

PRODUCT MONOGRAPH

Pr CENTRISA™ LO 21 and Pr CENTRISA™ LO 28

norgestimate and ethinyl estradiol Tablets, House Std.

0.180 mg norgestimate and 0.025 mg ethinyl estradiol

0.215 mg norgestimate and 0.025 mg ethinyl estradiol

0.250 mg norgestimate and 0.025 mg ethinyl estradiol

Oral Contraceptive

Patriot, a Division of Janssen Inc.
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PHARMACOLOGICAL CLASSIFICATION

Synthetic steroidal combination oral contraceptive.

CLINICAL PHARMACOLOGY

Oral Contraception

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Receptor binding studies, as well as studies in animals and humans, have shown that norgestimate and 17-deacetyl norgestimate (norelgestromin), the major serum metabolite, combine high progestational activity with minimal intrinsic androgenicity. Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in sex hormone binding globulin (SHBG), resulting in lower serum testosterone.

INDICATIONS AND CLINICAL USE

CENTRISA™ LO Tablets are indicated for conception control.

In an active controlled clinical trial including 1,673 subjects completing 11,003 cycles of CENTRISA™ LO use, a total of 20 pregnancies were reported among CENTRISA™ LO users. This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 2.36 per 100 women-years of use. This figure for Pearl Index is slightly higher than other Pearl Indices for similar products marketed in Canada and may be attributed to differences in clinical trial design.

Table 1: Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year.

Method	% of Women Experiencing an Unintended Pregnancy Within the First Year of Use		% of Women Continuing Use at One Year ³
	Typical Use ¹	Perfect Use ²	
Chance ⁴	85	85	
Spermicides ⁵	26	6	40
Periodic Abstinence	25		
Calendar		9	
Ovulation Method		3	
Sympto-Thermal ⁶		2	
Post-Ovulation		1	
Withdrawal	19	4	
Cap ⁷			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm ⁷	20	6	56
Condom ⁸			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		
Progestin Only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
CopperT380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Source: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

¹ Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop for any other reason.

² Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

³ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

⁴ The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

⁵ Foams, creams, gels, vaginal suppositories, and vaginal films.

⁶ Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.

⁷ With spermicidal cream or jelly.

⁸ Without spermicides.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who currently have the following conditions:

1. History of or actual thrombophlebitis or thromboembolic disorders.
2. History of or actual cerebrovascular disorders.
3. History of or actual myocardial infarction or coronary arterial disease.
4. Active liver disease or history of or actual benign or malignant liver tumours.
5. Known or suspected carcinoma of the breast.
6. Known or suspected estrogen-dependent neoplasia.
7. Undiagnosed abnormal vaginal bleeding.
8. Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
9. When pregnancy is suspected or diagnosed.
10. Valvular heart disease with complications.
11. Severe hypertension (persistent systolic values of ≥ 160 or persistent diastolic values of ≥ 100 mm Hg).
12. Diabetes with vascular involvement.
13. Cholestatic jaundice or history of jaundice of pregnancy.
14. Migraine with focal aura.
15. Hypersensitivity to any of the components of this product.

WARNINGS

The following information is provided from studies for combination oral contraceptives. The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

The information contained in this section is principally on studies carried out in women who used combination oral contraceptives with higher formulations of estrogens and progestins than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestin administered orally remains to be determined.

1. Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, especially with increasing age. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use by women who smoke.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these. Whether oral contraceptives accentuate this risk is unclear.

In low-risk, non-smoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low-dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in oral contraceptive users older than 35 years of age. Women should be counselled not to smoke.

2. *Discontinue Medication at the Earliest Manifestation of the Following:*

- A. Thromboembolic and Cardiovascular Disorders such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.
- B. Conditions that Predispose to Venous Stasis and to Vascular Thrombosis (e.g. immobilization after accidents or confinement to bed during long-term illness). Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **PRECAUTIONS**.
- C. Visual Defects – Partial or Complete
- D. Papilledema or Ophthalmic Vascular Lesions
- E. Severe Headache of Unknown etiology or Worsening of Pre-existing Migraine Headache

PRECAUTIONS

1. *Physical Examination and Follow-up*

Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities, and pelvic organs should also be examined. A Papanicolaou smear should be taken if the patient has been sexually active.

The first follow-up visit should be three months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Workshop on Screening for Cancer of the Cervix. Their suggestion was that, for women who had two consecutive negative Pap smears, screening could be continued every three years up to the age of 69.

2. *Pregnancy*

Oral contraceptives should not be taken by pregnant women. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child.

3. *Breast-feeding*

In breast-feeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any

effect on the quantity and quality of the milk. There is no evidence that low-dose oral contraceptives are harmful to the nursing infant.

4. *Hepatic Function*

Patients who have had jaundice, including a history of cholestatic jaundice during pregnancy, should be given oral contraceptives with great care and under close observation.

The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved.

If a patient develops jaundice that proves to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are extremely rare, they have caused fatal intra-abdominal hemorrhage and should be considered in women with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

5. *Hypertension*

Patients with essential hypertension whose blood pressure is well controlled may be given oral contraceptives but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary.

6. *Migraine and Headache*

The onset or exacerbation of migraine or the development of headache of a new pattern that is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause.

7. *Diabetes*

Current low-dose oral contraceptives exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives.

8. *Ocular Disease*

Patients who are pregnant or are taking oral contraceptives, may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type. Soft contact lenses usually do not cause disturbances. If visual changes or alterations in tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised.

9. Breasts

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age for first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than eight years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present.

Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended because, if a breast cancer should develop, drugs that contain estrogen may cause a rapid progression.

10. Vaginal Bleeding

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

11. Fibroids

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness require discontinuation of the use of oral contraceptives.

12. Emotional Disorders

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternative method of contraception should be made which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

13. Laboratory Tests

Results of laboratory tests should be interpreted in light of the fact that the patient is on oral contraceptives. The following laboratory tests are modified.

A. Liver Function Tests

Bromsulphthalein Retention Test (BSP)	Moderate increase
AST (SGOT) and GGT	Minor increase
Alkaline Phosphatase	Variable increase
Serum Bilirubin	Increased, particularly in conditions predisposing to or associated with hyperbilirubinemia

B. Coagulation Tests

Factors II, VII, IX, X, XII and XIII	Increased
Factor VIII	Mild increase
Platelet aggregation and adhesiveness	Mild increase in response to common aggregating agents
Fibrinogen	Increased

Plasminogen	Mild increase
Antithrombin III	Mild decrease
Prothrombin Time	Increased

C. Thyroid Function Tests

Protein-bound Iodine (PBI)	Increased
Total Serum Thyroxine (T ₄)	Increased
Thyroid Stimulating Hormone (TSH)	Unchanged
T ₃ resin-uptake	Decreased

D. Adrenocortical Function Tests

Plasma Cortisol	Increased
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E. Miscellaneous Tests

Serum Folate	Occasionally decreased
Glucose Tolerance Test	Variable increase with return to normal after 6 to 12 months
Insulin Response	Mild to moderate increase
c-Peptide Response	Mild to moderate increase

14. Tissue Specimens

Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

15. Return to Fertility

After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred in order to date the pregnancy. An alternative contraceptive method should be used during this time.

16. Amenorrhea

Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy.

Amenorrhea, especially if associated with breast secretion, that continues for six months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

17. Thromboembolic Complications - Post-surgery

There is an increased risk of thromboembolic complications in oral contraceptive users after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least one month prior to **MAJOR** elective surgery. Oral contraceptive use should not be resumed until the first menstrual period after hospital discharge following surgery.

18. Drug Interactions

The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent (Tables II and III). Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low-dose formulations. It is important to ascertain all

drugs that a patient is taking, both prescription and non-prescription, including herbal preparations/remedies, before oral contraceptives are prescribed.

The metabolism of oral contraceptives may be influenced by various drugs and herbal preparations including St. John's wort. Of potential clinical importance are drugs and herbal supplements that are known to affect the induction of enzymes that are responsible for the degradation of contraceptive steroid hormones (e.g. St. John's wort). Decreased effectiveness of the estrogenic component of oral contraceptives may result in spotting, breakthrough bleeding and possible pill failure. It is possible that induction of these enzymes may lead to reductions in the circulating levels of the progestational component of CENTRISA™ LO Tablets. In actual practice, reduced efficacy has been associated with concomitant use of St. John's wort.

Some drugs, such as cholestyramine, may impair the enterohepatic circulation of estrogens, and may result in hastened elimination and impaired effectiveness.

Some data has indicated a decrease in the serum levels of the estrogenic component of oral contraceptives in conjunction with topiramate. Therefore, the efficacy of low-dose oral contraceptives may be reduced with concomitant use. Patients should be encouraged to report any change in bleeding patterns.

Some protease inhibitors and some anti-retroviral agents have been found to either increase (e.g. indinavir) or decrease (e.g. ritonavir) circulating levels of combination hormonal contraceptives.

Refer to *Oral Contraceptives 1994* (Chapter 8), Health Canada, for other possible drug interactions with OCs.

TABLE II

Drugs That May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	Carbamazepine Ethosuximide Phenobarbital Phenytoin Primidone	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose OCs (50 µg ethinyl estradiol), another drug or another method.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces OC efficacy.	Use another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Other Drugs	Phenylbutazone Antihistamines Analgesics Antimigraine Preparations Vitamin E	Reduced OC efficacy has been reported. Remains to be confirmed.	

