Tri-VyLibra® Lo

(norgestimate and ethinyl estradiol tablets, USP) 0.180 mg/0.025 mg, 0.215 mg/0.025 mg, and 0.250 mg/0.025 mg

afaxys® pharma

We are in the process of updating our current packaging. You may receive existing packaging until updates are complete for all products.

TRI-VYLIBRA® LO IS AN AB-RATED GENERIC ORAL CONTRACEPTIVE

COMPARES TO:
Ortho Tri-Cyclen® Lo*, Tri-Lo-Estarylla®, Tri-Lo-Marzia™, Tri-Lo-Mili®, and Tri-Lo-Sprintec®

* Product may be discontinued.
Bold font indicates the product is the Reference Listed Drug for the Afaxys product.

- A progestin-estrogen combination oral contraceptive
- Triphasic administration regimen
  - 7 white to off-white tablets of 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
  - 7 pale-blue to bluish-white tablets of 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
  - 7 blue to light-blue tablets of 0.250 mg norgestimate and 0.025 mg ethinyl estradiol
  - 7 green placebo tablets to ease administration
  - Combined in a 28-day tablet blister pack

Packaging Description	NDC #	Dimensions
A Carton Containing 3 Packages	50102-231-13	70.5 mm x 73.5 mm x 101.5 mm

SEE ALL ORDERING INFORMATION

ADDITIONAL PRODUCT INFORMATION:

- Tri-VyLibra Lo may make periods lighter and shorter than usual

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.

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first 3 months of use. If bleeding persists or occurs after previously regular cycles, check for other causes, such as pregnancy or malignancy. Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was preexistent.

The most common adverse reactions associated with Tri-VyLibra Lo include headache/migraine, nausea/vomiting, breast issues, abdominal pain, menstrual disorders, mood disorders, acne, vulvovaginal infection, abdominal distension, weight increased, and fatigue.

Use of COCs 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.

Please see Important Safety Information below.

Tri-VyLibra® Lo

(norgestimate and ethinyl estradiol tablets, USP) 0.180 mg/0.025 mg, 0.215 mg/0.025 mg, and 0.250 mg/0.025 mg

Please see accompanying full Prescribing Information, including Boxed Warning.

IMPORTANT SAFETY INFORMATION for Tri-VyLibra® Lo (norgestimate and ethinyl estradiol tablets, USP 0.180 mg/0.025 mg, 0.215 mg/0.025 mg, and 0.250 mg/0.025 mg)

INDICATIONS

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is indicated for use by females of reproductive potential to prevent pregnancy.

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.

Consult the Package Insert or click here for Complete Prescribing Information.

CONTRAINDICATIONS

Tri-Vylibra-Lo is contraindicated in females who are known to have or develop the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35
  - Have deep vein thrombosis or pulmonary embolism, now or in the past
  - Have inherited or acquired hypercoagulopathies
  - Have cerebrovascular disease
  - Have coronary artery disease
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease or atrial fibrillation)
  - Have uncontrolled hypertension
  - Have diabetes mellitus with vascular disease
  - Have headaches with focal neurological symptoms, migraine headaches with aura, or women over age 35 with any migraine headaches
- Liver tumors (benign or malignant) or liver disease
- Undiagnosed abnormal uterine bleeding
- Pregnancy (because there is no reason to use combined oral contraceptives during pregnancy)
- Current diagnosis of, or history of, breast cancer, which may be hormone sensitive
- Use hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations

