

Table 1. Summary of Norethindrone (NE) and Ethinyl Estradiol (EE) Pharmacokinetics Following Single- and Multiple-Dose Oral Administration of Norethindrone Acetate/Ethinyl Estradiol Tablets to Healthy Female Volunteers Under Fasting Condition (n = 17)

Regimen	Analyte	Arithmetic Mean* (% CV) by Pharmacokinetic Parameter					
		C _{max} (pg/mL)	t _{max} (hr)	AUC ₀₋₂₄ (pg/mL·h)	C _{min} (pg/mL)	t _{1/2} (hr)	C _{tr} (pg/mL)
Day 1 (Single Dose)	NE	8420 (31)	1 (0.7–4)	33390 (40)	--	--	--
	EE	64.5 (27)	1.3 (0.7–4)	465.4 (26)	--	--	--
	SHBG	--	--	--	57.5 (37) [†]	--	--
Day 24 (Multiple Dose)	NE	16400 (26)	1.3 (0.7–4)	88160 (30)	880 (51)	8.4	3670 (30)
	EE	81.9 (24)	1.7 (1–2)	701.3 (28)	11.4 (43)	14.5	29.2 (28)
	SHBG	--	--	--	144 (24)	--	--

C_{max} = Maximum plasma concentration
t_{max} = Time of C_{max}
C_{min} = minimum plasma concentration at steady-state
AUC₀₋₂₄ = Area under plasma concentration versus time curve from 0 to 24 hours
t_{1/2} = Apparent first-order terminal elimination half-life
C_{tr} = Average plasma concentration = AUC₀₋₂₄/24
CV = Coefficient of Variation (%)
SHBG = Sex Hormone Binding Globulin (nmol/L)
*The harmonic mean (0.693/mean apparent elimination rate constant) is reported for t_{1/2} and the median (range) is reported for t_{max}.
†The SHBG concentration reported here is the pre-dose concentration.

Food Effect
MERZEE may be administered without regard to meals.

A single-dose administration of NA/EE capsules with food in 38 healthy, non-smoking premenopausal women decreased the maximum concentration of norethindrone and ethinyl estradiol by 38% and 33%, respectively. Food intake did not affect the extent of ethinyl estradiol absorption, but increased the extent of norethindrone absorption by 19%.

Distribution
Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and SHBG, whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

Metabolism
Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

Excretion
Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of norethindrone acetate/ethinyl estradiol tablets are approximately 8 hours and 14 hours, respectively.

Drug Interactions
No drug-drug interaction studies were conducted with MERZEE.

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
The data presented in Section 14 are from a clinical trial conducted with a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets. MERZEE capsules are bioequivalent to these norethindrone acetate/ethinyl estradiol tablets. In a clinical study, 743 women 18 to 45 years of age were studied to assess the efficacy of norethindrone acetate/ethinyl estradiol tablets, for up to six 28-day cycles providing a total of 3,823 treatment-cycles of exposure. The racial demographic of all enrolled women was: 70% Caucasian, 16% African-American, 10% Hispanic, 2% Asian and 2% Other. Women with body mass index (BMI) greater than 35 mg/m² were excluded from the study. The weight range for those women treated was 90 to 260 pounds, with a mean weight of 147 pounds. Among the women in the study, about 40% had not used hormonal contraception immediately prior to enrolling in this study. A total of 583 women completed 6 cycles of treatment. There were a total of 5 non-contraction pregnancies in 3,563 treatment cycles during which no backup contraception was used. The Pearl Index for norethindrone acetate/ethinyl estradiol tablets was 1.82 (95% confidence interval 0.59 - 4.25).

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
MERZEE (norethindrone acetate and ethinyl estradiol capsules and ferrous fumarate capsules) is available in blister cards (dispensers) containing 28 soft gelatin capsules:
Each blister card contains 28 capsules in the following order:
• 24 oval, opaque, pale pink (active) soft gelatin capsule with ‘SP’ printed on the outer shell in black and each containing 1 mg norethindrone acetate and 20 mcg ethinyl estradiol.
• 4 oval, opaque, maroon, (non-hormonal placebo) capsules imprinted with “SP” on one side and each containing 75 mg ferrous fumarate. The ferrous fumarate capsules do not serve any therapeutic purpose.

Each blister card is packed in a carton (NDC 43386-371-32).

