PRODUCT MONOGRAPH

Pr LOESTRIN® 1.5/30
(Norethindrone Acetate [NA] and Ethinyl Estradiol [EE] Tablets, USP)

1.5 mg NA and 30 *µg* EE Tablets

Oral Contraceptive

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PART I: HEALTH PROFESSIONAL INFORMATION

INDICATIONS AND CLINICAL USE

LOESTRIN 1.5/30 is indicated for the control of conception.

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 the revised *1994 Report on Oral Contraceptives*, Health Canada.

CONTRAINDICATIONS

LOESTRIN 1.5/30 is contraindicated in patients with any of the following disorders:

- History of/or actual thrombophlebitis or thromboembolic disorders
- History of/or actual cerebrovascular disorders
- History of/or actual myocardial infarction or coronary arterial disease
- Active liver disease or history of/or actual benign or malignant liver tumors
- Known or suspected carcinoma of the breast
- Known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal vaginal bleeding
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields
- When pregnancy is suspected or diagnosed

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

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

Oral contraceptives 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 oral contraceptives.

General

Before LOESTRIN 1.5/30 is used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities, and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active.

The first follow-up should be done 3 months after LOESTRIN 1.5/30 is 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. For women who had 2 consecutive negative Pap smears, screening could be continued every 3 years up to the age of 69.

Carcinogenesis and Mutagenesis

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 at 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 8 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, estrogen-containing drugs may cause a rapid progression.

Cardiovascular

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 (OC) 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.

Discontinue medication at the earliest manifestations of the following:

A. Thromboembolic and cardiovascular disorders, such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.

B. Conditions which 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 **Peri-Operative Considerations**.

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.

Hypertension

Patients with essential hypertension whose blood pressure is well controlled may be given LOESTRIN 1.5/30, 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.

Endocrine and Metabolism

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 LOESTRIN 1.5/30. 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 LOESTRIN 1.5/30.

Genitourinary

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness requires discontinuation of medication.

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, which continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

Hepatic/Biliary/Pancreatic

Patients, who have had jaundice, including a history of cholestatic jaundice during pregnancy, should be given LOESTRIN 1.5/30 with great care and under close observation.

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

If a patient develops jaundice, which proves to cholestatic in type, the use of LOESTRIN 1.5/30 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 presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

Neurologic

The onset or exacerbation of migraine or the development of headache of a new pattern, which is recurrent, persistent or severe, requires discontinuation of LOESTRIN 1.5/30 and evaluation of the cause.

Ophthalmologic

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.

Peri-Operative Considerations

There is an increased risk of thromboembolic complications in oral contraceptive users, after major surgery. If feasible, LOESTRIN 1.5/30 should be discontinued and an alternative method substituted at least one month prior to MAJOR elective surgery. Oral contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery.

Psychiatric

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have 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.

Sexual Function/Reproduction

After discontinuing LOESTRIN 1.5/30 therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred, in order to date the pregnancy. An alternative contraceptive method should be used during this time.

Special Populations

Pregnant Women:

LOESTRIN 1.5/30 should not be taken by pregnant women. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child.

Nursing Women:

In breastfeeding 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.

Monitoring and 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:** Aspartate serum transaminase (AST) – variously reported elevations. Alkaline phosphatase and gamma glutamine transaminase (GGT) – slightly elevated.

- **Coagulation Tests:** Minimal elevation of test values reported for such parameters as Factors VII, VIII, IX, and X.

- **Thyroid Function Tests:** Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T_3 resin uptake.

- **Lipoproteins:** Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.

- **Gonadotropins:** LH and FSH levels are suppressed by the use of oral contraceptives. Wait two weeks after discontinuing the use of LOESTRIN 1.5/30 before measurements are made.

Pathologists should be advised of LOESTRIN 1.5/30 therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

ADVERSE REACTIONS

Adverse events reported in clinical trials of LOESTRIN 1.5/30 at a frequency of ≥ 1% at cycles 1, 2, 3, 6, 9, 12, 18, 24, and Overall are shown in Table 1 below.

