PRODUCT MONOGRAPH

LO-FEMENAL® 21 and LO-FEMENAL® 28 TABLETS

(Norgestrel and Ethinyl Estradiol)

ORAL CONTRACEPTIVE

DATE OF PREPARATION:
September 24, 2010

Date of Revision:

® TM Wyeth
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Kirkland, Quebec H9J 2M5

Control #: 141616

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PRODUCT MONOGRAPH

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NAME OF DRUG

LO-FEMENAL® 21 AND LO-FEMENAL® 28 TABLETS

(Norgestrel and Ethinyl Estradiol)

THERAPEUTIC CLASSIFICATION

ORAL CONTRACEPTIVE

ACTION

Although the primary mechanism of action is inhibition of ovulation, the effectiveness of LO-FEMENAL® Tablets may also result from other mechanisms of action, such as hostility of the cervical mucus to sperm penetration and migration.

INDICATION

LO-FEMENAL® Tablets are indicated for conception control.

CONTRAINDICATIONS

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.

WARNINGS

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 in 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 OCs 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 OC 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 be examined and 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 to the age of 69.

2. **Pregnancy**

Oral contraceptives should not be taken by pregnant women. However, if conception accidently 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 OCs 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 OCs 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 requires discontinuation of the use of OCs.

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 alternate 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 the light that the patient is on OCs. The following laboratory tests are modified.

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

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

Thyroid Function Tests

Protein-bound Iodine (PBI)	Increased
Total Serum Thyroxine (T_4)	Increased
Thyroid Stimulating Hormone (TSH)	Unchanged

Adrenocortical Function Tests

Plasma Cortisol	Increased

Miscellaneous Tests

Serum Folate	Occassionally 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 alternate 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. 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, before oral contraceptives are prescribed.

For possible drug interactions with OCs, see Tables I and II.

TABLE I*
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 II

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.
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.

* Adapted from Dickey, RP, ed.: Managing Contraceptive Pill Patients, 5th edition Creative Informatics Inc., Durant, OK, 1987.

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.

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.

6. Other non-contraceptive benefits are outlined in *Oral Contraceptives 1994*, Health Canada.

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 fewer of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally.

Other Adverse Reactions:

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)

Mental 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

SYMPTOMS AND TREATMENT OF ACUTE OVERDOSAGE

With LO-FEMENAL®, acute doses in excess of clinical levels when administered to experimental animals, have been shown to have a minimal deleterious effect. The LD_{50} values for the combination of norgestrel and ethinyl estradiol in acute oral administration approximates 500,000 times the equivalent human oral dose. In humans, however, the extent of ill effects to be expected following accidental ingestion of a large dose of any oral contraceptive has not been firmly established.

Depending upon the amount ingested, liver toxicity, temporary interference with the function of the seminiferous tubules, or in the case of females, possible withdrawal bleeding[23] within a few days of consumption, are theoretically possible. However, case histories[6] of both male and female children, some of whom ingested more than half a month's supply of oral contraceptive tablets, indicate that the effects are asymptomatic and without immediate consequence. Despite the frequency of nausea and vomiting in adult females during the first few cycles of use, none of these children presented such symptoms.

Although the physiologic effects of oral contraceptives may be theoretically offset by concomitant administration of gonadotrophin preparations, there are no known chemotherapeutic agents which will neutralize their effects subsequent to accidental ingestion.[3]

In the practical management of an acute overdosage, gastric lavage may be of value if the offending agent has recently been swallowed. The general rules for observation and symptomatic resolution should be followed. Liver function tests should be conducted, particularly transaminase levels, 2 to 3 weeks after consumption.

DOSAGE AND ADMINISTRATION

LO-FEMENAL® 21 TABLETS REGIMEN

Each cycle consists of 21 days on medication and a 7-day interval without medication (three weeks on, one week off).

The dosage of LO-FEMENAL® Tablets is one tablet daily for 21 consecutive days per menstrual cycle, according to prescribed schedule.

For the first cycle of medication, the patient is instructed to take one LO-FEMENAL® Tablet daily for 21 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1.) The tablets are then discontinued for seven days (one week). Withdrawal bleeding should usually occur within three days following discontinuation of LO-FEMENAL®.

The patient begins her next and all subsequent 21-day courses of LO-FEMENAL® Tablets (following the same 21 days on, 7 days off) on the same day of the week that she began her first course. She begins taking her tablets seven days after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.

LO-FEMENAL® 28 TABLETS REGIMEN

Each cycle consists of 21 days of white LO-FEMENAL® Tablets followed by 7 days of pink inert tablets (three weeks on LO-FEMENAL®, one week on inert tablets).

The dosage of LO-FEMENAL® Tablets is one tablet daily for 21 consecutive days per menstrual cycle, according to prescribed schedule, followed by one inert tablet daily for 7 consecutive days according to prescribed schedule.

For the first cycle of medication, the patient is instructed to take one white tablet daily for 21 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1.) One pink tablet is taken daily for the following seven consecutive days. Withdrawal bleeding should usually occur within three days following the discontinuation of white LO-FEMENAL® Tablets, i.e., during the week the patient is taking the pink inert tablets. The patient begins her next and all subsequent 28-day courses of tablets on the same day of the week that she began her first course. She continues her next course of 28 tablets immediately after the last course, regardless of whether or not a period of withdrawal bleeding is still in progress. There is no need for the patient to count days between cycles because there are no "off-tablet days".

SPECIAL NOTES ON ADMINISTRATION

It is recommended that LO-FEMENAL® Tablets be taken at the same time each day, preferably after the evening meal or at bedtime.

LO-FEMENAL® is effective from the first day of therapy if the tablets are begun as described under "DOSAGE AND ADMINISTRATION".

If LO-FEMENAL® Tablets administration is initiated later than the fifth day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on LO-FEMENAL® until after the first seven consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered. In the nonlactating mother, LO-FEMENAL® may be prescribed in the postpartum period either immediately or at the first postpartum examination, whether or not menstruation has resumed.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding usually is transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician.