WARNINGS AND PRECAUTIONS

- **Thrombotic and other vascular problems**—Stop combined oral contraceptives (COCs) if an arterial or venous thrombotic event occurs, or 4 weeks before through 2 weeks after major surgery or surgeries known to have an elevated risk of thromboembolism, or if there is an unexplained loss or change of vision (evaluate for retinal thrombosis immediately). Start Tri-VyLibra Lo no earlier than 4 weeks after delivery, in women who are not breastfeeding. COCs should be used with caution in women with cardiovascular risk factors.
- **Malignant neoplasms**—Women with current or past history of breast cancer should not use COCs because breast cancer may be hormonally sensitive.
- **Liver disease**—Discontinue COCs if jaundice develops. Hepatic adenomas and very rare hepatocellular carcinomas are associated with long-term (>8 years) COC use.
- **High blood pressure**—Women with well-controlled hypertension should be monitored closely. Women with uncontrolled hypertension should not use COCs.
- **Other warnings and precautions** include gallbladder disease, carbohydrate and lipid metabolic effects, headache, bleeding irregularities, COC use before and during pregnancy, depression, interference with laboratory tests, hereditary angioedema, and chloasma.

ADVERSE REACTIONS

The most serious reactions are discussed elsewhere in the labeling and include serious cardiovascular events, vascular events, and liver disease. Commonly reported adverse reactions include irregular uterine bleeding, nausea, breast tenderness, and headache.

Patients should be counseled that Tr-VyLibra Lo does not protect against HIV infection (AIDS) and other sexually transmitted infections (STIs).

Reference: Tri-VyLibra Lo prescribing information, Charleston SC, USA: Afaxys Pharma, LLC; March 2023.

To report **SUSPECTED ADVERSE REACTIONS**, call 1-855-888-2467 or report via the FDA MedWatch Program at www.fda.gov/medwatch or 1-800-FDA-1088.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRI-VYLIBRA® LO safely and effectively. See full prescribing information for TRI-VYLIBRA® LO.

Tri-VyLibra® Lo (norgestimate and ethinyl estradiol) tablets for oral use

Initial U.S. Approval: 1989

WARNING: CIGARETTE SMOKING and SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **Tri-VyLibra Lo is contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. (4)**

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.11) 11/2021

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

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is an estrogen/progestin COC, indicated for use by women to prevent pregnancy. (1.1)

----------DOSAGE AND ADMINISTRATION----------

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

----------DOSAGE FORMS AND STRENGTHS----------

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets USP) consists of 21 round, biconvex, coated tablets and 7 round, mottled, biconvex, uncoated tablets in the following order (3):

- 7 white to off white tablets each containing 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 pale blue to bluish white tablets each containing 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 blue to light blue tablets each containing 0.250 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)
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

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

- Thromboembolic Disorders and Other Vascular Problems: Stop Tri-VyLibra Lo if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue Tri-VyLibra Lo if jaundice occurs. (5.2)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop Tri-VyLibra Lo if blood pressure rises significantly. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Tri-VyLibra Lo. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue Tri-VyLibra Lo if indicated. (5.7)
- Bleeding Irregularities and Amenorrhea: Evaluate irregular bleeding or amenorrhea. (5.8)

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

The most common adverse reactions reported during clinical trials (≥2%) were: 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 Afaxys Pharma, LLC at 1-855-888-2467 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: 03/2023

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-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is 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-VyLibra Lo (Norgestimate and Ethinyl Estradiol Tablets)

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is dispensed in a blister pack *[see How Supplied/Storage and Handling (16)]*. Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) 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-VyLibra Lo (Norgestimate and Ethinyl Estradiol Tablets)

Table 1: Instructions for Administration of Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets)

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-VyLibra Lo (norgestimate and ethinyl estradiol tablets) active tablets are white to off white (Day 1 to Day 7), pale blue to bluish white (Day 8 to Day 14) and blue to light blue (Day 15 to Day 21). • Tri-VyLibra Lo inactive tablets are green (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-VyLibra Lo (norgestimate and ethinyl estradiol tablets).** • 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-VyLibra Lo (norgestimate and ethinyl estradiol tablets) 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-VyLibra Lo (norgestimate and ethinyl estradiol tablets)	**Start Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets):**
• **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-VyLibra Lo (norgestimate and ethinyl estradiol tablets) after Abortion or Miscarriage

First-trimester

- After a first-trimester abortion or miscarriage, Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) may be started immediately. An additional method of contraception is not needed if Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is started immediately.
- If Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) 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-VyLibra Lo (norgestimate and ethinyl estradiol tablets).