TABLE III**Modification of Other Drug Action by Oral Contraceptives**

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	OCs increase clotting factors, decrease efficacy. However, OCs may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Fluid retention may increase risk of seizures.	Use another method.
Antidiabetic Drugs	Oral Hypoglycemics and Insulin	OCs may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin OC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen OC or use another method.
	Beta Blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of OCs.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because OCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity.

TABLE III (cont'd)**Modification of Other Drug Action by Oral Contraceptives**

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Caffeine		The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol Lowering Agents	Clofibrate	Their action may be antagonized by OCs. OCs may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		OCs have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All Phenothiazines, Reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose OCs. If galactorrhea or hyperprolactinemia occurs, use other method.
Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic Antidepressants	Clomipramine (possibly others)	Increased side effects; i.e. depression.	Use with caution.
Vitamin B ₁₂		OCs have been reported to reduce serum levels of Vitamin B ₁₂ .	May need to increase dietary intake, or supplement.

NON-CONTRACEPTIVE BENEFITS OF ORAL CONTRACEPTIVES

Several health advantages other than contraception have been reported.

1. Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.
2. Oral contraceptives reduce the likelihood of developing benign breast disease and, as a result, decrease the incidence of breast biopsies.
3. Oral contraceptives reduce the likelihood of development of functional ovarian cysts.
4. Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
5. The use of oral contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome, and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders. CENTRISA™ LO Tablets are also used to treat moderate acne in females who are able to take oral contraceptives.
6. Oral contraceptives decrease the incidence of acute pelvic inflammatory disease and, thereby, reduce as well the incidence of ectopic pregnancy.
7. Oral contraceptives have potential beneficial effects on endometriosis.

Oral contraceptives **DO NOT PROTECT** against sexually transmitted diseases including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** oral contraceptives.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives:

- Thrombophlebitis
- Pulmonary embolism
- Mesenteric thrombosis
- Neuro-ocular lesions (e.g. retinal thrombosis)
- Myocardial infarction
- Cerebral thrombosis
- Cerebral hemorrhage
- Hypertension
- Benign hepatic tumours
- Gallbladder disease

The following adverse reactions also have been reported in patients receiving oral contraceptives.

Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10 per cent or less patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally, as follows:

- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Dysmenorrhea
- Amenorrhea during and after treatment
- Temporary infertility after discontinuance of treatment
- Edema
- Chloasma or melasma which may persist
- Breast changes: tenderness, enlargement, and secretion
- Change in weight (increase or decrease)
- Endocervical hyperplasias
- Possible diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- Increase in size of uterine leiomyomata
- Rash (allergic)
- Depression
- Reduced tolerance to carbohydrates
- Vaginal candidiasis
- Premenstrual-like syndrome
- Intolerance to contact lenses
- Change in corneal curvature (steepening)
- Cataracts
- Optic neuritis
- Retinal thrombosis

Changes in libido
Chorea
Changes in appetite
Cystitis-like syndrome
Rhinitis
Headache
Nervousness
Dizziness
Hirsutism
Loss of scalp hair
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Vaginitis
Porphyria
Impaired renal function
Raynaud's phenomenon
Auditory disturbances
Hemolytic uremic syndrome
Pancreatitis

TREATMENT OF OVERDOSE OR ACCIDENTAL INGESTION

In case of overdose or accidental ingestion by children, the physician should observe the patient closely although generally no treatment is required. Gastric lavage may be utilized if considered necessary.

DOSAGE AND ADMINISTRATION

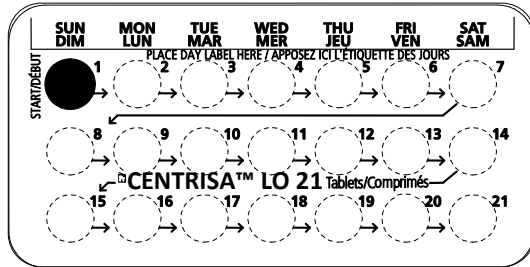
INFORMATION TO PATIENTS ON HOW TO TAKE THE BIRTH CONTROL PILL

1. **READ THESE DIRECTIONS**
 - before you start taking your pills, and
 - any time you are not sure what to do.

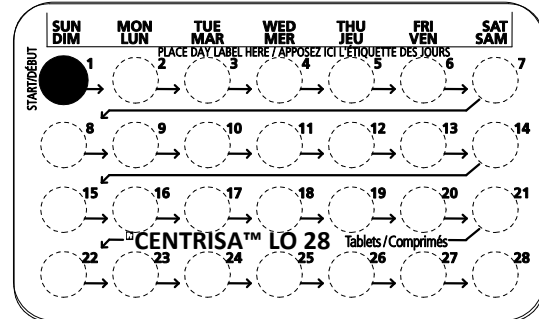
2. **LOOK AT YOUR PILL PACK** to see if it has 21 or 28 pills:
 - **21-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week or
 - **28-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

ALSO CHECK the pill pack for instructions on 1) where to start and 2) direction to take pills.

21-Day
DISCREET Package



28-Day
DISCREET Package



3. You may wish to use a second method of birth control (e.g. latex condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.
4. **When receiving any medical treatment, be sure to tell your doctor that you are using birth control pills.**
5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL.** If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.
6. **MISSING PILLS ALSO CAN CAUSE SOME SPOTTING OR LIGHT BLEEDING,** even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take two pills to make up for missed pills.
7. **IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:**
 - when you start a pack late, or
 - when you miss pills at the beginning or at the very end of the pack.
8. **ALWAYS BE SURE YOU HAVE READY:**
 - **ANOTHER KIND OF BIRTH CONTROL** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
 - **AN EXTRA, FULL PACK OF PILLS.**
9. **IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES,** such as antibiotics, your pills may not work as well. Use a back-up method, such as latex condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

10. **IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW**, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
11. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

WHEN TO START THE *FIRST* PACK OF PILLS

BE SURE TO READ THESE INSTRUCTIONS:

- before you start taking your pills, and
- any time you are not sure what to do.

Decide with your doctor or clinic what is the best day for you to start taking your first pack of pills. Your pills may be either a 21-day or a 28-day type.

DIRECTIONS FOR 21-DAY AND 28-DAY PILL PACKS

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** The pills may be started up to Day 6 of your cycle. Your starting day will be chosen in discussion with your doctor. You will always begin taking your pill on this day of the week. Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

2. **IF YOU ARE USING A:**

21-DAY Pill Pack:

With this type of birth control pill, you are on pills for 21 days and off pills for seven days. You must not be off the pills for more than seven days in a row.

Take one pill at approximately the same time every day for 21 days. **THEN DO NOT TAKE A PILL FOR SEVEN DAYS.** Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period.)

28-DAY Pill Pack:

With this type of birth control pill, you take 21 pills that contain hormones and seven pills that contain no hormones.

Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS ON THE PILLS.** Your period should occur during the last seven days of using that pill pack.

INSTRUCTIONS FOR USING YOUR DISCREET PACKAGE FOR BOTH 21-DAY AND 28-DAY PACKS:

FOLLOW THESE INSTRUCTIONS CAREFULLY:

1. **For Day 1 start:** Label the DISCREET Package by selecting the day label that starts with Day 1 of your menstrual period (the first day of menstruation is Day 1). For example, if your first day of menstruation is Tuesday, attach the day label that begins with **TUE** in the space provided.

OR

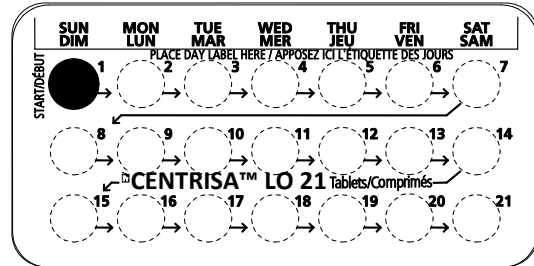
For Day 5 start: Label the DISCREET Package by selecting the day label that starts with the day that is 5 days after your period begins. (Count 5 days including the first day of menstruation.) For example, if your first day of menstruation is Saturday, place the day label that starts with **WED** in the space provided.

OR

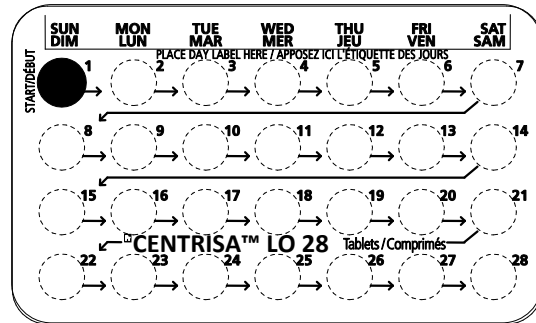
For Sunday start: No day label is required. The DISCREET Package is printed for a Sunday start. (The first Sunday after your period begins, or, if your period starts on Sunday, start that same day.)

2. Place the day label in the space where you see the words "Place day label here". Having the DISCREET Package labelled with the days of the week will help remind you to take your pill every day.
3. To begin taking your pills, start with the pill inside the coloured circle (where you see the word **START**). This pill should correspond to the day of the week that you are taking your first pill. To remove the pill, push through the back of the DISCREET Package.
4. On the following day, take the next pill in the same row, always proceeding from left to right (→). Each row will always begin on the same day of the week.