Table 1. Incidence of Adverse Reactions Reported at a Frequency of ≥ 1% of Patients with Loestrin 1.5/30

Adverse Reactions	Incidence Rate (%)								
	1	2	3	6	9	12	18	24	Overall
Irregular Bleeding	33.61	26.90	25.12	19.37	22.48	17.92	17.51	15.50	20.18
Amenorrhea	0.00	2.42	2.52	2.96	3.11	3.58	4.77	3.43	3.13
Abdominal	11.15	7.05	5.64	4.08	3.41	3.41	23.30	2.95	3.85

Cramps/Pain									
Headache	7.93	4.50	3.57	2.92	2.42	1.71	0.76	1.48	2.50
Nausea	6.28	2.47	1.22	1.17	0.14	0.34	0.00	0.37	1.03
Vaginal Discharge	1.65	0.62	0.85	0.47	0.14	0.34	0.00	0.37	0.48
Backache	2.23	1.15	0.85	0.58	0.57	0.68	0.51	0.37	0.64
Dizziness	1.65	0.53	0.38	0.47	0.43	0.17	0.00	0.37	0.33
Breast Soreness	1.73	0.62	0.66	0.58	0.28	0.17	0.00	1.48	0.44
Nervousness	1.07	0.44	0.19	0.12	0.14	0.34	0.00	0.37	0.23

Less Common Clinical Trial Adverse Drug Reactions

Adverse events reported in controlled clinical trials at a frequency of > 0.2% to < 1% are shown in Table 2.

Table 2. Incidence of Adverse Reactions Reported at a Frequency of > 0.2% to < 1% of Patients with Loestrin 1.5/30

Adverse Reactions	**Incidence Rate (%)**								
	1	**2**	**3**	**6**	**9**	**12**	**18**	**24**	**Overall**
Depression	0.58	0.88	0.28	0.23	0.14	0.17	0.25	0.00	0.30
Bloating	0.66	0.53	0.38	0.23	0.28	0.17	0.25	0.37	0.25

Post-Market Adverse Drug 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
- Hypertension
- Benign hepatic tumors
- 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% or less of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally.

- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Dysmenorrhea
- Amenorrhea during and after treatment
- Temporary infertility after discontinuation of treatment
- Edema
- Chloasma or melasma which may persist
- Breast changes: tenderness, enlargement, and secretion
- Change in weight (increase or decrease)
- Endocervical hyperplasia
- Possible diminution in lactation when given immediately post-partum
- 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

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.

Refer to the revised *1994 Report on Oral Contraceptives*, Health Canada, for possible drug interactions with OCs.

DOSAGE AND ADMINISTRATION

21-PILL PACK: One active tablet (green) is taken daily for three weeks, and then no tablets are taken for one week.

28-PILL PACK: One active tablet (green) is taken daily for three weeks, and then one inert tablet (pale orange) is taken daily for one week.

For complete instructions, refer to **Part III: Consumer Information** (under Usual Dose).

Overdosage

In case of overdosage or accidental ingestion by children, the physician should observe the patient closely although no medication is required. Gastric lavage should be given if considered necessary.

For management of suspected drug overdose, contact your regional Poison Control Centre.

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

LOESTRIN 1.5/30 achieves its contraceptive effect primarily by inhibition of ovulation through gonadotropin suppression.

It is well established that oral contraceptives containing estrogen and progestogen affect hypothalamic, pituitary and ovarian functions. They may alter many other physiological systems. Although the exact mechanisms of action are incompletely understood, there is universal agreement that the inhibition of the "ovulatory peak" of luteinizing hormone (LH) is a constant and contributing factor. Oral contraceptives may exert their contraceptive action in at least 4 ways.

1. Alteration of the physical and chemical properties of the cervical mucus, thereby inhibiting sperm penetration.
2. Endometrial changes hindering implantation.
3. Inhibition of ovulation.
4. Subtle changes in the hypothalamic-pituitary-ovarian axis with possible altered corpus luteum function. The steroid profiles quite often indicate either an absence of or an insufficient luteal activity, or a significant and gradual decrease in several of the indices of luteal function.

Probably none of these factors alone accounts for the high degree of anti-fertility effect of any oral contraceptive. They may all play a part in the production of effective contraception.