16.2 Storage Conditions
Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Patient Information).
Counsel patients on the following information:
• Cigarette smoking increases the risk of serious cardiovascular events from COC use, and women who are over 35 years old and smoke should not use COCs.
• 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.
• MERZEE does not protect against HIV infection (AIDS) and other sexually transmitted infections.
• The Warnings and Precautions associated with COCs.
• MERZEE is not to be used during pregnancy; if pregnancy occurs during use of MERZEE, instruct the patient to stop further intake.
• Take one capsule daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. See “What to Do if You Miss Capsules” section in *FDA-approved patient labeling*.
• Use a back-up or alternative method of contraception when enzyme inducers are used with MERZEE.
• COCs may reduce breast milk production. This is less likely to occur if breast-feeding is well established.
• 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 pink capsule for 7 consecutive days.
• Amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, MD 21202.

FDA-Approved Patient Labeling

Guide for Using MERZEE (Norethindrone Acetate and Ethinyl Estradiol Capsules and Ferrous Fumarate Capsules)

WARNING TO WOMEN WHO SMOKE

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

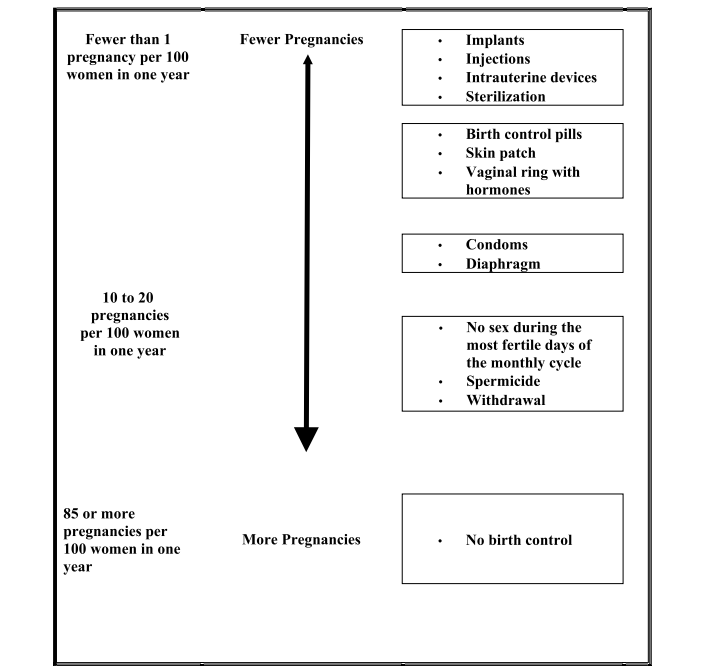
Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted infections.

What is MERZEE?
MERZEE is a birth control pill. It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called norethindrone acetate.

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

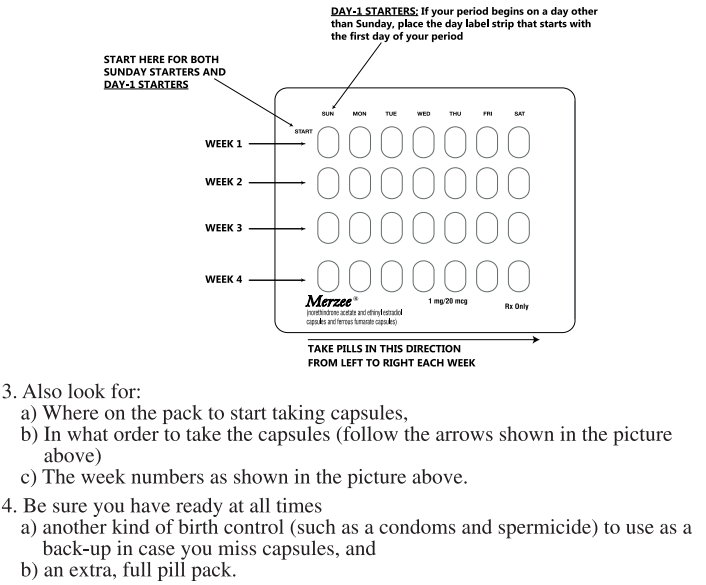
Based on the results of one clinical study of a 24-day regimen of norethindrone acetate 1 mg/ethinyl estradiol 0.020 mg tablets lasting six months, about 1 to 4 out of 100 women may get pregnant during the first year they use MERZEE.
Women with a BMI above 35 kg/m² were not studied in the clinical trial, so it is not known how well MERZEE protects against pregnancy in such women. If you are overweight, discuss with your healthcare provider whether MERZEE is the best choice for you.