21-Day DISCREET Package



28-Day DISCREET Package



WHAT TO DO DURING THE MONTH

1. **TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
 - Try to associate taking your pill with some regular activity such as eating a meal or going to bed.
 - Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
 - Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK**
 - **21 PILLS**
WAIT SEVEN DAYS to start the next pack. You will have your period during that week.
 - **28 PILLS**
Start the next pack **ON THE NEXT DAY**. Take one pill every day. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

The following chart outlines the actions you should take if you miss one or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack.

<p style="text-align: center;">SUNDAY START MISS ONE PILL</p>	<p style="text-align: center;">OTHER THAN SUNDAY START MISS ONE PILL</p>
<p>Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.</p>	<p>Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.</p>
<p style="text-align: center;">MISS TWO PILLS IN A ROW</p>	<p style="text-align: center;">MISS TWO PILLS IN A ROW</p>
<p>First Two Weeks</p> <ol style="list-style-type: none"> 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. <p>Third Week</p> <ol style="list-style-type: none"> 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>	<p>First Two Weeks</p> <ol style="list-style-type: none"> 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. <p>Third Week</p> <ol style="list-style-type: none"> 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>
<p style="text-align: center;">MISS THREE OR MORE PILLS IN A ROW</p>	<p style="text-align: center;">MISS THREE OR MORE PILLS IN A ROW</p>
<p>Any Time in the Cycle</p> <ol style="list-style-type: none"> 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>	<p>Any Time in the Cycle</p> <ol style="list-style-type: none"> 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>

NOTE: 28-DAY PACK – If you forget any of the seven "reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

Always be sure you have on hand:

- a back-up method of birth control (such as latex condoms and spermicidal foam or gel) in case you miss pills, and
- an extra, full pack of pills.

IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW, TALK TO YOUR DOCTOR OR CLINIC about ways to make pill-taking easier or about using another method of birth control.

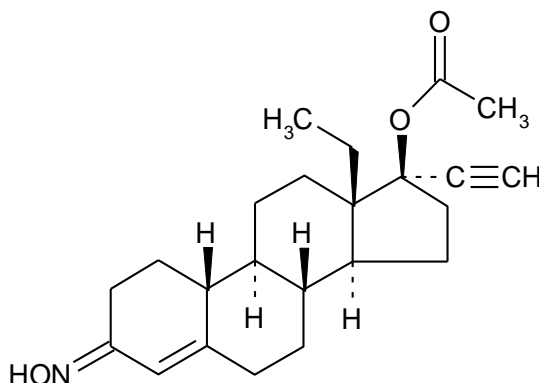
PHARMACEUTICAL INFORMATION

(i) DRUG SUBSTANCE

Norgestimate:

Chemical Name: 18,19-dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α)-(+)-

Structural Formula:



Molecular Weight: 369.51

Molecular Formula: C₂₃ H₃₁ NO₃

Description:

Norgestimate is a white to off-white fine granular powder. Melting and decomposition begin at 213°C.

Solubility:

<u>Solvent Solubility</u>	<u>Solubility</u>	<u>Criteria for USP</u>
Distilled Water (DW)	0.076 μ g/mL	Insoluble
Methanol	20.9 mg/mL	Sparingly Soluble
Ethanol	18.0 mg/mL	Sparingly Soluble
Octanol 10.5 mg/mL	Sparingly Soluble	
Acetonitrile	10.6 mg/mL	Sparingly Soluble
Methylene chloride	>80 mg/mL	Freely to Very Soluble
Heptane	29.9 μ g/mL	Insoluble
Sesame Oil	1.4 mg/mL	Slightly Soluble

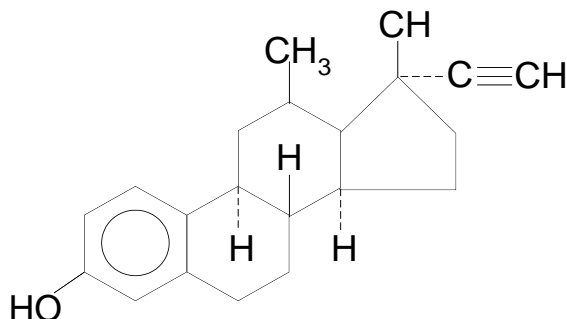
Norgestimate has a partition coefficient of Log P = 5.28 (Octanol/water). No pKa was determined because of its poor solubility in water.

Norgestimate is an optically active mixture of syn and anti isomers having a specific rotation of + 40° to + 46° (1% in chloroform at 25°C at the sodium D line).

Ethinyl Estradiol:

Chemical Name: 19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol

Structural Formula:



Molecular Weight: 296.41

Molecular Formula: C₂₀ H₂₄ O₂

Description:

Ethinyl estradiol is a white to creamy white, odourless, crystalline powder with a melting range of 183°C - 184°C. It is insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils and solutions of fixed alkali hydroxides.

(ii) COMPOSITION

Each white CENTRISA™ LO Tablet contains 0.180 mg norgestimate plus 0.025 mg ethinyl estradiol. Each white tablet also contains lactose, magnesium stearate, microcrystalline cellulose, croscarmellose sodium, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol, and carnauba wax.

Each light blue CENTRISA™ LO Tablet contains 0.215 mg norgestimate plus 0.025 mg ethinyl estradiol. Each light blue tablet also contains lactose, magnesium stearate, microcrystalline cellulose, croscarmellose sodium, carnauba wax, hydroxypropylmethylcellulose, FD & C Blue # 2 aluminum lake, titanium dioxide, and polyethylene glycol.

Each dark blue CENTRISA™ LO Tablet contains 0.250 mg norgestimate plus 0.025 mg ethinyl estradiol. Each dark blue tablet also contains lactose, magnesium stearate, microcrystalline cellulose, croscarmellose sodium, carnauba wax, hydroxypropylmethylcellulose, titanium dioxide, polyethylene glycol, FD & C Blue #2 aluminum lake, and polysorbate 80.

Each green tablet contains inert ingredients, namely lactose, starch, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, FD & C Blue #2 aluminum lake, and yellow iron oxide.

(iii) STORAGE RECOMMENDATIONS

Store between 15°C - 30°C. Leave contents in protective packaging until time of use.

AVAILABILITY OF DOSAGE FORMS

21-day DISCREET Package Tablet Dispenser Units that contain:

- 7 WHITE tablets each containing 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 LIGHT BLUE tablets each containing 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 DARK BLUE tablets each containing 0.250 mg norgestimate and 0.025 mg ethinyl estradiol

28-day DISCREET Package Tablet Dispenser Units that contain:

- 7 WHITE tablets each containing 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 LIGHT BLUE tablets each containing 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 DARK BLUE tablets each containing 0.250 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 GREEN tablets with inert ingredients

INFORMATION FOR THE CONSUMER
PACKAGE INSERT FOR PATIENTS USING ORAL CONTRACEPTIVES
(BIRTH CONTROL PILLS)

You should know that a supplementary information booklet which describes the benefits and risks of taking birth control pills (oral contraceptives) is available from your doctor or pharmacist. Be sure to obtain a copy and read it carefully before you start taking pills.

CENTRISA™ LO Tablets are birth control pills (oral contraceptives) that contain two female sex hormones:

- White tablets - 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
- Light blue tablets - 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- Dark blue tablets - 0.250 mg norgestimate and 0.025 mg ethinyl estradiol

Birth control pills have been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills, except in smokers older than age 35.

The birth control pill is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a risk to you. The use of the birth control pill always should be supervised by your doctor.

WHO SHOULD NOT USE BIRTH CONTROL PILLS

You should not use birth control pills if you have or have had any of the following conditions:

- unusual vaginal bleeding that has not yet been diagnosed;
- blood clots in the legs, lungs, eyes, or elsewhere;
- a stroke, heart attack, heart problems, or chest pain (angina pectoris);
- severe high blood pressure;
- known or suspected cancer of the breast or sex organs;
- liver tumour associated with the use of the pill or other estrogen-containing products;
- diabetes with complications of the kidneys, eyes, nerves, or blood vessels;
- jaundice (yellowing of skin and eyes) or liver disease if still present;
- migraines with visual and/or sensory disturbances; and/or
- allergic reaction to any ingredient in this product.

The pill should not be taken if you are pregnant or if pregnancy is suspected.

IF YOU DECIDE TO TAKE BIRTH CONTROL PILLS

If you and your doctor decide that, for you, the benefits of birth control pills outweigh the risks, you should be aware of the following:

1. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users over 35 years of age. Women should not smoke.
2. Take the pills only on the advice of your doctor and carefully follow all directions given to you. You must take the pills exactly as prescribed. Otherwise, you may become pregnant.
3. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.
4. Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:
 - sharp pain in the chest, coughing blood, or sudden shortness of breath - these symptoms could indicate a possible blood clot in the lung;
 - pain in the calf - this symptom could indicate a possible blood clot in the leg;
 - crushing chest pain or heaviness - this symptom could indicate a possible heart attack;
 - sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg - these symptoms could indicate a possible stroke;
 - sudden partial or complete loss of vision - this symptom could indicate a possible blood clot in the eye;
 - severe pain or lump in the abdomen - these symptoms could indicate a possible tumour of the liver;
 - severe depression;
 - yellowing of the skin (jaundice);
 - unusual swelling of the extremities; and/or
 - breast lumps. **ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.**
5. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing.
6. You will have a menstrual period when you stop taking birth control pills. You should delay pregnancy until another menstrual period occurs within four to six weeks. Contact your doctor for recommendations on alternative methods of contraception during this time.
7. Your doctor will advise you of the appropriate time to start the use of birth control pills after childbirth, miscarriage, or therapeutic abortion.
8. The hormones in birth control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. If birth control pills are not resumed until nursing is

established, however, the quantity and quality of breast milk does not seem to be affected. There is no evidence that birth control pills are harmful to the nursing infant.