DOSAGE FORMS, COMPOSITION, AND PACKAGING

LOESTRIN 1.5/30 is available in compact dispensers of 21 tablets (green) and 28 tablets (21 green tablets and 7 pale orange inert tablets). Each green tablet contains 1.5 mg of norethindrone acetate and 30 mcg of ethinyl estradiol. Compact dispensers for LOESTRIN 1.5/30 of 21 and 28 tablets are available in packages of 5.

PART II: SCIENTIFIC INFORMATION

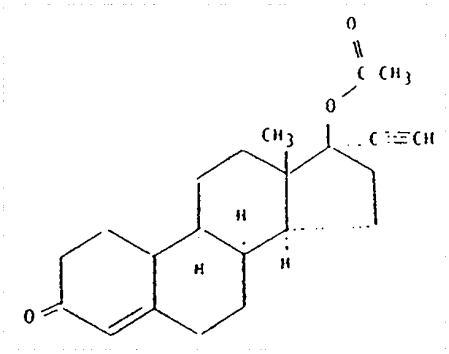
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Norethindrone Acetate

Chemical name: 17-alpha-ethinyl-19-nortestosterone acetate ester

Molecular Formula and Molecular Weight: $C_{22}H_{28}O_3$ and 340.07

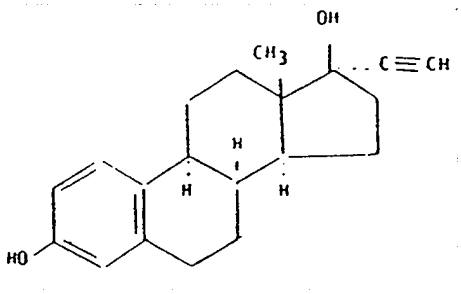


Physicochemical properties: A white solid with a melting point of 157° to 163°C, freely soluble in dioxane, sparingly soluble in ether, and insoluble in water.

Proper name: Ethinyl Estradiol

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

Molecular Formula and Molecular Weight: $C_{20}H_{24}O_2$ and 296.41



Physicochemical properties: A fine white, odourless crystalline powder, insoluble in water but soluble in vegetable oils and organic solvents.

CLINICAL TRIALS

Summary of Drug Experience for LOESTRIN 1.5/30, 28-Day Regimen

Total Subjects Enrolled in Study	1289
Total Subjects Still Active	0
Total Study Days of Experience	467680
Total Cycles of Experience	17139
Number of Pregnancies	
Treatment Failure	1
Subject Failure	6
Pregnancies Per 100 Woman Years (Pearl Index)	
Therapeutic Effectiveness	0.07
Subject Failure	0.42
Use Effectiveness	0.49

Menstrual Cycle

Information on the incidence of spotting and bleeding is presented in Table 3.

Table 3. Percentage of Total Incidence

Effect	Cycle 1	Cycle 2	Cycle 3	Cycle 6	Cycle 12	Cycle 24	Overall
Intermenstrual							
Spotting	12.6	8.7	8.8	6.3	5.7	3.8	6.0
Light	20.4	17.8	14.2	12.2	10.6	9.5	11.7
Moderate	9.9	9.8	6.9	6.6	6.3	5.7	6.8
Heavy	4.2	3.3	2.4	1.8	1.0	-	1.8
Irregular Bleeding	33.6	26.9	25.1	19.4	17.9	15.5	20.18
Amenorrhea	0	2.42	2.52	2.96	3.58	3.43	3.13

Weight Changes

Information on weight changes is presented in Table 4.

Table 4. Summary of Weight Gain or Loss

Last Weight Data Available During	Decrease	No Change	Increase	Median Weight Change (lbs.)
	No. of Subjects (%)	No. of Subjects (%)	No. of Subjects (%)	
Cycle Interval 1-3	306 (39.08)	119 (15.19)	358 (45.72)	0.00
Cycle Interval 4-6	331 (42.00)	88 (10.27)	376 (47.71)	0.00
Cycle Interval 7-12	307 (41.65)	61 (8.27)	369 (50.06)	1.01
Last Cycle	216 (41.86)	28 (5.42)	272 (52.71)	1.52
Total	**1160 (41.07)**	**289 (10.23)**	**1375 (48.69)**	**0.00**

The differences between the percentage of weight gain or loss throughout the study were not great, however, the reports were higher for weight gain. Overall, 48.6% of the subjects reported weight gain, 41.0% weight loss and 10.2 % reported no change in weight.