Second-trimester

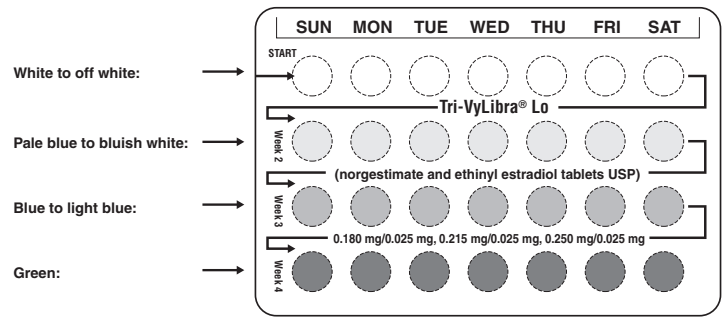
- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets), following the instructions in Table 1 for Day 1 or Sunday start, as desired. If using Sunday start, use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

Starting Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) following the instructions in Table 1 for women not currently using hormonal contraception.
- Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) 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-VyLibra Lo (norgestimate and ethinyl estradiol tablets). *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1 and 8.3), and FDA-Approved Patient Labeling]*.

Blister Pack:

1. Decide what time of day you want to take your pill.
   It is important to take it at about the same time every day.
2. The 28-pill pack has 21 white to off white, pale blue to bluish white, and blue to light blue "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of green "reminder" pills (without hormones).
3. Also find:
   1) where on the pack to start taking pills,
   2) in what order to take the pills, and
   3) the week numbers as shown in the picture below.



4. Be sure you have ready at all times:
   Another kind of birth control (such as condoms or spermicide) to use as a back-up method in case you miss pills.
   An extra, full pill pack.

You have a choice of which day to start taking your first pack of pills. Tri-VyLibra Lo is available in a blister pack which is preset for a Sunday Start. Day 1 Start stickers are also provided. Decide with your healthcare professional which is the best day for you. Pick a time of day that will be easy to remember.

Sunday Start:

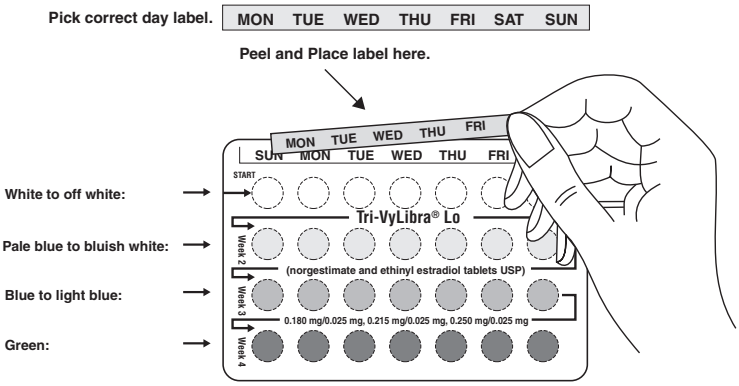
Take the first white to off white "active" pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

Use another method of birth control (such as condoms or spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

Day 1 Start:

Take the first white to off white "active" pill of the first pack during the first 24 hours of your period.

1. Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins).
2. Place this day label strip in the cycle tablet over the area that has the days of the week (starting with Sunday) imprinted in the plastic.



Note: If the first day of your period is a Sunday, you can skip steps #1 and #2.