9. Should you require **MAJOR** surgery, inform your surgeon that you are using birth control pills.
10. **If you see a different doctor, inform him or her that you are taking birth control pills.** Tell the doctor that your birth control pills are **CENTRISA™ LO Tablets**.

11. **Inform your doctor if you are taking or if you start to take other medications.** This applies to both prescription and non-prescription drugs, including herbal or “natural” preparations or remedies (for example, St. John’s Wort). These medications may change the effectiveness and/or cycle control of your birth control pills. **You may need to use a back-up method of birth control.**

12. **THERE IS NO NEED TO STOP TAKING BIRTH CONTROL PILLS FOR A REST PERIOD.**

13. Birth control pills **DO NOT PROTECT** against sexually transmitted diseases (STDs), including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

HOW TO TAKE BIRTH CONTROL PILLS

1. READ THESE DIRECTIONS

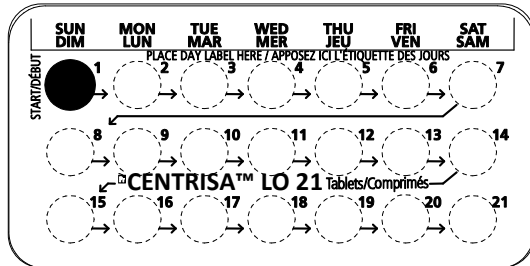
- before you start taking your pills, and
- any time you are not sure what to do.

2. LOOK AT YOUR PILL PACK to see if it has 21 or 28 pills:

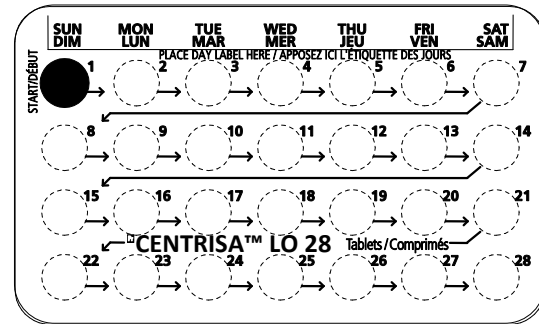
- 21-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week
- or
- 28-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

ALSO CHECK: the pill pack for instructions on 1) where to start and 2) direction to take pills.

21-Day
DISCREET Package



28-Day
DISCREET Package



3. You may wish to use a second method of birth control (e.g. latex condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.
4. **When receiving any medical treatment, be sure to tell your doctor that you are using birth control pills.**
5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL.** If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.
6. **MISSING PILLS ALSO CAN CAUSE SOME SPOTTING OR LIGHT BLEEDING,** even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take two pills to make up for missed pills.
7. **IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:**
 - when you start a pack late, or
 - when you miss pills at the beginning or at the very end of the pack.
8. **ALWAYS BE SURE YOU HAVE READY:**
 - **ANOTHER KIND OF BIRTH CONTROL** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
 - **AN EXTRA, FULL PACK OF PILLS.**
9. **IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES,** such as antibiotics, your pills may not work as well. Use a back-up method, such as latex condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

10. **IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW**, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
11. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

**WHEN TO START THE *FIRST* PACK OF PILLS
BE SURE TO READ THESE INSTRUCTIONS:**

- before you start taking your pills, and
- any time you are not sure what to do.

Decide with your doctor or clinic what is the best day for you to start taking your first pack of pills. Your pills may be either a 21-day or a 28-day type.

DIRECTIONS FOR 21-DAY AND 28-DAY PILL PACKS

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** The pills may be started up to Day 6 of your cycle. Your starting day will be chosen in discussion with your doctor. You will always begin taking your pill on this day of the week. Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

2. **IF YOU ARE USING A:
21-DAY Pill Pack:**

With this type of birth control pill, you are on pills for 21 days and off pills for seven days. You must not be off the pills for more than seven days in a row.

Take one pill at approximately the same time every day for 21 days. **THEN DO NOT TAKE A PILL FOR SEVEN DAYS.** Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period.)

28-DAY Pill Pack:

With this type of birth control pill, you take 21 pills that contain hormones and seven pills that contain no hormones.

Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS ON THE PILLS.** Your period should occur during the last seven days of using that pill pack.

INSTRUCTIONS FOR USING YOUR DISCREET PACKAGE FOR BOTH 21-DAY AND 28-DAY PACKS:

FOLLOW THESE INSTRUCTIONS CAREFULLY:

1. **For Day 1 start:** Label the DISCREET Package by selecting the day label that starts with Day 1 of your menstrual period (the first day of menstruation is Day 1). For example, if your first day of menstruation is Tuesday, attach the day label that begins with **TUE** in the space provided.

OR

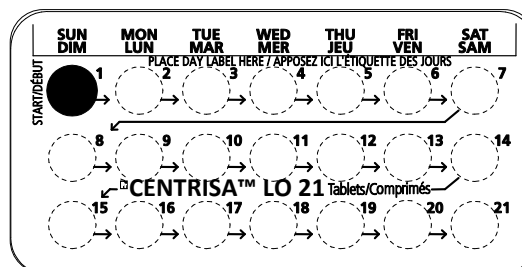
For Day 5 start: Label the DISCREET Package by selecting the day label that starts with the day that is 5 days after your period begins. (Count 5 days including the first day of menstruation.) For example, if your first day of menstruation is Saturday, place the day label that starts with **WED** in the space provided.

OR

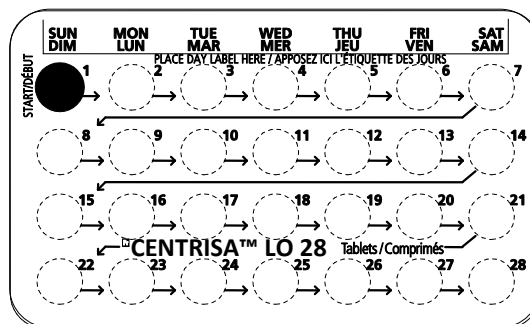
For Sunday start: No day label is required. The DISCREET Package is printed for a Sunday start. (The first Sunday after your period begins, or, if your period starts on Sunday, start that same day.)

2. Place the day label in the space where you see the words "Place day label here". Having the DISCREET Package labelled with the days of the week will help remind you to take your pill every day.
3. To begin taking your pills, start with the pill inside the coloured circle (where you see the word **START**). This pill should correspond to the day of the week that you are taking your first pill. To remove the pill, push through the back of the DISCREET Package.
4. On the following day, take the next pill in the same row, always proceeding from left to right (→). Each row will always begin on the same day of the week.

21-Day DISCREET Package



28-Day DISCREET Package



WHAT TO DO DURING THE MONTH

1. **TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
 - Try to associate taking your pill with some regular activity such as eating a meal or going to bed.
 - Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
 - Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK**
 - **21 PILLS**
WAIT SEVEN DAYS to start the next pack. You will have your period during that week.
 - **28 PILLS**
Start the next pack **ON THE NEXT DAY**. Take one pill every day. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

The following chart outlines the actions you should take if you miss one or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack.

SUNDAY START MISS ONE PILL	OTHER THAN SUNDAY START MISS ONE PILL
Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.
MISS TWO PILLS IN A ROW	MISS TWO PILLS IN A ROW
<p>First Two Weeks</p> <ol style="list-style-type: none"> 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. <p>Third Week</p> <ol style="list-style-type: none"> 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>	<p>First Two Weeks</p> <ol style="list-style-type: none"> 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. <p>Third Week</p> <ol style="list-style-type: none"> 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>
MISS THREE OR MORE PILLS IN A ROW	MISS THREE OR MORE PILLS IN A ROW
<p>Any Time in the Cycle</p> <ol style="list-style-type: none"> 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>	<p>Any Time in the Cycle</p> <ol style="list-style-type: none"> 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>

NOTE: 28-DAY PACK – If you forget any of the seven "reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

Always be sure you have on hand:

- a back-up method of birth control (such as latex condoms and spermicidal foam or gel) in case you miss pills, and
- an extra, full pack of pills.

IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW, TALK TO YOUR DOCTOR OR CLINIC about ways to make pill-taking easier or about using another method of birth control.

**SUPPLEMENTARY INFORMATION
FOR PATIENTS CONSIDERING THE USE OF ORAL CONTRACEPTIVES
(BIRTH CONTROL PILLS)**

Read this information carefully and discuss it with your doctor.

INTRODUCTION

The following information will help you to make an informed choice on the use of oral contraceptives. Oral contraceptives are also known as birth control pills or "the pill".

You should read this information if you are thinking about any method of birth control. If you have decided to take birth control pills, this information will help you understand both the risks and the benefits. This information also will give you detailed instructions on how to use birth control pills.

When taken as directed, birth control pills are a very effective way to prevent pregnancy. Only sterilization is more effective. The pill is convenient and has many benefits other than birth control. Most women do not develop serious and unpleasant side effects from using birth control pills.

The pill has important advantages over other methods of birth control. It also has certain risks that no other method has. Your doctor is the best person to explain the consequences of any possible risks.

You can help your doctor prescribe birth control pills as safely as possible. Tell your doctor about yourself, and be alert for the earliest signs of possible trouble.