The patient should be instructed to use the following chart if she misses one or more of her birth control pills. She should be told to match the number of pills with the appropriate starting time for her type of pill.

SUNDAY START	OTHER THAN SUNDAY START
Miss One Pill	**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**
First two weeks: 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. **Third Week**: 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**First two weeks**: 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. **Third Week**: 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**
Miss Three or More Pills in a Row	**Miss Three or More Pills in a Row**
Anytime in the Cycle: 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. **If You Miss Two Periods in a Row, Call your Doctor or Clinic.**	**Anytime in the Cycle**: 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Names: Norgestrel

Ethinyl Estradiol

Chemical Names:

Norgestrel : 18,19-Dinorpregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-,(17α)-(±)-

Ethinyl Estradiol: 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-

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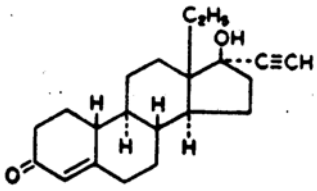

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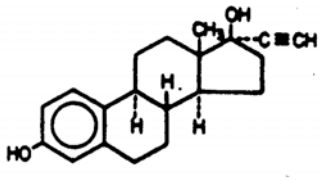


ETHINYL ESTRADIOL

Molecular Formulae:

Norgestrel: $C_{21}H_{28}O_2$

Ethinyl Estradiol: $C_{20}H_{24}O_2$

Molecular Weights:

Norgestrel: 312.46

Ethinyl Estradiol: 296.41

Solubility: (USP Classification)

Norgestrel: Slightly soluble in alcohol, insoluble in water.

Ethinyl Estradiol: Insoluble in water, soluble in alcohol, chloroform, ether, in vegetable oils and in solutions of fixed alkali hydroxides.

Melting Point:

Norgestrel: 205˚ - 212˚C

Ethinyl Estradiol: 180° - 186°C

Biological Properties:

Norgestrel: Unique, totally synthetic progestogen in which only the d-enantiomer is biologically active. The International Nonproprietary Name for this biologically active enantiomer, also referred to as d-norgestrel, is Levonorgestrel.

Ethinyl Estradiol: A semisynthetic estrogen. The presence of the ethinyl group at C 17 on ring D of the steroid nucleus prevents enzymatic degradation of the estradiol molecule and results in an orally active compound.

AVAILABILITY OF DOSAGE FORMS

PrLO-FEMENAL® Tablets are available in 21-day regimen (LO-FEMENAL® 21) and 28-day regimen (LO-FEMENAL® 28) packages.

Each package consists of 21 white LO-FEMENAL® Tablets, each tablet containing 150 µg of d-norgestrel (as 300 µg of the dl-racemate) and 30 µg ethinyl estradiol. In the 28-day regimen package, there are, in addition, 7 pink tablets containing inert ingredients.

INFORMATION FOR THE CONSUMER

A. INFORMATION TO PATIENTS ON HOW TO TAKE THE BIRTH CONTROL PILL

1.**READ THESE DIRECTIONS**

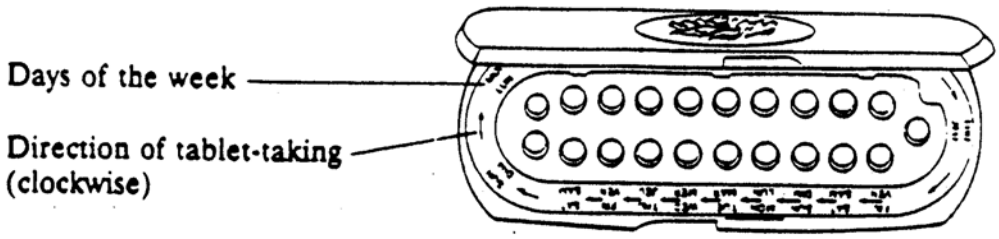
■before you start taking your pills, and

■any time you are not sure what to do.

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

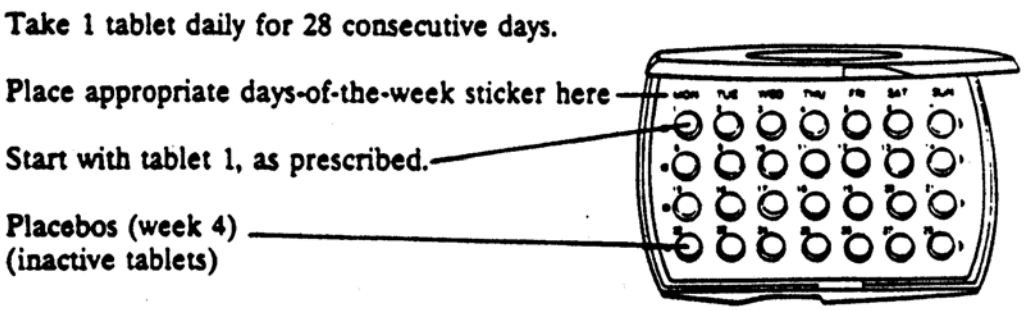
- **21-PILL PACK:** 21 active pills (with hormones) taken daily for three weeks, and then take no pills for one week or
- **28-PILL PACK:** 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

ALSO CHECK:



Take 1 tablet daily for 21 consecutive days, then discontinue tablets for seven days (one week). Start by taking first tablet on appropriate day.

LO-FEMENAL® 21



LO-FEMENAL® 28

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.

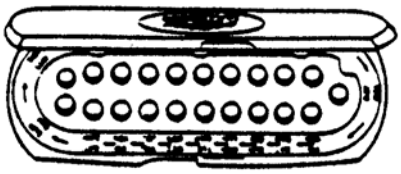
10. **IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW**, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

11. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

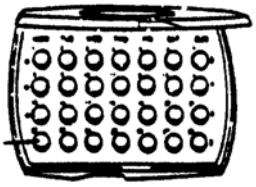
WHEN TO START THE *FIRST* PACK OF PILLS BE SURE TO READ THESE INSTRUCTIONS:

- 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.