You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

2.3 Missed Tablets

Table 2: Instructions for Missed Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets)

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

2.4 Advice in Case of Gastrointestinal Disturbances

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

3 DOSAGE FORMS AND STRENGTHS

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets USP) is available in a blister pack. Each blister pack contains 28 tablets in the following order:

- 7 white to off white, round, biconvex, coated tablets, debossed with "S" on one side and "15" on other side of the tablet contains 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 pale blue to bluish white, round, biconvex, coated tablets, debossed with "S" on one side and "16" on other side of the tablet contains 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 blue to light blue, round, biconvex, coated tablets, debossed with "S" on one side and "17" on other side of the tablet contains 0.250 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 green, round, mottled, biconvex, uncoated tablets, debossed with "S" on one side and "24" on other side of the tablet contains inert ingredients

4 CONTRAINDICATIONS

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is contraindicated in females who are known to have or develop the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or migraine headaches with aura *[see Warnings and Precautions (5.7)]*
    - Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.7)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.2)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9)* and *Use in Specific Populations (8.1)]*
- Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive *[see Warnings and Precautions (5.11)]*
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

- Stop Tri-VyLibra Lo if an arterial thrombotic event or venous thrombotic (VTE) event occurs.
- Stop Tri-VyLibra Lo if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately *[see Adverse Reactions (6.2)]*.
- If feasible, stop Tri-VyLibra Lo at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during and following prolonged immobilization.
- Start Tri-VyLibra Lo no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued.
- Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.
- Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function

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

Liver Tumors

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

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

5.3 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

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

5.4 High Blood Pressure

Tri-VyLibra Lo is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop Tri-VyLibra Lo if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may worsen existing gallbladder disease. A past history of COC-related

cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC related cholestasis.

5.6 Carbohydrate and Lipid Metabolic Effects

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

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

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

5.7 Headache

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

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

5.8 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

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

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

Amenorrhea and Oligomenorrhea

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

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.9 COC Use Before or During Early Pregnancy

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

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

5.10 Depression

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

5.11 Malignant Neoplasms

Breast Cancer

Tri-VyLibra Lo is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see Contraindications (4)]*.

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

Cervical Cancer

A causal relationship between the use of CHCs and the development of cervical cancer and intraepithelial neoplasia has not been clearly established. In observational studies, 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 taking Tri-VyLibra Lo.

6 ADVERSE REACTIONS

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

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

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

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

The safety of Tri-VyLibra Lo was evaluated in 1,723 subjects who participated in a randomized, partially blinded, multicenter, active-controlled clinical trial of Tri-VyLibra Lo 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-VyLibra Lo 4% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions leading to discontinuation were headache/migraine (1.2%), nausea/vomiting (0.7%), cervical dysplasia (0.7%), abdominal pain (0.4%), ovarian cyst (0.3%), acne (0.2%), flatulence (0.2%) and depression (0.2%).

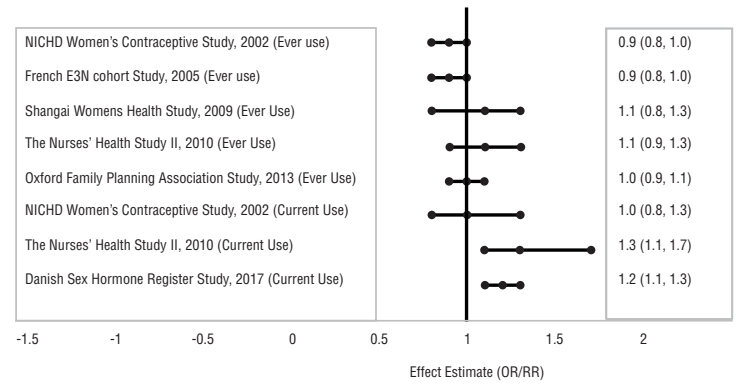
Serious Adverse Reactions: carcinoma of the cervix *in situ* (1 subject) and cervical dysplasia (1 subject).