TYPES OF BIRTH CONTROL PILLS

There are two types of birth control pills:

1. The "combination pill" is the most common type. It contains two female sex hormones - an estrogen and a progestin. The amounts and types of estrogen and progestin differ from one preparation to another. The amount of estrogen is more important. The effectiveness and some dangers of birth control pills are related mainly to the amount of estrogen.
2. The "mini-pill" is the second type. It contains only one female sex hormone - a progestin.

HOW BIRTH CONTROL PILLS WORK

The birth control pills work in two ways:

1. They inhibit the monthly release of an egg by the ovaries.
2. They change the mucus produced by the cervix. This slows the movement of the sperm through the mucus and through the uterus (womb).

EFFECTIVENESS OF BIRTH CONTROL PILLS

Combination birth control pills are more than 99 per cent effective in preventing pregnancy when

- the pill is **TAKEN AS DIRECTED**, and
- the amount of estrogen is 20 micrograms or more.

A 99 per cent effectiveness rate means that if 100 women used birth control pills for one year, one woman in the group would get pregnant.

The mini-pill (progestin only) is slightly less effective than combination birth control pills.

OTHER WAYS TO PREVENT PREGNANCY

Other methods of birth control are available to you. They are usually less effective than birth control pills. Used properly, however, other methods of birth control are effective enough for many women.

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

REPORTED PREGNANCIES PER 100 WOMEN PER YEAR

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

Pregnancy rates vary widely because people differ in how carefully and regularly they use each method. (This does not apply to IUDs since they are implanted in the uterus.) Regular users may achieve pregnancy rates in the lower ranges. Others may expect pregnancy rates more in the middle ranges.

The effective use of birth control methods other than birth control pills and IUDs requires more effort than taking a single pill every day. It is an effort that many couples undertake successfully.

WHO SHOULD NOT USE BIRTH CONTROL PILLS

You should not use birth control pills if you have or have had any of the following conditions:

- unusual vaginal bleeding that has not yet been diagnosed;
- blood clots in the legs, lungs, eyes, or elsewhere;
- a stroke, heart attack, heart problems, or chest pain (angina pectoris);
- severe high blood pressure;
- known or suspected cancer of the breast or sex organs;
- liver tumour associated with the use of birth control pills or other estrogen-containing products;
- diabetes with complications of the kidneys, eyes, nerves, or blood vessels;
- jaundice (yellowing of skin and eyes) or liver disease if still present;
- migraines with visual and/or sensory disturbances; and/or
- allergic reaction to any ingredient in this product.

The pill should not be taken if you are pregnant or if pregnancy is suspected.

There are also conditions that your doctor will want to watch closely or that might cause your doctor to recommend a method of contraception other than birth control pills:

- breast conditions
 - A strong family history of breast cancer
 - Breast disorders including pain, discharge from the nipples, thickenings, or lumps. In some circumstances, benefit may be derived from taking the pill; in other cases, adverse effects may follow.
- diabetes
- high blood pressure
- abnormal levels of fats in the bloodstream (high cholesterol or triglycerides)
- cigarette smoking
- migraine headaches
- heart or kidney disease
- epilepsy
- depression
- fibroid tumours of the uterus
- gallbladder or pancreatic disease
- plans for forthcoming surgery
- history of jaundice or other liver disease.

You should also inform your doctor about a family history of blood clots, heart attacks or strokes.

THE RISKS OF BIRTH CONTROL PILLS

1. *Circulatory disorders (including blood clots in legs, lungs, heart, eyes or brain)*

Blood clots are the most common serious side effect of birth control pills. Clots can occur in many areas of the body.

- In the brain, a clot can result in a stroke.
- In a blood vessel of the heart, a clot can result in a heart attack.
- In the legs and pelvis, a clot can break off and travel to the lung resulting in a pulmonary embolus.

- In a blood vessel leading to an arm or leg, a clot can result in damage to or loss of a limb.

Any of these conditions can cause death or disability. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impaired vision.

Women who use birth control pills have a higher incidence of blood clots. The risk of clotting seems to increase with higher estrogen doses. **It is important, therefore, to use as low a dosage of estrogen as possible.**

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users over 35 years of age. Women should not smoke.

2. ***Breast cancer***

The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include obesity, never having children, and having your first full-term pregnancy at a late age.

Some women who use birth control pills may be at increased risk of developing breast cancer before menopause which occurs around age 50. These women may be long-term users of birth control pills (more than eight years) or women who start using birth control pills at an early age. In a few women, the use of birth control pills may accelerate the growth of an existing but undiagnosed breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to birth control pills seem to be small, however.

Women with the following conditions should be examined yearly by their doctors no matter what method of contraception they use:

- a strong history of breast cancer in the family;
- breast nodules or thickenings; and/or
- discharge from the nipple.

3. ***Dangers to developing child if birth control pills are used during pregnancy***

Birth control pills should not be taken by pregnant women. There is no evidence, however, that the pill can damage a developing child.

There is also no evidence that the use of birth control pills immediately before a pregnancy will adversely affect a baby's development. When a woman stops taking birth control pills to become pregnant, however, her doctor may recommend a different method of contraception until she has a period on her own. In this way, the pregnancy can be more accurately dated.

4. ***Gallbladder disease and liver tumours***

Users of birth control pills have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

The short- and long-term use of birth control pills also has been linked with the growth of liver tumours. Such tumours are **EXTREMELY** rare.

5. *Other side effects of birth control pills*

Some users of birth control pills have unpleasant side effects. These side effects are temporary and not hazardous to health.

There may be tenderness of the breasts, nausea and vomiting. Some users will experience weight gain or loss. Many of these side effects occurred with high-dose combination birth control pills. These side effects are less common with the low-dose pills prescribed today.

Unexpected vaginal bleeding or spotting and changes in the usual menstrual period also may occur. These side effects usually disappear after the first few cycles. They are **NOT** an indication to stop taking the birth control pills. Unless more significant complications occur, a decision to stop using the pill or to change the brand of pill should be made only after three consecutive months of use. Occasionally, users develop high blood pressure that may require stopping the use of birth control pills.

Other side effects may include:

- growth of pre-existing fibroid tumours of the uterus;
- depression;
- liver problems with jaundice (yellowing of the skin);
- an increase or decrease in hair growth, sex drive and appetite;
- skin pigmentation;
- headaches;
- rash; and/or
- vaginal infections.

Infrequently, there is a need to change contact lens prescription or an inability to use contact lenses.

A woman's menstrual period may be delayed after stopping birth control pills. There is no evidence that the use of the pill leads to a decrease in fertility. As mentioned, it is wise to delay starting a pregnancy for one menstrual period after stopping birth control pills.

NON-CONTRACEPTIVE BENEFITS OF BIRTH CONTROL PILLS

Several health advantages have been linked to the use of birth control pills.

- Combination estrogen and progestin birth control pills reduce the incidence of cancer of the uterus and ovaries.
- Birth control pills reduce the likelihood of developing benign (non-cancerous) breast disease and ovarian cysts.
- Users of birth control pills lose less menstrual blood and have more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and premenstrual syndrome (PMS).
- Acne, excessive hair growth and male-hormone-related disorders also may be improved.

Birth control pills **DO NOT PROTECT** against sexually transmitted diseases (STDs), including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

PERIODIC EXAMINATION

A complete medical and family history is necessary before birth control pills are prescribed. A physical examination should include measuring blood pressure, and examining the breasts, abdomen, pelvic organs, and limbs.

A second visit to your doctor should take place three months or sooner after starting birth control pills. During this visit, any side effects should be evaluated and your blood pressure checked again. Afterward, an annual examination similar to the first visit is recommended. A Pap smear is usually taken before starting birth control pills and then at intervals recommended by your doctor.

IF YOU DECIDE TO TAKE BIRTH CONTROL PILLS

REFER TO THE SECTION ENTITLED INFORMATION FOR THE CONSUMER (PACKAGE INSERT FOR PATIENTS USING ORAL CONTRACEPTIVES).

Store between 15°C - 30°C. Leave contents in protective packaging until time of use.

Keep out of the reach of children.

PHARMACOLOGY

Pharmacodynamics

Oral Contraception

Norgestimate, alone and in combination with ethinyl estradiol, is an effective antioviulatory agent.⁽³⁾ It is moderately potent in the standard *in vivo* progestational assay which measures endometrial proliferation in rabbits, and it effectively blocks ovulation in rats, hamsters and rabbits. In rats, this blockade correlates well with suppression of the proestrus LH surge and the antioviulatory activity of norgestimate is overcome by LHRH. The blockade appears, like that of other progestational agents, to be the result of inhibition of the hypothalamic/pituitary axis. Norgestimate is an active progestin when administered either orally or parenterally and binds to progestational receptors *in vitro*. Like other progestins, norgestimate inhibits the action of estrogen but is not estrogenic itself. Studies measuring the stimulation of ventral prostate growth in rats, the ability to bind to human SHBG *in vitro*, and the effects on serum SHBG levels in rabbits demonstrate that in contrast to levonorgestrel, norgestimate is not androgenic. It also does not inhibit the action of androgen in rats. No adverse effects on the reproductive, thyroid or adrenal endocrine systems were seen in rats given norgestimate orally for 7 days at doses up to 100 times the clinical dose. *In vitro* studies indicate that norgestimate does not directly alter ovarian aromatase activity. Norgestimate does not exhibit central nervous system or autonomic nervous system activities in rats and does not interfere with autonomic-mediated responses of the cardiovascular system in dogs. *In vitro* studies indicate that norgestimate does not possess antimicrobial activity against diverse pathogenic microorganisms. Ethinyl estradiol is a potent estrogen which stimulates the uterus and the vagina. Its preclinical pharmacology is well established.^(4,5) In humans, the primary mechanism of action of the combination is an inhibition of ovulation. Additionally, other effects caused by the treatment, i.e. alteration of the endometrium and the thickening of the cervical mucus appear to interfere with implantation and conception. Studies evaluating the effect of the combination on cervical mucus characteristics, hormonal levels and also on the endometrial tissue yielded results that were consistent with the known mechanism of action (i.e. suppression of ovulation) of the combination.

