE (UNII: LMD4O6S133)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D6 1U)	
CROSCARMELLOSE SODIUM (UNII: M28 OL1HH48)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POVIDONE (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	BLUE (Light blue)	**Score**	no score
Shape	ROUND (Round)	**Size**	5mm
Flavor		**Imprint Code**	LU;E22
Contains			

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA201641	01/08/2016	

Part 3 of 4

TRI-LO-MARZIA

norgestimate and ethinyl estradiol tablet, film coated

Product Information	
Route of Administration	ORAL

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.025 mg
NORGESTIMATE (UNII: C2168FXJDV) (NORGESTIMATE - UNII:C2168FXJDV)	NORGESTIMATE	0.25 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ALUMINUM OXIDE (UNII: LMD4O6S133)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D6 1U)	
CROSCARMELLOSE SODIUM (UNII: M28 OL1HH48)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
POVIDONE (UNII: FZ989GH94E)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	BLUE (Blue)	**Score**	no score
Shape	ROUND (Round)	**Size**	5mm
Flavor		**Imprint Code**	LU;E23
Contains			

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA201641	01/08/2016	

Part 4 of 4

INERT

inert tablet, film coated

Product Information	
Route of Administration	ORAL

Inactive Ingredients	
Ingredient Name	**Strength**
CROSCARMELLOSE SODIUM (UNII: M28 OL1HH48)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FERRIC OXIDE YELLOW (UNII: EX43802 MRT)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
POLYETHYLENE GLYCOL 400 (UNII: B697894SGQ)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D6 1U)	

LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: GFOOV2J9P)	

Product Characteristics

Color	GREEN (Green)	**Score**	no score
Shape	ROUND (Round)	**Size**	5mm
Flavor		**Imprint Code**	LUE24
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205541	03/18/2016	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205541	03/18/2016	

Labeler - LUPIN LIMITED (675923163)

Registrant - LUPIN LIMITED (675923163)

Establishment

Name	Address	ID/FEI	Business Operations
LUPIN LIMITED		650582330	manufacture(57297-837) , pack(57297-837)

Revised: 5/2016 LUPIN LIMITED