6.2 Postmarketing Experience

Five studies that compared breast cancer risk between ever-users (current or past use) of COCs and never-users of COCs reported no association between ever use of COCs and breast cancer risk, with effect estimates ranging from 0.90 to 1.12 (Figure 1).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure 1). One of these studies reported no association between breast cancer risk and COC use. The other two studies found an increased relative risk of 1.19 to 1.33 with current or recent use. Both of these studies found an increased risk of breast cancer with current use of longer duration, with relative risks ranging from 1.03 with less than one year of COC use to approximately 1.4 with more than 8 to 10 years of COC use.

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



RR = relative risk; OR = odds ratio; HR = hazard ratio. "ever COC" are females with current or past COC use; "never COC use" are females that never used COCs.

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

Infections and Infestations: Urinary tract infection

Neoplasms Benign, Malignant and Unspecified (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-VyLibra Lo.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances Decreasing the Plasma Concentrations of COCs

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

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

Substances Increasing the Plasma Concentrations of COCs

Co-administration of atorvastatin or rosuvastatin and certain COCs containing EE increase AUC values for EE by approximately 20 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.

7.4 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

8.6 Hepatic Impairment

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

8.7 Renal Impairment

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

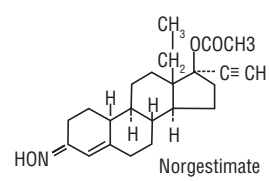
10 OVERDOSAGE

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

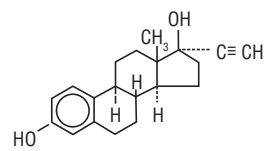
11 DESCRIPTION

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

- Each active white to off white tablet contains 0.180 mg of norgestimate USP and 0.025 mg of ethinyl estradiol USP. Inactive ingredients include croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.
- Each active pale blue to bluish white tablet contains 0.215 mg of norgestimate USP and 0.025 mg of ethinyl estradiol USP. Inactive ingredients include croscarmellose sodium, FD&C Blue #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.
- Each active blue to light blue tablet contains 0.250 mg of norgestimate USP and 0.025 mg of ethinyl estradiol USP. Inactive ingredients include croscarmellose sodium, FD&C Blue #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.
- Each green placebo tablet contains only inert ingredients, as follows: anhydrous lactose, FD&C Blue No. 2 aluminum lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, and povidone.



Norgestimate



Ethinyl Estradiol

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Tri-VyLibra Lo.

12.3 Pharmacokinetics

Absorption

Norgestimate (NGM) and EE are rapidly absorbed following oral administration. NGM is rapidly and completely metabolized by first pass (intestinal and/or hepatic) mechanisms to norelgestromin (NGMN) and norgestrel (NG), which are the major active metabolites of NGM. Mean pharmacokinetic parameters for NGMN, NG and EE during three cycles of administration of Tri-VyLibra Lo are summarized in Table 3.

Peak serum concentrations of NGMN and EE were generally reached by 2 hours after administration of Tri-VyLibra Lo. Accumulation following multiple dosing of the 0.180 mg NGM / 0.025 mg EE dose is approximately 1.5 to 2 fold for NGMN and approximately 1.5 fold for EE compared with single dose administration, in agreement with that predicted based on linear kinetics of NGMN and EE. The pharmacokinetics of NGMN is dose proportional following NGM doses of 0.180 to 0.250 mg. Steady-state conditions for NGMN following each NGM dose and for EE were achieved during the three cycle study. Non-linear accumulation (4.5 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-VyLibra Lo During a Three Cycle Study

Analyte[1]	Cycle	Day	C_{max}	t_{max}(h)	$AUC_{0\text{-}24h}$	$t_{1/2}$(h)
NGMN[(2-4)]	**1**	**1**	**0.91** (0.27)	**1.8** (1)	**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[(2-4)]	**1**	**1**	**0.32** (0.14)	**2** (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** (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[(2,3,5)]	**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)