LO-FEMENAL® 21



LO-FEMENAL® 28

A. **21-DAY COMBINATION**

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.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** 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. Take one pill at approximately the same time every day for 21 days, **THEN TAKE NO PILLS 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.)

B. **28-DAY COMBINATION**

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

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** 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. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS**. Your period should occur during the last seven days of using that pill pack.

WHAT TO DO DURING THE MONTH

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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 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	OTHER THAN SUNDAY START
Miss One Pill	**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**
First two weeks 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. **Third Week** 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. **IF You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**First two weeks** 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. **Third Week** 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**
Miss Three or More Pills in a Row	**Miss Three or More Pills in a Row**
Anytime in the cycle 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**Anytime in the cycle** 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**

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.

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B. PACKAGE INSERT FOR PATIENTS USING ORAL CONTRACEPTIVES (BIRTH CONTROL PILLS)

> A supplementary information booklet that 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 these pills.

LO-FEMENAL® is a birth control pill (oral contraceptive) that contains two female sex hormones in a specific ratio. Each white tablet contains 300 µg norgestrel and 30 µg ethinyl estradiol. Each pink tablet (contained in LO-FEMENAL® 28) is inert. It has 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 that 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.

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, or chest pain (angina pectoris);
- known or suspected cancer of the breast or sex organs;
- a liver tumour associated with the use of the pill or other estrogen-containing products; and/or
- jaundice or liver disease if still present.

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 INSTRUCTION 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 **LO-FEMENAL®**.

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. 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.

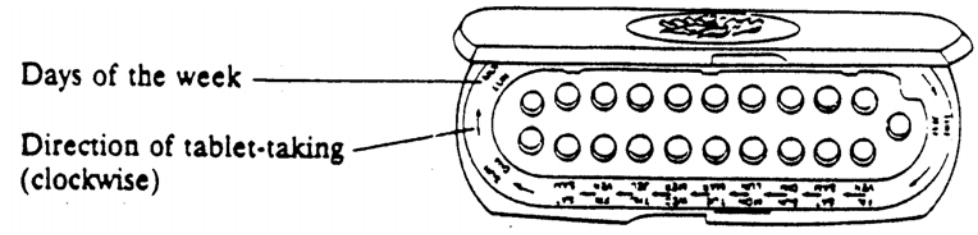
2. **LOOK AT YOUR PILL PACK** to see if it has 21 or 28 pills:

- **21-Pill Pack**: 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week

  or

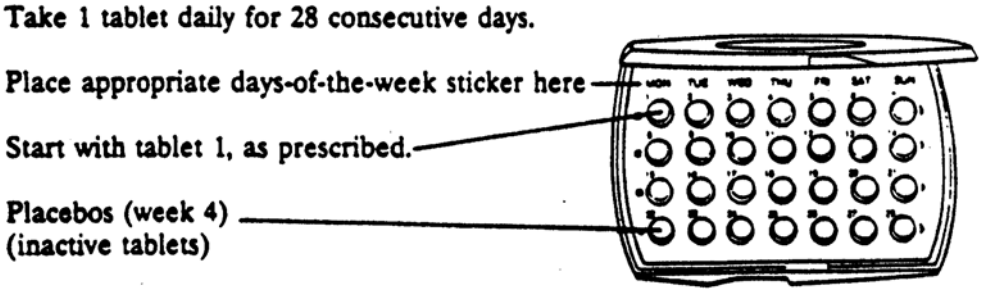
- **28-Pill Pack**: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

ALSO CHECK:



Take 1 tablet daily for 21 consecutive days, then discontinue tablets for seven days (one week). Start by taking first tablet on appropriate day, as prescribed.

LO-FEMENAL® 21



LO-FEMENAL® 28

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.

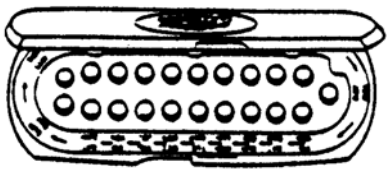
10. **IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW**, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

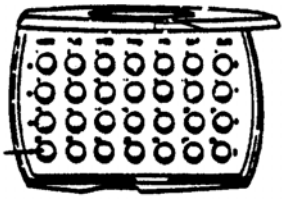
11. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

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.





LO-FEMENAL® 21LO-FEMENAL® 28

A. **21-DAY COMBINATION**

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.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** 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. Take one pill at approximately the same time every day for 21 days, **THEN TAKE NO PILLS 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.)

B. **28-DAY COMBINATION**

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

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** 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. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS**. Your period should occur during the last seven days of using that pill pack.

WHAT TO DO DURING THE MONTH

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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 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	OTHER THAN SUNDAY START
Miss One Pill	**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**
First two weeks 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. **Third Week** 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. **IF You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**First two weeks** 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. **Third Week** 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**

Miss Three or More Pills in a Row	Miss Three or More Pills in a Row
Anytime in the cycle 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**Anytime in the cycle** 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**

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.

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C. SUPPLEMENTARY INFORMATION BOOKLET FOR PATIENTS CONSIDERING THE USE OF ORAL CONTRACEPTIVES (BIRTH CONTROL PILLS)

Introduction

This booklet will give you information 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 booklet if you are thinking about any method of birth control. If you have decided to take birth control pills, this booklet will help you understand both the risks and the benefits. It also will give you information 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.

> Read this booklet carefully and discuss its contents with your doctor.

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

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 percent effective in preventing pregnancy when

- the pill is **TAKEN AS DIRECTED**, and

- the amount of estrogen is 20 micrograms or more.