Norgestimate plus ethinyl estradiol elevated HDL levels across all studies. Norgestimate plus ethinyl estradiol exhibited minimal androgenicity. Sex hormone binding globulin levels were increased and testosterone was not readily displaced from its binding sites by norgestimate.

Pharmacokinetics

Absorption

Norgestimate (NGM) and ethinyl estradiol (EE) are rapidly absorbed following oral administration. Norgestimate is rapidly and completely metabolized by first-pass (intestinal and/or hepatic) mechanisms to norelgestromin (NGMN) and norgestrel (NG), which are the primary and secondary active metabolites of norgestimate, respectively. Mean pharmacokinetic parameters for NGMN, NG and EE during three cycles of administration of CENTRISA™ LO Tablets are summarized in Table 4.

Table 4 provides a summary of norelgestromin, norgestrel and ethinyl estradiol pharmacokinetic parameters.

Table 4: Mean (SD) Pharmacokinetic Parameters of CENTRISA™ LO During a Three Cycle Study

Analyte ¹	Cycle	Day	C _{max}	t _{max} (h)	AUC _{0-24h}	t _{1/2} (h)	
NGMN ⁽²⁻⁴⁾	1	1	0.91 (0.27)	1.8 (1.0)	5.86 (1.54)	NC	
		3	7	1.42 (0.43)	1.8 (0.7)	11.3 (3.2)	NC
			14	1.57 (0.39)	1.8 (0.7)	13.9 (3.7)	NC
			21	1.82 (0.54)	1.5 (0.7)	16.1 (4.8)	28.1 (10.6)
NG ⁽²⁻⁴⁾	1	1	0.32 (0.14)	2.0 (1.1)	2.44 (2.04)	NC	
		3	7	1.64 (0.89)	1.9 (0.9)	27.9 (18.1)	NC
			14	2.11 (1.13)	4.0 (6.3)	40.7 (24.8)	NC
			21	2.79 (1.42)	1.7 (1.2)	49.9 (27.6)	36.4 (10.2)
EE ^(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_{0-24h} = 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_{0-24h} = h.ng/mL

⁵ units for EE only - C_{max} = pg/mL, AUC_{0-24h} = h.pg/mL

NC = not calculated

These results indicate that: (1) Peak serum concentrations of NGMN and EE were generally reached by 2 hours after dosing; (2) Accumulation following multiple dosing of the 180 µg NGM /25 µg 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; (3) The kinetics of NGMN are dose proportional following NGM doses of 180 to 250 µg; (4) Steady-state conditions for NGMN following each NGM dose and for EE were achieved during the three-cycle study; (5) Non-linear accumulation (4.5-14.5-fold) of norgestrel was observed as a result of high affinity binding to SHBG, which limits its biological activity.

Distribution

Norelgestromin and norgestrel (a serum metabolite of norelgestromin) are highly bound (>97%) to serum proteins. Norelgestromin is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG. Ethinyl estradiol is extensively bound (> 97%) to serum albumin.

Metabolism

Norgestimate is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. Norgestimate's primary active metabolite is norelgestromin. Subsequent hepatic metabolism of norelgestromin occurs and secondary metabolites include norgestrel, which is also active and various hydroxylated and conjugated metabolites. Ethinyl estradiol is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Excretion

Following 3 cycles of administration of CENTRISA™ LO, the mean (SD) elimination half-life values, at steady-state, for norelgestromin, norgestrel and ethinyl estradiol were 28.1 (10.6) hours, 36.4 (10.2) hours and 17.7 (4.4) hours, respectively (Table 4). The metabolites of norelgestromin and ethinyl estradiol are eliminated by renal and fecal pathways.

Special 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 norelgestromin, norgestrel and ethinyl estradiol were evaluated in 79 healthy women using pooled data following single-dose administration of NGM 180 or 250 µg /EE 25 µg tablets in four pharmacokinetic studies. Increasing body weight and body surface area were each associated with decreases in C_{max} and AUC_{0-24h} values for norelgestromin and ethinyl estradiol and increases in CL/F (oral clearance) for ethinyl estradiol. Increasing body weight by 10 kg is predicted to reduce the following parameters: NGMN C_{max} by 9% and AUC_{0-24h} by 19%, norgestrel C_{max} by 12% and AUC_{0-24h} by 46%, EE C_{max} by 13% and AUC_{0-24h} 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_{0-24h} for norelgestromin and were statistically significant, but there was no significant effect for norgestrel or ethinyl estradiol. Only a small to moderate fraction (5-40%) of the overall variability in the pharmacokinetics of norelgestromin and ethinyl estradiol following CENTRISA™ LO Tablets may be explained by any or all of the above demographic parameters.

In clinical studies involving 1673 subjects with a mean weight of 141 pounds, there was no association between pregnancy and weight.

Renal and Hepatic Impairment

No studies with CENTRISA™ LO have been conducted in women with renal or hepatic impairment.

Drug-Drug Interactions

Although norelgestromin and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, under the recommended dosing regimen, the in vivo concentrations of norelgestromin and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant (K_i).

Interactions between oral contraceptives and other drugs have been reported in the literature. No formal drug-drug interaction studies were conducted with CENTRISA™ LO (see

PRECAUTIONS).

TOXICOLOGY

Toxicology studies have evaluated norgestimate alone as well as in combination with ethinyl estradiol in the mouse, rat, rabbit, dog and monkey.⁽³⁾ Ethinyl estradiol has also been evaluated both alone and in combination with synthetic steroidal progestogens in the rat, rabbit, dog and monkey.^(3,8-10) Compound-related gross and microscopic lesions have been minimal and show the typical pathological changes that are known to occur with the administration of progestogen and estrogen.

Acute Toxicity Studies

Mice

In HaM/1CR CD-1 mice oral norgestimate alone and oral norgestimate + ethinyl estradiol (5:1) each had an LD₅₀ greater than 5 g/kg body weight. Norgestimate alone at 5 g/kg caused no overt signs of toxicity while the combination caused transient changes in behaviour and one death (one female out of 10 females and 10 males) at 5 g/kg. Oral ethinyl estradiol alone at 5 g/kg caused a transient period of depression and slightly laboured breathing (in males only) with no mortality. The drug was given as a single dose, suspended in carboxymethylcellulose or carboxymethylcellulose and sesame oil.

Rats

In hooded Long-Evans rats no deaths or toxic signs were seen at 5 g/kg or 6.2 g/kg orally of norgestimate alone. Norgestimate in combination with ethinyl estradiol (5:1) orally at 5 g/kg caused no deaths or overt signs of toxicity other than a slight decrease in body weight compared to controls. At autopsy prostate, seminal vesicles and testes were smaller in animals receiving 5 g/kg of the combination than in controls. Ethinyl estradiol alone had an oral LD₅₀ of 5.3 g/kg for males and 3.2 g/kg for females. Drug was administered suspended in carboxymethylcellulose.

Dogs

Oral norgestimate at 5 g/kg caused no deaths or signs of toxicity in female beagles. Also, no deaths or signs of toxicity were seen in female beagles given ethinyl estradiol 5.0 g/kg orally. Drugs were given suspended in carboxymethylcellulose.

Norgestimate (14.3 mg/kg) plus ethinyl estradiol (2.0 mg/kg) in ethanol given by i.v. infusion caused no deaths and the only toxic signs were those of acute ethanol intoxication and were also seen in controls.

Subacute Toxicity Studies

Rats

In female hooded Long-Evans rats oral norgestimate at 10.0, 2.5, 1.0, 0.5 and 0 mg/kg/day for 90 days caused no deaths, and all animals appeared normal on the 90th day. Daily observation showed no symptoms of drug-induced effect or toxicity. Hematological examination results were within normal range and urinalysis results gave no indication of toxicity throughout the test period. Biochemical evaluation showed blood components to be within normal range at termination. A dose-related decrease in cholesterol levels was seen. Gross pathological and histopathological examination did not reveal any toxic effects at any dose level.

Norgestimate plus ethinyl estradiol (10:1) was given orally 11.0, 2.75, 1.10, 0.55 mg/kg/day for 90 days, caused no deaths nor symptoms indicating drug-induced toxicity. Lab testing and necropsy results were all in the normal range although treated animals appeared to have an increased incidence of nephrocalcinosis and unilateral hydronephrosis.

Dogs

Female beagles were given oral doses of norgestimate up to 5.0 mg/kg/day. No deaths were seen. Hematological test results were normal as were clinical chemistry values except for a slight depression of cholesterol in higher-dose animals early in the study. Urinalysis results were normal.

Some test groups showed a decrease in organ weight or organ/body weight ratio for uterus and ovaries when compared to controls and test animals showed suppression of luteinization and/or follicular maturation. Glandular cystic hyperplasia of gallbladder was seen in treated dogs. An extremely low degree of toxicity was exhibited.