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.



- How do I take MERZEE?**
- Be sure to read these directions before you start taking your capsules or anytime you are not sure what to do.
 - The right way to take the capsule is to take one capsule every day at the same time in the order directed on the package. MERZEE can be taken without regard to meals.
If you miss capsules you could get pregnant. This includes starting the pack late. The more capsules you miss, the more likely you are to get pregnant. See “WHAT TO DO IF YOU MISS CAPSULES” below.
 - Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach during the first 1 to 3 packs of capsules.
If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the capsules. The problem will usually go away. If it does not go away, check with your healthcare provider.
 - Missing capsules can also cause spotting or light bleeding, even when you make up these missed capsules.
On the days you take two capsules, to make up for missed capsules, you could also feel a little sick to your stomach.
 - If you have vomiting (within 3 to 4 hours after you take your capsule), you should follow the instructions for “WHAT TO DO IF YOU MISS CAPSULES.” If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John’s Wort, your capsules may not work as well.
Use a back-up method (such as condoms and spermicides) until you check with your healthcare provider.
 - If you have trouble remembering to take MERZEE, talk to your healthcare provider about how to make capsule-taking easier or about using another method of birth control.
 - If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

- Before You Start Taking Your MERZEE**
- Decide What Time of Day You Want to Take Your Capsule. It is important to take MERZEE in the order directed on the package at the same time every day. MERZEE can be taken without regard to meals.
 - Look at Your Capsule Pack – It has 28 Capsules
The MERZEE-pill pack has 24 “active” pink capsules (with hormones) to be taken for 24 days, followed by 4 “reminder” maroon capsules (without hormones) to be taken for the next four days.



- Also look for:
a) Where on the pack to start taking capsules.
b) In what order to take the capsules (follow the arrows shown in the picture above)
c) The week numbers as shown in the picture above.
 - Be sure you have ready at all times
a) another kind of birth control (such as a condoms and spermicide) to use as a back-up in case you miss capsules, and
b) an extra, full pill pack.
- When to Start the First Pack of Capsules**
You have a choice for which day to start taking your first pack of capsules. Decide with your healthcare provider which is the best day for you. Pick a time of day which will be easy to remember.
- Day 1 Start:**
- 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).
 - Place this day label strip on the capsule dispenser over the area that has the days of the week (starting with Sunday) printed on the plastic.
 - Take the first pink pill of the pack during the first 24 hours of your period.
 - You will not need to use a back-up method of birth control, since you are starting the capsule at the beginning of your period. However, if you start MERZEE later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 pink capsules.

- Sunday Start:**
- Take the first pink capsule of the 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 a condom and 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). This also applies if you start MERZEE after having been pregnant, and you have not had a period since your pregnancy.

When You Switch From a Different Birth Control Tablet
When switching from another birth control pill, finish all the tablets, then MERZEE should be started on the same day that a new pack of the previous birth control tablet would have been started.

When You Switch From Another Type of Birth Control Method
When switching from a transdermal patch or vaginal ring, finish the 21 days of use, wait 7 days, then MERZEE should be started when the next application would have been due.

When switching from an injection, MERZEE should be started when the next injection would have been due. When switching from an intrauterine device or an implant, MERZEE should be started on the day of removal.

- What to Do During the Month**
- Take one capsule at the same time every day until the pack is empty.
Do not skip capsules even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
 - Do not skip capsules even if you do not have sex very often.

When you finish a pack of capsules, start the next pack on the day after your last maroon capsule. Do not wait any days between packs.

What to Do if You Miss Capsules
NA/EE and Fe may not be as effective if you miss any pink capsules, especially if you miss the first few or the last few pink capsules in a pack.

- If you miss 1 pink capsule:**
- Take the capsule as soon as you remember. Take the next capsule at your regular time. This means you may take two capsules in one day.
 - You do not need to use a back-up birth control method if you have sex.
- If you miss 2 pink capsules in a row in week 1 OR week 2 of your pack:**
- Take two capsules on the day you remember and two capsules the next day.
 - Then take one capsule a day until you finish the pack.
- You could become pregnant if you have sex in the 7 days after you restart your capsules.** You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.
- If you miss 2 pink capsules in a row in week 3 or week 4 of your pack:**
- If you are a Day 1 Starter:
Throw out the rest of the MERZEE pack and start a new pack that same day.