A 99 percent 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 or chest pain (angina pectoris);
- 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; and/or
- jaundice or liver disease if still present.

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 also should 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 are 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 may also occur. These side effects usually disappear after the first few cycles. They are **not** an indication to stop taking 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

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 older than 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 INSTRUCTION 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 **LO-FEMENAL®**.

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. These medications may change the effectiveness and/or cycle control of our 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**

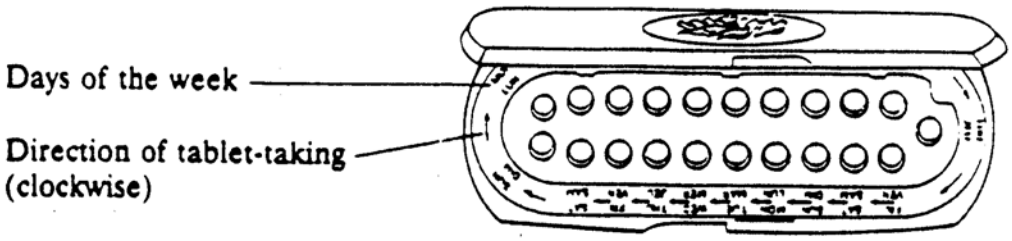
   - before you start taking your pills, and
   - any time you are not sure what to do.

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

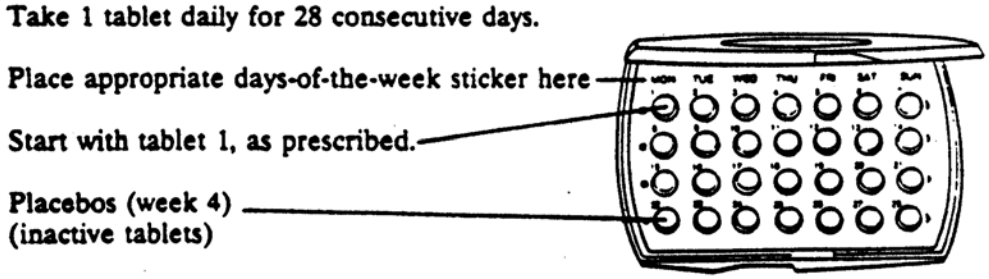
- **28-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

ALSO CHECK:



Take 1 tablet daily for 21 consecutive days, then discontinue tablets for seven days (one week). Start by taking first tablet on appropriate day, as prescribe.

LO-FEMENAL® 21



LO-FEMENAL® 28

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 SOME 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.

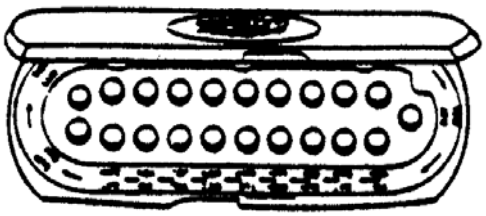
10.**IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW**, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

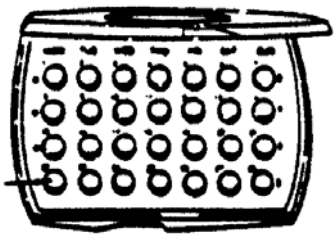
11.**IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

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.





LO-FEMENAL® 21 LO-FEMENAL® 28

A. **21-DAY COMBINATION**

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.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** 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. Take one pill at approximately the same time every day for 21 days; **THEN TAKE NO PILLS 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.)

B. **28-DAY COMBINATION**

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

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** 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. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS.** Your period should occur during the last seven days of using that pill pack.

WHAT TO DO DURING THE MONTH

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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 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	OTHER THAN SUNDAY START
Miss One Pill	**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**
First two weeks 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. **Third Week** 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. **IF You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**First two weeks** 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. **Third Week** 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**
Miss Three or More Pills in a Row	**Miss Three or More Pills in a Row**
Anytime in the cycle 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**Anytime in the cycle** 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. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**

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.

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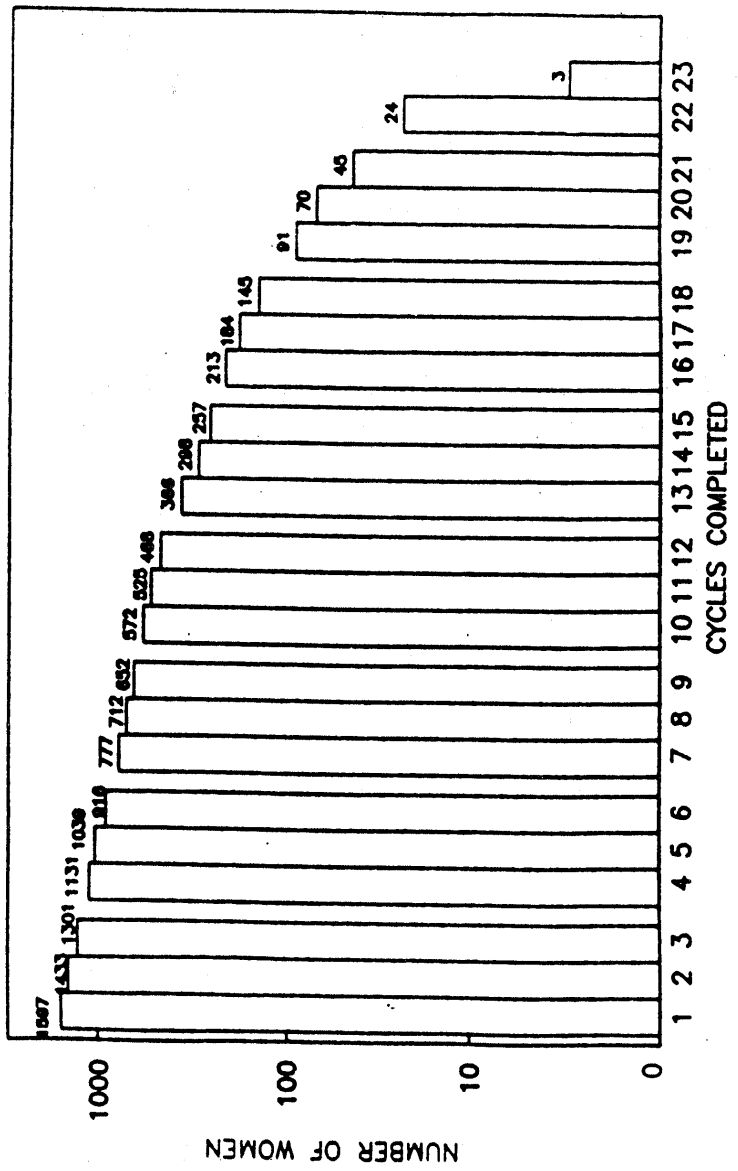
CLINICAL TRIALS