[1] NGMN = Norelgestromin, NG = norgestrel, EE = ethinyl estradiol

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

[3] units for all analytes; h = hours

[4] units for NGMN and NG – C_{max} = ng/mL, $AUC_{0\text{-}24h}$ = h•ng/mL

[5] units for EE only – C_{max} = pg/mL, $AUC_{0\text{-}24h}$ = h•pg/mL

NC = not calculated

Food Effect

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

Distribution

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

Metabolism

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

Excretion

Following 3 cycles of administration of Tri-VyLibra Lo, 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 0.180 or 0.250 mg / EE 0.025 mg tablets in four pharmacokinetic studies. Increasing body weight and body surface area were each associated with decreases in C_{max} and $AUC_{0\text{-}24h}$ 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 $AUC_{0\text{-}24h}$ by 19%, NG C_{max} by 12% and $AUC_{0\text{-}24h}$ by 46%, EE C_{max} by 13% and $AUC_{0\text{-}24h}$ 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 $AUC_{0\text{-}24h}$ 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-VyLibra Lo tablets may be explained by any or all of the above demographic parameters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.2, 5.11) 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-VyLibra Lo use and a total of 20 pregnancies were reported in Tri-VyLibra Lo users. The racial demographic of those treated with Tri-VyLibra Lo was: Caucasian (86%), African-American (6%), Asian (2%), and Other (6%). There were no exclusions on the basis of weight; the weight range for women treated was 90 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-VyLibra Lo (norgestimate and ethinyl estradiol tablets USP) are available in a blister pack.

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

- 7 white to off white, round, biconvex, coated tablets (active), debossed with "S" on one side and "15" on other side of the tablet contains 0.180 mg, norgestimate USP and 0.025 mg ethinyl estradiol USP
- 7 pale blue to bluish white, round, biconvex, coated tablets (active), debossed with "S" on one side and "16" on other side of the tablet contains 0.215 mg norgestimate USP and 0.025 mg ethinyl estradiol USP
- 7 blue to light blue, round, biconvex, coated tablets (active), debossed with "S" on one side and "17" on other side of the tablet contains 0.250 mg norgestimate USP and 0.025 mg ethinyl estradiol USP
- 7 green, round, mottled, biconvex, uncoated tablets (non-hormonal placebo), debossed with "S" on one side and "24" on other side of the tablet contains inert ingredients

The blister packs are available in the following packages:

- The blister packs are packaged in mono cartons

Carton of 1 Blister Pack	NDC 50102-231-11
Carton of 3 Blister Packs packaged in mono cartons	NDC 50102-231-13

16.2 Storage Conditions

- **Store at** 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
- Protect from light.
- Keep out of the 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 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-VyLibra Lo does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- Tri-VyLibra Lo is not to be used during pregnancy; if pregnancy occurs during use of Tri-VyLibra Lo instruct the patient to stop further use *[see Warnings and Precautions (5.9)]*.
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed *[see Dosage and Administration (2.2)]*.
- Use a back-up or alternative method of contraception when enzyme inducers are used with Tri-VyLibra Lo *[see Drug Interactions (7.1)]*.
- COCs may reduce breast milk production, this is less likely to occur if breastfeeding is well established *[see Use in Specific Populations (8.3)]*.
- Women who start COCs postpartum; and who have not yet had a period, should use an additional method of contraception until they have taken a white to off 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 (5.8)]*.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 03/2023

Patient Information
Tri-VyLibra® Lo
(norgestimate and ethinyl estradiol tablets USP)

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

Do not use Tri-VyLibra Lo 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-VyLibra Lo?