- If you are a Sunday Starter:**
- Keep taking one capsule every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of capsules that same day.
- You could become pregnant if you have sex in the 7 days after you restart your capsules.** You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.
- You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

- If you miss 3 or more pink capsules in a row during any week:**
- If you are a Day 1 Starter:
Throw out the rest of the capsule pack and start a new pack that same day.
 - If you are a Sunday Starter:
Keep taking 1 capsule every day until Sunday. On Sunday, throw out the rest of the pack and start a new pack of capsules that same day.

- You could become pregnant if you have sex on the days when you missed capsules or during the first 7 days after you restart your capsules.** You must use another birth control method (such as a condom and spermicide) as a back-up the next time you have sex and for the first 7 days after you restart your capsules.
- You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.**

- If you miss any of the 4 maroon capsules in Week 4:**
- Throw away the capsules you missed.
 - Keep taking one capsule each day until the pack is empty.
 - You do not need a back-up method.
 - Start the next pack of MERZEE as scheduled.

Finally, if you are still not sure what to do about the capsules you have missed:

- Use a back-up method (such as a condom and spermicide) anytime you have sex.
- Contact your healthcare provider and continue taking one active pink capsule each day until otherwise directed.

Who should not take MERZEE?
Your healthcare provider will not give you MERZEE if you have:
• Ever had blood clots in your arms, legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
• Ever had a stroke
• Ever had a heart attack
• Certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
• An inherited problem with your blood that makes it clot more than normal
• High blood pressure that medicine cannot control
• Diabetes with kidney, eye, nerve, or blood vessel damage
• Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or have any migraine headaches if you are over age 35
• Ever had breast cancer or any cancer that is sensitive to female hormones
• Liver disease, 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.

Also, do not take birth control pills if you:
• Smoke and are over 35 years old
• Are or suspect you are pregnant
• Have any unexplained bleeding from the vagina
Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy, also called cholestasis of pregnancy.

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider may recommend another method of birth control).

What else should I know about taking MERZEE?
Birth control pills do not protect you against any sexually transmitted infection, including HIV, the virus that causes AIDS.
Do not skip any pills, even if you do not have sex often.

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:
• Think you are pregnant
• Miss one period and have not taken your birth control pills every day
• Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects. You should stop MERZEE at least four weeks before you have surgery and not restart it until at least two weeks after the surgery, due to an increased risk of blood clots.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like MERZEE, may decrease the amount of milk you make. A small amount of the pill’s hormones pass into breast milk.

Tell your healthcare provider about all medicines and herbal products that you take. Some medicines and herbal products may make birth control pills less effective, including:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John’s wort
- topiramate

Use a back-up or alternative birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

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

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

If you are scheduled for any laboratory tests, tell your healthcare provider that you are taking birth control pills. Certain blood tests may be affected by birth control pills.

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

It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke.

Some examples of serious blood clots are blood clots in the:
• Legs (deep vein thrombosis)
• Lungs (pulmonary embolism)
• Eyes (loss of eyesight)
• Heart (heart attack)
• Brain (stroke)

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

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain or pressure in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the common side effects of birth control pills?
The most common side effects of birth control pills are:
• Spotting or bleeding between menstrual periods
• Nausea
• Breast tenderness
• Headache

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

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

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 should I know about my period when taking MERZEE?
Irregular vaginal bleeding or spotting may occur while you are taking MERZEE. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding, which is a flow much like a regular period. Irregular bleeding occurs most often during the first few months of oral contraceptive use, but may also occur after you have been taking the pill for some time. Such bleeding may be temporary and usually does not indicate any serious problems. It is important to continue taking your pills on schedule. If the bleeding occurs in more than one cycle, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long as you have taken the pills according to direction.








What if I miss my scheduled period when taking MERZEE?
It is not uncommon to miss your period. However, if you go two or more months in a row without a period, or you miss your period after a month where you did not take all your pills correctly, call your healthcare provider because you may be pregnant. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. Stop taking MERZEE if you are pregnant.

What if I want to become pregnant?
You may stop taking the capsule whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the capsule.

General Advice about MERZEE
Your healthcare provider prescribed NA/EE and Fe for you. Please do not share MERZEE with anyone else. Keep MERZEE out of the reach of children.
If you have concerns or questions, ask your healthcare provider. You may also ask your pharmacist for a more detailed label written for healthcare professionals.
This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Lupin Pharmaceuticals, Inc.
Baltimore, MD 21202.
Manufactured at:
NextPharma Ploermel,
56800 Ploermel,
France (FRA).

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