A total of 1,597 patients have completed 12,819 cycles with the drug over 23 months of use (Table 1). Of these, 72.8% were of proven fertility. In this study, one pregnancy was reported which could be attributed to medication failure. Three other pregnancies occurred during the first cycle of medication and were associated with omission of tablets. The overall pregnancy rate as calculated by the Life Table Method is 0.52 and the Pearl Index is 0.45 per 100 woman-years. The corrected pregnancy rate (excluding the three pregnancies which were classified as patient failures) is 0.34 as calculated by the Life Table Method and the Pearl Index is 0.1 per 100 woman-years. This rate was registered in spite of many cycles in which tablets were reportedly missed, in some instances more than 6 tablets in one cycle.

TABLE 1: HISTOGRAM OF NUMBER OF WOMEN
BY NUMBER OF CYCLES COMPLETED



In keeping with the pattern generally noted with combination oral contraceptives, LO-FEMENAL® maintained a regular cyclic pattern to menstruation. The mean length of the menstrual cycle was 28.5 (SD 4.5) days, the mean duration of the menstrual flow 4.2 (SD 1.0) days with an average amount of menstrual flow in 79.9% of women. The latent period between the taking of the last pill in a cycle and the onset of the period averaged 2-3 days in 74% of the patients. No significant change was noted between pre-treatment and during-treatment indices of cycle length, menses length, degree of flow or latency.

Commonly associated side effects which occur during the use of oral contraceptives and with LO-FEMENAL® are listed by the number and percentage of their occurrence in each cycle in Table 2.

TABLE 2 - SIDE EFFECTS BY PERCENTAGE IN LO-FEMENAL® TREATED PATIENTS

NO. ENROLLED 1,672	CYCLE 1	CYCLE 2	CYCLE 3	CYCLE 6	CYCLE 12	CYCLE 18	CYCLE 20	TOTAL CYCLES 12,797
Acne	1.5	0.8	0.8	1.1	0.6	---	---	1.0
Amenorrhea	3.7	2.2	2.2	1.3	2.1	---	---	2.0
Appetite Decrease	0.4	0.2	0.1	---	---	---	---	0.2
Appetite Increase	0.9	0.8	0.5	0.1	0.4	---	---	0.4
Breakthrough Bleeding	11.0	6.4	3.9	3.5	2.4	1.4	1.4	4.4
Breast Discomfort	0.8	0.6	0.9	0.3	0.9	1.4	---	0.6
Breast Enlargement	0.4	0.6	0.5	0.2	0.2	---	---	0.3
Breast Secretion	0.1	0.1	0.1	0.1	---	---	---	0.1
Change in Mentrual flow	0.5	0.5	0.6	0.2	0.2	---	---	0.3
Depression	0.9	0.9	0.9	0.3	0.4	1.4	2.9	0.6
Dizziness	0.6	0.4	0.4	0.2	0.2	---	---	0.3
Dysmenorrhea	1.4	1.0	0.8	0.7	0.4	0.7	---	0.7
Edema, other	0.4	0.2	0.2	0.1	---	---	---	0.2
Edema, premenstrual	0.2	0.1	---	---	0.2	---	---	0.1
Fatigue	1.0	0.6	0.5	0.3	0.6	---	---	0.4
G.I. Symptoms	1.3	1.2	0.8	0.8	0.4	0.7	---	0.8
Headache, Migraine	0.3	0.1	0.2	0.1	0.2	---	---	0.1
Headache, Simple	2.7	1.8	1.9	1.1	0.6	---	---	1.3
Leg Cramps	---	0.4	0.5	0.5	---	---	---	0.3
Libido Increase	0.1	0.1	0.1	---	---	---	---	0.1
Libido Decrease	0.4	0.4	0.3	0.2	---	---	---	0.3
Nausea	3.2	1.8	1.3	0.3	0.2	---	---	1.0
Nervousness, premenstrual	0.9	0.5	0.2	0.4	---	---	---	0.4
Spotting	11.7	8.0	7.0	4.3	3.2	0.7	4.3	5.7
Vomiting	0.4	0.2	0.2	---	---	---	---	0.1
Vaginal Infection	0.8	0.5	0.9	0.9	0.9	0.7	---	0.7

The most common side effects noted were spotting and/or breakthrough bleeding. The occurrence of these was more frequent in the early months of therapy. The medication should not be halted during intermenstrual bleeding. If the bleeding persists, the usual diagnostic procedures should be undertaken to determine the cause of the vaginal bleeding.

The incidence of amenorrhea is low with the use of LO-FEMENAL® (Table 2). If one period is missed, however, appropriate diagnostic procedures should be undertaken to rule out pregnancy and medication should be discontinued during this time and an alternate method of contraception employed. Prompt return to fertility has been demonstrated following discontinuation of therapy with LO-FEMENAL®. Of 335 women who discontinued LO-FEMENAL®, 325 menstruated within 30 days and the remaining 10 within 60 days of terminating therapy.