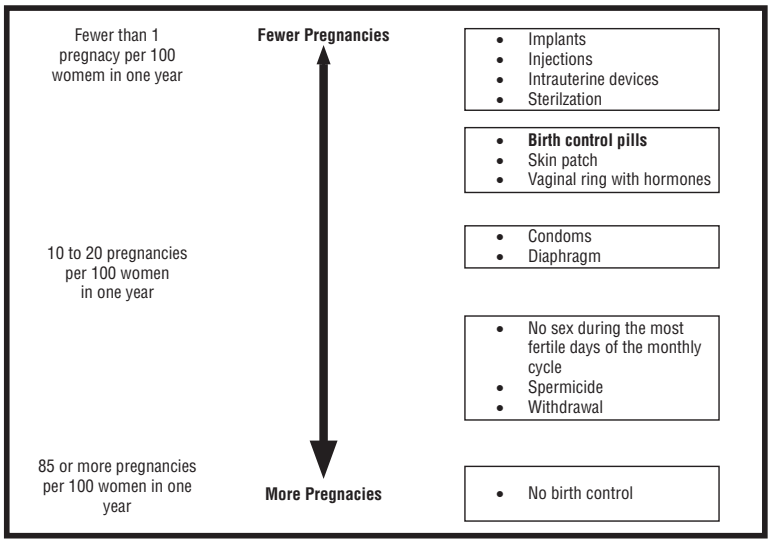
Tri-VyLibra Lo is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

How does Tri-VyLibra Lo 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-VyLibra Lo.

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-VyLibra Lo?

Do not take Tri-VyLibra Lo 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 "alanine aminotransferase" (ALT) in the blood.
- have any unexplained vaginal bleeding
- are pregnant
- had breast cancer or any cancer that is sensitive to female hormones

If any of these conditions happen while you are taking Tri-VyLibra Lo, stop taking Tri-VyLibra Lo right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking Tri-VyLibra Lo.

What should I tell my healthcare provider before taking Tri-VyLibra Lo?

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-VyLibra Lo may decrease the amount of breast milk you make. A small amount of the hormones in Tri-VyLibra Lo 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-VyLibra Lo may affect the way other medicines work, and other medicines may affect how well Tri-VyLibra Lo 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-VyLibra Lo?

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

What are the possible serious side effects of Tri-VyLibra Lo?

- **Like pregnancy, Tri-VyLibra Lo 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-VyLibra Lo.**
- **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-VyLibra Lo. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of Tri-VyLibra Lo?

- 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-VyLibra Lo. For more information, ask your healthcare provider or pharmacist.

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

What else should I know about taking Tri-VyLibra Lo?

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

How should I store Tri-VyLibra Lo?

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

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

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

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

For more information, call Afaxys Pharma, LLC at 855-888-2467.

Does hormonal birth control cause cancer?

It is not known if hormonal birth control pills causes 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 Tri-VyLibra Lo?

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-VyLibra Lo, 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-VyLibra Lo?

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

Inactive ingredients:

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

Pale blue to bluish white pills: croscarmellose sodium, FD&C Blue #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Blue to light blue pills: croscarmellose sodium, FD&C Blue #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Green pills: anhydrous lactose, FD&C Blue No. 2 aluminum lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, and povidone.

Instructions For Use

Tri-VyLibra® Lo

(norgestimate and ethinyl estradiol tablets USP)

Important Information about taking Tri-VyLibra Lo

- Take **1** pill every day at the same time. Take the pills in the order directed on your pill blister pack.
- 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-VyLibra Lo, talk to your healthcare provider. When you first start taking Tri-VyLibra Lo, 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-VyLibra Lo. 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-VyLibra Lo 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-VyLibra Lo 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-VyLibra Lo.
- 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 pill blister pack. If you do not have an extra pill blister pack, take the next pill in your pill blister pack. Continue taking all your remaining pills in order. Start the first pill of your next pill blister pack the day after finishing your current pill blister pack. 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-VyLibra Lo 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-VyLibra Lo:

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

When should I start taking Tri-VyLibra Lo?

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

If you start taking Tri-VyLibra Lo and you are switching from another birth control pill:

- Start your new Tri-VyLibra Lo 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-VyLibra Lo and previously used a vaginal ring or transdermal patch:

- Start using Tri-VyLibra Lo on the day you would have reapplied the next ring or patch.