Female beagles were given oral doses of norgestimate + ethinyl estradiol (5:1) up to 5.5 mg/kg/day for 90 days. No deaths occurred. Hematological test values were normal for control and low-dose (0.28 mg/kg) animals while WBC was elevated in the two higher-dose groups. Clinical chemistry results were normal except for 1 dog in the high-dose and 2 in middle-dose groups which had slightly depressed BUN values. Uterus weight increased and ovary weight decreased in test animals when compared to controls. Test animals showed suppression of luteinization and/or follicular maturation and gallbladder glandular hyperplasia.

Monkeys

Female Rhesus monkeys given norgestimate orally at doses of 5.0, 1.50, 0.25 and 0 mg/kg/day for 90 days showed no signs of toxicity in their behaviour, body weight, hematology results, urinalysis, or clinical chemistry values.

Histological examination revealed no lesions attributable to the drug. The same was seen for oral norgestimate + ethinyl estradiol (10:1) for doses of 5.5, 1.65, 0.275 and 0 mg/kg/day for 90 days except in high-dose animals. These animals showed hypertrophy of cervical mucus glands and an increase in size and number of mammary acini. Evidence of hyperplasia and epithelial sloughing of uterine endometrium was also noted. There was a dose-dependent stimulation of mucus secretion of the cervix.

Long-Term Toxicity Studies

Rats

Adult female Long-Evans rats were given norgestimate + ethinyl estradiol (5:1) at doses of 3.00, 0.60, 0.15 and 0 mg/kg/day orally for 24 months. There were 70 animals in each group receiving drug and 110 animals in the vehicle-only group.

One hundred and five animals did not survive the dosing schedule. The highest mortality rate was seen in controls. In drug-treated rats, the middle-dose group had the lowest mortality rate while the low-dose group had the highest.

Mean body weights of all treated groups decreased slightly as compared to controls, while the mean food consumption was not significantly different. In all test groups, there was a slight to moderate decrease in RBCs, hematocrit and hemoglobin compared to controls. Clinical chemistry showed a significant decrease in serum cholesterol in all drug-treated groups.

Hepatic changes were seen in all groups (including controls) at 2 years. The severity and incidence of these changes was higher in high- and mid-dose groups than in others. These changes were: nodular or generalized hepatocyte hypertrophy and hyperplasia, hyperplasia foci of hepatocyte coagulation necrosis, sinusoidal telangiectasis, and formation of hematocysts. The reproductive organs showed little microscopic evidence of drug effect, although uterine endometrial hyperplasia was increased in treated animals. The incidence of benign mammary tumours was higher in treated animals than in controls. However, the incidence was statistically significant only in the highest dose group. At 50 to 1000 times the human dose, this combination produced effects remarkably similar to those of other progestin-estrogen combinations.

In a second study, female Long-Evans rats were given norgestimate + ethinyl estradiol at (5:1) at 0.150, 0.0375 and 0.01875 mg/kg/day (6.5 to 50 times the human dose), norgestimate alone and ethinyl estradiol alone each at 0.025 mg/kg/day (50 times human dose) or d-norgestrel at 0.150, 0.075, and 0.0375 mg/kg/day (50 times human dose) for 104 weeks. There were 50 rats in each test group and 100 vehicle controls. Mortality was 55.9% overall with no difference between groups. Minor transient changes were seen for food consumption and body weight early in the study. Periodic hematological examination showed no deviations beyond normal range except for a slight decrease in hematocrit in the high-dose norgestimate + ethinyl estradiol groups. All clinical chemistry parameters measured demonstrated large variations associated with aging in all groups. The only statistically significant changes were a decrease in the cholesterol in ethinyl estradiol only and norgestimate + ethinyl estradiol high-dose groups, and an elevation of triglycerides in all combination groups. There was no significant difference between control and test rats for either benign or malignant tumours.

Dogs

Adult female beagles were given norgestimate + ethinyl estradiol orally at doses of 0.60 mg/kg/day (16 dogs) and 0.15, 0.06, and 0 (vehicle controls) mg/kg/day (20 dogs/group) for two years. This constitutes 20 to 200 times the human dose.

No deaths occurred. All animals were in good health at termination and no changes in behaviour were noted. In year 1, estrus was seen in all controls. In year 2, it was seen in 13 of 16 controls and was not seen in any test dog during the study. High-dose dogs had decreased RBCs and hematocrit throughout the study and an increased WBC count from 3 to 18 months of study. Decreased lymphocytes were seen in high- and mid-dose dogs and cholesterol was decreased in the low- and

mid-dose dogs. Histologic changes were all estrogenic in nature with minimal evidence of progestational response. In a 7-year study, 15 female beagles/group were given oral doses of 0.1425, 0.057, 0.0057 and 0 mg/kg/day norgestimate + ethinyl estradiol in the 21 days on followed by 7 days off cycle. There were 9 deaths during the study: 2 in the control, 2 in the high-dose, 4 in the mid-dose and 1 in the low-dose group. Daily observation revealed no unexpected adverse effects. Near the end of the study, slight to moderate alopecia and enlarged uteri were palpated in some dogs from the high- and the intermediate-dose groups. Hysterectomies resulting from pyometra were greatest in high-dose and least in low-dose and control animals. Nodules palpated during mammary exams were greatest in number for the low-dose group followed by controls and lowest in the high-dose groups; none appeared drug-related. Heart rate, blood pressure and ECG intervals were all within normal range and no meaningful differences were seen in mean body weights between treated and control dogs.

Hematology findings in the last year included decreases in hematocrit, hemoglobin, and red blood cell mean values in the high-dose group. Throughout, a decline in hematocrit was observed in all groups, but was most evident in the high-dose group, and appears to be drug-related. White blood cell counts were generally normal. Mean percent of segmented neutrophil values were higher in the high-dose group at the 84-month interim, but over the course of the study, this was not generally the case. Mean sedimentation rates at 84-months were increased, primarily in the high-dose group. However, over the entire study, changes in sedimentation rates noted were related to isolated individual increases observed in all test groups.

Coagulation parameters showed sporadic, statistically significant differences, but in general, values over the study were within normal limits. No trends were observed. Decreases in cholesterol and triglycerides and slight increases in potassium and albumin values occurred during the study in treated dogs.

Urinalysis results were generally normal although near the end of the study some dogs from control, high- and low-dose groups had trace to 4 + protein.

Monkeys

Norgestimate + ethinyl estradiol was given orally to female Rhesus monkeys (20/group except for the high-dose group which had 16) at 0.60, 0.30, 0.06 and 0 mg/kg/day in a 21-day treatment followed by a 7-day no-treatment cycle for 2 years. This dose represents 20 to 200 times the human dose. During the study 1 control, 1 high-dose and 4 mid-dose monkeys died.

No changes in behaviour were observed. A grey mammary discharge was seen more frequently in treated animals as compared to controls, and was seen mainly during withdrawal periods. Early in the study, treated monkeys had lower mean RBC, hematocrit and hemoglobin values, but were comparable to controls and within normal limits by month 12. All treated groups showed elevated triglycerides and decreased alkaline phosphatase values throughout the study. Decreased serum albumin and low total serum protein values were seen at various times during the study. Other clinical chemistry results were within normal limits, as were clotting study results, urinalysis and urinary steroid determinations. Pap smears produced no evidence of neoplasia.

At autopsy, no drug-related gross or microscopic pathologic lesions were observed in any monkeys, including those that died during the study. Isolated cases of focal hepatic sinusoidal dilation, congestion and/or small hemorrhages were seen at the capsular surfaces. It is believed that they are of little pathological importance due to an absence of any significant liver changes over the 2-year

dosing period and the high-(up to 200 times the human dose) dose levels of drug. Except for an increase in intralobular stromal tissue in a high-dose monkey, mammary nodules found were focal nodular hyperplasia and these occurred in both control and treated animals. The only organ weight changes seen were decreased ovarian and uterine weights in treated monkeys from the 0.30 and 0.60 mg/kg/day groups.

In a 10-year study, female Rhesus monkeys (16/group) were given oral norgestimate + ethinyl estradiol (5:1) at 150, 30, 3, and 0 $\mu\text{g}/\text{kg}/\text{day}$ in a 21-day on followed by 7 days off repeating cycle for the first 4 years. For the remaining 6 years, the monkeys received the medications in a 7:1 ratio, (285, 57, 5.7, 0 mg/kg/day) in the same cycle. Six (3 control, 1 low- and 2 high-dose) monkeys died during the study.

While there were some early differences in weight gains all groups were similar from the second year on. Mammary nodules were noted in all groups during the study and most regressed or disappeared. At the end of the study, the number of animals with nodules was 0, 0, 1 and 1 in the low, mid, high, and control dose groups, respectively. Mammary secretions were noted in some mid- and high-dose monkeys throughout the study.

Hematocrit, erythrocytic parameter changes, mean corpuscular volume, mean leukocyte counts and coagulation parameters were generally similar for all groups.

Clinical chemistry showed a dose-related increase in SGPT. All groups also showed an increase with time, generally lower alkaline phosphatase values for treated monkeys and intermittent slight decreases in serum protein for treated monkeys. BUN for all groups was well within reference range and no difference between groups was noted for glucose. Reports from the literature indicate a dose-related increase in triglycerides and a decrease in cholesterol for the mid-dose group.⁽⁵⁾

Thyroid function test results were typical of those expected for oral contraceptive use in humans. Urinalysis results showed no difference between groups and the results for urinary steroids were unremarkable.

Terminal organ weights for the liver and pituitary were increased while the ovary weights decreased.