Of 1,597 patients who completed one cycle, some 123 (7.7%) dropped out for medical reasons, viz., acne 3, allergic rash 1, amenorrhea 8, appetite increase 1, breakthrough bleeding 23, breast discomfort 1, breast enlargement 1, change in menstrual flow 4, depression 2, dysmenorrhea 1, edema 4, G-I symptoms 2, migraine headache 2, simple headache 8, hypertension 2, hirsutism 1, irregular cycles 1, libido decrease 1, loss of scalp hair 1, multiple complaints 9, nausea 10, nervousness 5, premenstrual nervousness 1, spotting 15, thrombophlebitis 1, vaginal discharge 3, vomiting 2, weight decrease 1, and weight increase 4.

CLINICAL LABORATORY RESULTS

As LO-FEMENAL® is a reduced dosage formulation of the marketed product Ovral, only routine clinical laboratory safety studies were run.

In only two instances did women discontinue LO-FEMENAL® because of the presence of hypertension and in both, a previous history of the disease was present. Some 5,008 estimations

of systolic and diastolic pressures were taken and variate analyses done. This indicated that the majority of patients showed no upward or downward trend in systolic or diastolic blood pressure throughout the study. Five patients with a history of hypertension remained normotensive during treatment and one woman with a hypertensive history developed readings in excess of 140/90 mmHg again.

Seven normotensives registered readings in excess of 140/90 mmHg during treatment.

Laboratory indices on 1,597 patients were obtained (Table 3). No clinically significant changes from normal, attributable to LO-FEMENAL® were registered.

Pap smears were done in 1,168 women pre-treatment and rated Grade I (94.3%), Grade II (5.4%) and Grade III (0.3%). Of those Pap smears done during treatment, 94.0% were read Grade I, 5.8% read Grade II, 0.2% Grade III and 0.1% (one case) Grade IV (Classified Grade II, pre-treatment).

Physical examinations conducted regularly throughout the course of treatment completed the safety aspect of the investigation. These examinations revealed only two findings of major clinical significance, one case of thrombophlebitis and one case of cervical malignancy.

TABLE 3

LABORATORY VALUES

INDEX	Pretreatment (Percentage) Low	Normal	High	Treatment (Percentage) Low	Normal	High
HEMATOLOGYHEMATOLOGY						
Hemoglobin	6.5	80.9	3.6	3.9	94.4	1.7
Hematocrit	4.8	94.6	0.6	4.2	94.7	1.0
RBC	32.9	66.1	1.0	23.4	75.5	1.1
WBC	5.4	85.6	8.9	6.8	87.3	5.9
Platelets	0.4	98.4	1.2	0.2	99.5	0.4
BIOCHEMISTRY BIOCHEMISTRY						
Tot. Protein	1.4	83.1	15.5	-	91.6	8.4
Albumin	17.1	70.7	12.2	6.3	76.6	17.2
Cholesterol	10.8	86.7	2.4	6.2	90.3	3.5
Bilirubin	-	94.3	5.7	0.3	95.5	4.2
SGOT	-	91.3	8.8	-	96.3	3.7
SGPT	-	89.9	10.1	-	98.0	2.0
Alk. Phos.	1.2	97.6	1.2	1.3	97.3	1.3
Bl. sugar	18.9	80.6	0.5	6.1	93.6	0.3
BUN	7.2	90.0	2.8	3.6	93.7	2.6
PBI	1.2	75.3	23.5	-	86.4	13.6
URINALYSISURINALYSIS						
Spec. Gravity	0.5	95.5	4.0	0.8	96.2	3.0
pH	-	99.1	0.9	0.2	99.0	0.7
Albumin	-100.0	-	-100.0	-		
Glucose	-	99.8	0.2	0.1	99.7	0.2
Culture	-	92.0	8.0	-	86.5	13.5

PHARMACOLOGY

Animal

Norgestrel is a racemate, composed of equal parts of d- and l-enantiomers. The d-enantiomer accounts for all biological activity.

Intensive biological investigations have been carried out with norgestrel alone and in combination with ethinyl estradiol in rats, mice, rabbits, dogs and monkeys.

In tests for progestational alteration of the endometrium of rabbits, norgestrel by the subcutaneous route proved to be about nine times more active than progesterone and about one hundred times more active than norethisterone by oral and subcutaneous routes. In contrast to norethisterone, which is inactive, norgestrel will maintain pregnancy in spayed laboratory rats and produce endometrial gland development in rabbits when administered directly into the uterine lumen. In a broad series of biological tests, its activities are similar to those of progesterone. Although certain androgenic effects typical of many relatives of 19-nortestosterone are evident at high doses, norgestrel is devoid of such effects at usual clinical doses, and the separation of progestational from androgenic effects for norgestrel is greater than for related compounds. Norgestrel is not estrogenic, nor is it apparently converted in vivo to estrogen; it is an exceedingly potent estrogen antagonist. When combined with ethinyl estradiol, norgestrel tends to ameliorate the effects of the estrogen, while the estrogen will modify the effects of the progestogen. In rats, suppression of fertility with norgestrel/ethinyl estradiol combinations is followed by recovery of normal fertility and fecundity.

Additional experiments in laboratory animals were directed toward evaluating the endocrine effects and safety of the norgestrel and ethinyl estradiol formulation at dose levels

approximating those employed clinically (on a milligram per kilogram basis). Metrotropic effects (uterine glandular development and growth) were most clearly demonstrated. Blockade of pituitary gonadotrophins can be produced by the estrogenic component alone at the clinical dose range; this pituitary effect does not appear to be modified by addition of the progestogen.

The following properties, observed with high doses of norgestrel or norgestrel/ethinyl estradiol combinations, were absent at doses approximating the clinical range: pregnancy maintenance in spayed female rats; parturition delay in pregnant rats; estrogenic changes in mouse vaginal cytology; anti-estrogenic effect in mouse uterine growth or vaginal smear tests; androgenic, myotrophic or fetal masculinizing effects in rats; claudogenic (antinidatory) effects in rats; thymolymphatic involution in mice; mineralocorticoid effects in rats and dogs and antimineralocorticoid effects in rats. No glucocorticoid (rat liver glycogen) or anti-inflammatory (Selye pouch, TBR-arthritis or granuloma pellet tests) effects have been seen at any dose.