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

- Start taking Tri-VyLibra Lo 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-VyLibra Lo and you are switching from an intrauterine device or system (IUD or IUS):

- Start taking Tri-VyLibra Lo 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-VyLibra Lo.

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-VyLibra Lo?**" above. Follow these instructions for either a **Sunday Start** or a **Day 1 Start**.

Sunday Start:

You will use a **Sunday Start** if your healthcare provider told you to take your first pill on a Sunday.

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

Day 1 Start:

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

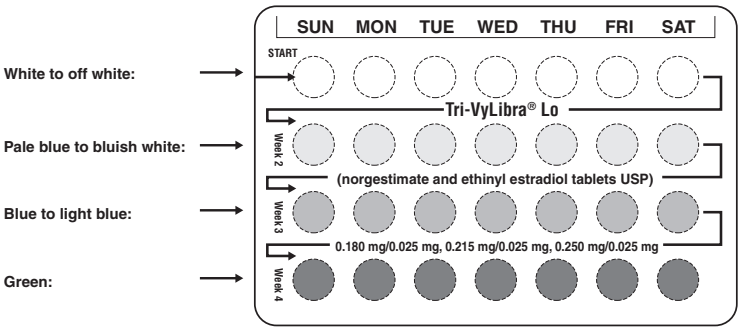
- Take **1** pill every day in the order of the pill blister pack, at the same time each day, for **28** days.
- After taking the last pill on **Day 28** from the pill blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack. Take the first pill in the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

Tri-VyLibra Lo comes in Blister Pack.

1. Decide what time of day you want to take your pill.
   It is important to take it at about the same time every day.
2. The 28-pill pack has 21 white to off white, pale blue to bluish white, and blue to light blue

"active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of green "reminder" pills (without hormones).

3. Also find:
   1) where on the pack to start taking pills,
   2) in what order to take the pills, and
   3) the week numbers as shown in the picture below.



4. Be sure you have ready at all times:
   Another kind of birth control (such as condoms or spermicide) to use as a back-up method in case you miss pills.
   An extra, full pill pack.

You have a choice of which day to start taking your first pack of pills. Tri-VyLibra Lo is available in a blister pack which is preset for a Sunday Start. Day 1 Start stickers are also provided. Decide with your healthcare professional which is the best day for you. Pick a time of day that will be easy to remember.

Sunday Start:

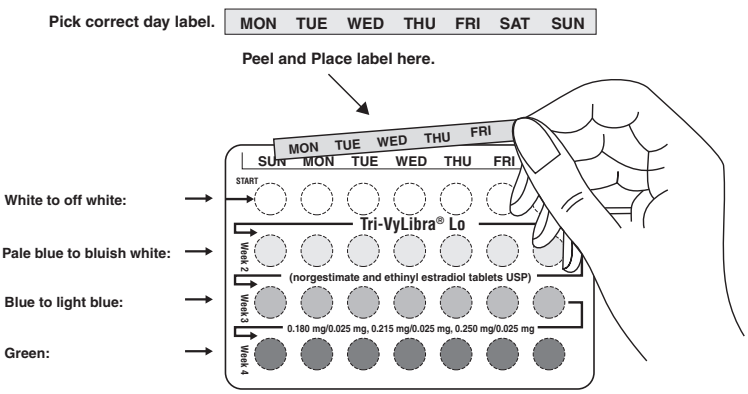
Take the first white to off white "active" pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

Use another method of birth control (such as condoms or spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

Day 1 Start:

Take the first white to off white "active" pill of the first pack during the first 24 hours of your period.

1. Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins).
2. Place this day label strip in the cycle tablet over the area that has the days of the week (starting with Sunday) imprinted in the plastic.



Note: If the first day of your period is a Sunday, you can skip steps #1 and #2.

You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

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

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

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

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

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

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

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

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

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

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