The salient non-neoplastic histologic findings consisted predominantly of genito-urinary changes and multifocal myocardial fibrosis. Except for minor histopathologic differences in the ovaries, findings affecting the lower dose animals were essentially comparable with those of the controls. The findings seen in the tissues of the genital tracts and related tissues in the mid- and high-dose animals, included: ovarian atrophy associated with absence of active corpora lutea and occasional reduction in the number of maturing follicles, varying degrees of endometrial atrophy occasionally associated with stromal proliferation and/or decidualization of the endometrial stroma, increased mucus secretion of the cervix often associated with villous elongation and crypt dilation of the mucosa, atrophy and columnar cell metaplasia of the vaginal mucosa, occasional atrophy of the oviduct, lobular hyperplasia of some of the mammary glands and dose-related hypertrophy of the pars distalis of the pituitary gland. Multifocal myocardial fibrosis was noted in animals of each group, including controls, although in a slightly higher incidence in the treated groups. This finding was most prominent in 4 of 7 affected high-dose animals. The significance of this lesion is uncertain based on its presence in controls and the known spontaneous occurrence especially in aging animals.

Neoplasms of tissues other than the genitourinary tract were few and all were considered to be spontaneous. Neoplasms associated with the genito-urinary tract were as follows:

<u>Neoplasm</u>	<u>Dose Group</u>
One muco-epidermoid adenocarcinoma of cervix	high ^a
One leiomyoma of vagina	high ^a
One lobular carcinoma <i>in situ</i> of mammary gland	high ^b
One papilloma of mammary gland	high ^b
One adenoma of mammary gland	high
One urinary bladder papilloma	mid

a = Same Animal; b = Same Animal

The previously listed tumours of monkeys are single occurrences and are generally in different organs. Each of these tumour types have been reported in the literature as spontaneous occurrences. It is difficult to make a definitive etiologic association of the single cervical adenocarcinoma in one high-dose monkey. However, the absence of any antecedent changes (dysplasia, carcinoma *in situ*) in any of the other 47 treated monkeys, the known spontaneous occurrence (although rare in monkeys) suggest the tumour is probably spontaneous in origin.

Reproductive Studies

A fertility and general reproductive performance study was conducted in female Long-Evans rats to assess the effects of norgestimate + ethinyl estradiol (5:1) at 0.120, 0.0833, 0.060, 0.050 and 0.030 mg/kg/day on conception rates, fetal development, parturition and lactation and the viability, growth and reproductive performance of the offspring.

Norgestimate + ethinyl estradiol results in a dose-related suppression of fertility, decreased implantation efficiency and litter size, and an increased fetal resorption in the F₀ females at all dose levels. Slight increases in the incidence of stillbirths were noted in all of the treated females. In addition, there was a decrease in neonatal survival at 0.060, 0.0833 and 0.120 mg/kg/day.

Similar dose-related findings were observed for the F₁ females but to a lesser degree than the F₀ generation. Trends toward decreased fertility, decreased implantation, F₂ litter size, and increased resorptions were noted in all dose groups. Dystocia and an increased number of stillbirths occurred at the 0.060 mg/kg level. At the 0.060 and 0.0833 mg/kg dose levels, survival of offspring was reduced.

Teratology and Fetal Toxicity

Rat

Female Long-Evans rats were treated orally with norgestimate + ethinyl estradiol (5:1) at 0 (vehicle), 0.012, 0.060, and 0.300 mg/kg/day dose levels on days 6-15 of gestation. An increase in "wavy ribs" was noted in rats receiving 0.060 (3/159 fetuses) and 0.300 mg/kg/day (9/128 fetuses) which was statistically significant only in the high-dose group compared to controls (1/152 fetuses). A reduction in the implantation efficiency and an increase in the number of resorptions were also noted in the high-dose group.

In addition, norgestimate + ethinyl estradiol (5:1) was administered orally to pregnant Long-Evans rats from day 15 of pregnancy through day 21 of lactation at dose levels of 0 (vehicle), 0.03, 0.18,

0.30, and 0.060 mg/kg/day. These levels represent approximately 10, 60, 100, and 200 times the proposed human dose levels. In the F₀ generation, no significant adverse effects were seen on maternal growth, behaviour and reproductive performance. However, there was some evidence of lactational insufficiency at the high-dose level.

In the F₁ generation, viability, growth and reproductive performance were unaffected in the 0.03 mg/kg/day group. At 0.18, 0.30 and 0.60 mg/kg/day, there was a dose-related reduction in female fertility. The remaining drug effects were limited to the high-dose level which showed significantly decreased offspring viability from birth to weaning and depressed pup weight during the mid-lactation period.

There was no significant drug effect on F₂ generation development at any dose level.

Rabbit

Female New Zealand white rabbits were given oral doses of 0.5% sodium carboxymethylcellulose suspensions of norgestimate + ethinyl estradiol (5:1) at concentrations of 0 (vehicle), 0.012, 0.060 or 0.300 mg/kg/day from day 7 through day 19 of gestation. The only drug-related effect was the high rate of fetal resorptions observed in the high and intermediate 100% and 65.5% dose groups, respectively. No drug-related teratogenic changes were observed in any of the fetuses examined.

CLINICAL STUDIES

Clinical Efficacy of Norgestimate and Ethinyl Estradiol Tablets

Contraception

In a pivotal controlled phase III study, there were 20 on-therapy pregnancies in the 1,673 efficacy evaluable subjects treated with the norgestimate-ethinyl estradiol regimen and 19 on-therapy pregnancies in the 1,141 efficacy evaluable subjects treated with the comparator norethindrone acetate-ethinyl estradiol containing product (1/20) regimen. Through Cycle 13, the cumulative probability of no pregnancy was 98.1% for the norgestimate-ethinyl estradiol treatment group and 97.4% for the norethindrone acetate-ethinyl estradiol containing product (1/20) treatment group. The respective probabilities of no on-therapy pregnancies due to method failure were 98.5% and 97.6%. The overall Pearl Index has been reported as 2.36 for norgestimate-ethinyl estradiol Tablets and 3.29 for norethindrone acetate-ethinyl estradiol containing product (1/20).

The proportion of subjects who experienced intermenstrual bleeding during Cycle 3 was the primary endpoint for the analysis of cycle control data in this study. The incidence of intermenstrual bleeding during Cycle 3 was lowest in the norgestimate-ethinyl estradiol treatment group (23.6%) compared to the norethindrone acetate-ethinyl estradiol containing product (1/20) group (37.2%), (p<0.001).

Clinical Safety of Norgestimate and Ethinyl Estradiol Tablets

Phase III Study: The Primary Safety Population

A total of 3,059 subjects were randomized to two treatment regimens: 1,826 to norgestimate-ethinyl estradiol tablets and 1,233 subjects to norethindrone acetate-ethinyl estradiol containing product (1/20). A total of 2,894 subjects were known to have taken at least one tablet of study medication and/or had safety information following randomization and thus were evaluable for

safety norgestimate-ethinyl estradiol, 1,723; norethindrone acetate-ethinyl estradiol containing product (1/20), 1,171].

The incidence of discontinuation for specific reasons was similar across treatment groups. The most frequently stated reason for premature discontinuation was "subject choice" (norgestimate-ethinyl estradiol, 11.6%; norethindrone acetate-ethinyl estradiol containing product (1/20), 11.1%) and "lost to follow-up" (norgestimate-ethinyl estradiol, 6.5%; norethindrone acetate-ethinyl estradiol containing product (1/20), 5.8%). The incidence of discontinuation due to adverse events was 4.2% and 3.4%, respectively.

Phase III Study: Overall Incidence of Treatment Emergent Adverse Events

The percentage of subjects reporting treatment emergent adverse events was similar in the norgestimate-ethinyl estradiol (78.2%) and norethindrone acetate-ethinyl estradiol containing product (1/20) (78.1%) treatment groups. There were no notable differences between the treatment groups based on the incidence of the most common Treatment Emergent Adverse Events.

The most frequently reported treatment emergent adverse events in the norgestimate-ethinyl estradiol or norethindrone acetate-ethinyl estradiol containing product (1/20) treatment groups were headache (29.4% and 27.0%, respectively); upper respiratory tract infection (16.8% and 17.8%, respectively); nausea (14.7% and 13.8%, respectively); abdominal pain (13.7% and 14.3%, respectively); breast pain (9.8% and 7.9%, respectively); dysmenorrhea (9.7% and 7.3%, respectively); and sinusitis (9.1% and 8.4%, respectively). There were no notable trends in the incidence of less common treatment emergent adverse events (those reported by < 5% of subjects in any treatment group).

Phase III Study: Laboratory Tests

A broad range of clinical laboratory data has been collected in a number of studies. Statistically significant laboratory changes were generally clinically insignificant and consistent with use of low-dose oral contraceptives.

There were no clinically meaningful changes in mean values for any red blood cell indices, white blood cell counts or differentials, liver enzyme values, or any other laboratory tests, based on changes between baseline and Cycle 6, baseline and Cycle 13, or baseline and Last Visit.

The most common laboratory abnormality reported as a Treatment Emergent Adverse Event related to study medication was hypertriglyceridemia. The incidence of hypertriglyceridemia was similar in the norgestimate-ethinyl estradiol (0.4%) and norethindrone acetate-ethinyl estradiol containing product (1/20) (0.3%) treatment groups. There was no indication that treatment with norgestimate-ethinyl estradiol increased the incidence of treatment-related laboratory abnormalities relative to treatment with norethindrone acetate-ethinyl estradiol containing product (1/20).

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