Human

Progestogens can have, in addition to progestational activity, estrogenic, anti-estrogenic and androgenic activity. When combined with estrogen, the progestogen will markedly affect the overall biological activity by producing a synergistic, summative or diminutional effect on activity. Comparisons of progestogen potency are not considered scientifically valid because the effects of one progestogen cannot be directly compared with those of another.[10]

A study of serum luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone and 17β-estradiol in patients taking LO-FEMENAL® indicated reduction or abolition of the mid-cycle ovulatory peak and post-ovulatory levels commonly associated with these hormones and gonadotrophins respectively.

Although endometrial biopsies taken during the course of Ovral therapy (250 μg d-norgestrel as the dl-racemate plus 50 μg ethinyl estradiol) revealed a histological sequence in the menstrual cycle of early glandular epithelial stimulation followed by later inhibition after the first half of the menstrual cycle, such studies have not been reported with LO-FEMENAL®.

No cervical mucus studies were done with LO-FEMENAL® but consideration of the effect of Ovral (250 μg d-norgestrel as the dl-racemate plus 50 μg ethinyl estradiol), and Ovrette (37.5 μg d-norgestrel as 75 μg dl-racemate) would suggest a similar action for LO-FEMENAL® on the cervical mucus, viz., absence of ferning and decreased spinnbarkeit, indicative of poor conditions for sperm penetration and migration.

The results of assays for prolactin in a group of 11 normally ovulating women given LO-FEMENAL® over a continuous period of three months indicated no clinically or statistically significant elevation or depression of hormone levels during the course of active drug ingestion, nor in the first post-treatment cycle.

A human study of the metabolism of ^{14}C-labelled norgestrel, the progestogen component of LO-FEMENAL®, revealed that most of the urinary excretion of norgestrel occurred on the first day. There was no difference in the rate of excretion of norgestrel whether administered orally or intravenously. The amount of radioactivity in plasma fell rapidly within the first few hours and at the end of two days only small amounts were present. The foregoing and other studies with ^{14}C-labelled and unlabelled norgestrel have shown that saturation of the 4,5-double bond with and without concomitant reduction of the 3-carbonyl to a 3-hydroxyl group are important reactions during metabolism.

TOXICOLOGY

ACUTE TOXICITY

Norgestrel alone, ethinyl estradiol alone and the two agents combined in a 10:1 ratio were given as single oral doses to rats, mice and dogs. LD_{50} values for norgestrel alone and in combination were greater than 5000 mg/kg in all species tested. The values for ethinyl estradiol were 2952 (rat), 1737 (mouse) and greater than 2500 (dog) mg/kg.

The value for the combination exceeds 500,000 times the human oral dose of LO-FEMENAL®.

SUBACUTE TOXICITY

In subacute toxicity trials in rats, ethinyl estradiol was fed at doses which approximated up to 8 mg/kg and norgestrel was fed at doses which approximated up to 200 mg/kg. Studies of a 10:1 ratio of norgestrel and ethinyl estradiol utilized doses which approximated up to 100 and 10 mg/kg, respectively. This last study represents a dose approximately 10,000 times the equivalent human oral dose of LO-FEMENAL®.

Since estrogens are known to enhance a reduction in both food consumption and growth rate in rodents, it was not unexpected that studies involving high doses of ethinyl estradiol either alone or in combination with norgestrel exhibited such findings. Studies of norgestrel alone at high doses demonstrated a similar but less marked reduction of food consumption and growth rate.

There were increases in the ratio of organ weight to body weight for the pituitary, heart, lungs, kidneys, spleen, pancreas, thyroid, brain and uterus. A decrease in the organ weight to body weight ratio was found for the seminal vesicles, ventral prostate, testes and ovaries. With the exception of the expected endocrine target organ effects, any interpretation of organ weight

changes must consider the compounding influence of the substantial body weight changes cited above.

In subacute toxicity trials in dogs, ethinyl estradiol was administered at doses up to 1 mg/kg and norgestrel at doses up to 50 mg/kg. Studies of a 10:1 ratio of norgestrel and ethinyl estradiol combined utilized doses up to 10 and 1 mg/kg, respectively. This last study represents a dose in excess of 1,000 times the equivalent human dose of d-norgestrel 150 μg and ethinyl estradiol 30 μg. At these dosage levels, there was a trend downward in hematocrits and hemoglobins. These changes were small and are not considered of biological importance. A similar interpretation was given to essentially incidental findings in assays of blood and urine chemistry. These changes were not seen at dosage levels approximating 100 times the human dose and lower.

CHRONIC TOXICITY

(Norgestrel and Ethinyl Estradiol)

Long-term toxicity studies were conducted in rats and dogs for periods of up to 30 months. The dosage levels utilized approximated 700 times (rats) and 100 times (dogs) the usual human dose of d-norgestrel 150 μg and ethinyl estradiol 30 μg. Those hormones were also studied individually in both species at a majority of the dosage levels used in the combination program.

Patchy, transient hair loss was observed in a few controls and occurred in the drug treatment group almost exclusively in animals treated with ethinyl estradiol or with ethinyl estradiol + norgestrel.

At doses of 35-50 times the human dose and above, a dose and time related incidence of lenticular opacities was seen in rats receiving ethinyl estradiol and ethinyl estradiol +

norgestrel. The opacities are considered due to the ethinyl estradiol component and may be species specific since they were not seen in dogs.

In rats given doses of higher than 100 times the clinical dose of either ethinyl estradiol alone or in combination with norgestrel, there was a significant increase in the incidence of malignant mammary tumors. The data on norgestrel alone indicate that this material did not increase the incidence of mammary tumors in the rat. The overall results are similar to those cited in the literature for other estrogens. The meaning of these data is obscure since such effects have not been noted in human clinical use. Superficial mammary masses of varying sizes were seen to develop in treated rats as well as controls. Histopathological examination of the wall and content of these masses and clinical analysis of their content indicate that these masses are "milk cysts", possibly aggravated by continued secretion of acinar tissue despite obstruction of mammary ducts. There was no evidence of preneoplastic process or of benign or malignant neoplasia. In studies terminated by 9-12 months, there was a precocious appearance of masses in groups receiving ethinyl estradiol at 400-500 times the human use level of 30 μg, irrespective of the level of norgestrel present. Norgestrel alone at over 700 times the human dose may have suppressed the spontaneous appearance of masses, but there was no evidence that norgestrel exerted a protective effect in any of the combinations tested.

In dogs, ongoing mammary gland studies ran for 7 years and were completed in November 1974. In monkeys, ongoing mammary gland studies ran for 10 years and were completed in December 1977.

Changes in organ weights observed after chronic studies were similar to those reported after shorter term tests and were due in part to reductions in food consumption and body weight.

Other findings related to treatment include cornification and cystic hyperplasia of the vaginal mucosa and exocervix, as well as cystic dilation and squamous hyperplasia and metaplasia of

endometrial glands as expected. Similarly, endometritis and myometritis with pyometra were observed in dogs and endometritis with abscess formation was seen in rats; these effects were not noted at levels approaching the clinical dose and were most severe at 100 times (dogs) and 700 times (rats) the human dose. Epiphora with slight eversion of the lower eyelid, and mild hyperplasia of the gallbladder mucosa were seen in some dogs receiving norgestrel; and a brown pigment in the epithelium of the kidney tubules was seen in rats receiving ethinyl estradiol.

(Norgestrel Alone)

Studies were conducted in the mouse, the rat, the dog and the monkey. Mice were administered norgestrel at levels of up to 0.0014% in their diet for approximately 80 weeks. The histopathology reports showed that this level of dosing appeared quite innocuous and tumor incidence was not significant in relation to drug treatment at any dose level. When norgestrel was administered to rats in the diet at levels of up to 0.1% over 80 weeks, growth rate and food consumption were depressed in a dose-related manner. Small differences in hematology data from controls were well within normal limits. Superficial mammary masses were seen to develop in treated as well as control animals. Histopathological examination of the wall and content of these masses and chemical analysis of their contents indicate that these masses are "milk cysts", possibly aggravated by continued secretion of acinar tissue despite obstruction of mammary ducts. There was no evidence of preneoplastic process or of benign or malignant neoplasia. Histological changes seen in female rats following administration of norgestrel alone were those to be expected from a progestational agent.

Chronic studies in dogs have been completed using continuous dosing of up to 20 mg/kg for 52 weeks and 0.2 mg/kg for 102 weeks. An ongoing lifetime study at 0.25 mg/kg given cyclically has been undertaken and the study is now completed at 84 months. At the end of 84 months (ninety-two cycles) no findings giving rise to concern were reported. A 7-year report of a

chronic oral study in beagle dogs receiving norgestrel continuously in doses up to 37.5 μg/kg daily indicated no untoward changes in general pharmacology, blood chemistry, urinary steroids, hematology and hemostatis function have occurred in comparison to control animals. At 84 months, ophthalmoscopy showed macular eye changes for 5 control dogs and 16 treated dogs. During the study, one or more nodules were noted in the mammary or contiguous tissues of 6 control dogs and 11 treated dogs (5 dogs at the 3 μg/kg/day, 3 dogs at the 15 μg/kg/day and 3 dogs at the 37.5 μg/kg/day dosage levels).

In chronic studies in the female Rhesus monkey, norgestrel was dosed on a cyclic basis up to a multiple of 50 times the daily human dose. No changes related to the drug have been noted in the observation, hematology, biochemical studies, diabetogenic studies and urinary steroid excretion. Cytological examination after 112 months of treatment revealed no evidence of vaginal neoplasia and palpation of mammae revealed no untoward findings. No differences believed to be related to treatment were seen between control and treated monkeys. A long-term oral study in female Rhesus monkeys in which norgestrel was administered continuously at dosage levels up to 75 μg/kg daily has been completed at 120 months. No changes considered to be related to the drug were seen in hematology, biochemistry, clotting studies or urinary steroids. At 120 months, fundic alterations (changes in the macula and/or fovea) were noted for 0 control monkeys and 7 treated monkeys (2 monkeys at the 3 μg/kg/day, 3 monkeys at the 15 μg/kg/day and 2 monkeys at the 75 μg/kg/day dosage levels). In a similar previous study, 8 monkeys in the control group had fundic alterations. One or more nodules were present in the mammary or contiguous tissues of 1 control monkey and 4 treated monkeys (1 monkey at the 3 μg/kg/day, 2 monkeys at the 15 μg/kg/day and 1 monkey at the 75 μg/kg/day dosage levels) throughout the study.

Reproduction and Teratology

At doses in the clinical range, norgestrel, ethinyl estradiol and their combinations have no demonstrable effects on pregnant rats, their pregnancies, their offspring or the reproductive potential of the young.

Also at doses approximating the clinical range, norgestrel and/or ethinyl estradiol have no observable effects on lactating rats, the lactation process or the nursing young.

At doses in the clinical range and above, a small dose-related increase in the number of abnormal fetuses is observed in mice treated during pregnancy with norgestrel/ethinyl estradiol combinations in a ratio of 5:1. Abnormalities include open eye, cleft palate, exencephaly and umbilical hernia. Rabbits treated during pregnancy with doses of norgestrel and ethinyl estradiol in the clinical range and above, failed to demonstrate any teratogenic potential for the drug.

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