Patient Drop Out

The largest number of patient drop out was 292 subjects or 22.6% due to loss of contact; 223 or 18.0% dropped because of adverse reactions. Continuing in numerical sequence, 63 or 4.8% moved from the area of study, 43 or 3.6 % dropped for personal reasons, 35 or 2.7% dropped to become pregnant, 43 or 3.3% changed method of contraception, 41 or 3.2% dropped for medical reasons, 35 or 2.7% dropped giving no reason.

Cytology

Initial Papanicolaou smears were taken for almost all the subjects enrolled (1275 patients). All Pap smears were classified within the normal range with the exception of one subject reported to have a Grade III smear. Throughout the study, Pap smears were done randomly, a total of 3436 Pap smears during the 49 cycles of treatment. Over 99% of the Pap smear observations were classified as within the normal range. Only five subjects had Grade III smears, however, none had a diagnosis of cancer.

DETAILED PHARMACOLOGY

Both norethindrone (NET) and ethinyl estradiol (EE) have been subject to extensive biological examination over the past two decades. Norethindrone, using the Clauberg assay with rabbits, has been variously estimated to possess an oral progestational activity at least 10 times that of injected progesterone. Only slight estrogenic activity along with some androgenic activity (9% that of methyl testosterone) has been evident. Ethinyl

estradiol has been demonstrated to be slightly more active than 17ß-estradiol using the vaginal cornification test in rats.

Norethindrone/ethinyl estradiol, in the ratio of 1.0/0.035, fed to female rats for 22 days at a daily dose of 0.15 mg/kg was effective in reducing the littering activity during a period of 15 days cohabitation with fertile males. Subsequent to the dosing period, these females regained their fertility.

Estrogenic, progestational and antigonadotropic characteristics are revealed for the endocrine profile of this combination. In female rats, a uterotropic effect is clearly demonstrated for a range of 0.1-0.4 mcg, total oral dose. In rabbits a McPhail index of 2.6 is recorded at a total oral dose of 0.8 mg of this progestogen/estrogen combination. At a total dose of 450 mcg (based on EE content) compensatory ovarian hypertrophy is completely inhibited in hemicastrate female rats.

TOXICOLOGY

Toxicity Studies of Norethindrone Acetate in Animals

The LD_{50} value of norethindrone acetate on intraperitoneal administration to rats was greater than 1000 mg per kg body weight. The drug produced no toxic effects or abnormalities when administered orally to dogs in a single 30 mg dose.

Administration of norethindrone acetate by the drug-diet method in rats over a period of 41 weeks produced depression in food intake and weight gain comparable to that following the use of norethindrone. Animals received average daily doses of 6, 14, and 27 mg per kg body weight.

Hematocrit, hemoglobin and leukocyte counts were not noticeably affected. Cholesterol values were low in all drug-fed animals, but all other microchemical determinations (minerals, transaminase, proteins, bilirubin, glucose and urea nitrogen) revealed normal values. Histologic examination of tissues showed functional depression of testes and seminal vesicles and atrophy of pituitary and adrenal glands at the two higher dosage levels. Liver cell atrophy and several deviations of a minor nature were also noted. Results indicated that the acetate is as well tolerated as norethindrone in continuous long-term use.

Long-Term Use of Norethindrone in Monkeys

Long-term oral administration of norethindrone to female rhesus monkeys produced only temporary changes in ovarian function. Six monkeys were treated for two years and 12 monkeys for one year at a dosage of 2.5 mg daily for 21 days of each cycle. This is comparable to a dosage of 25 mg daily for eight-and four-year periods in humans.

Extensive studies were conducted on the blood, bone marrow, and on the various other tissues and organs, particularly the ovaries. The only noteworthy differences between control and treated animals were found in the genital organs and the pituitary. The treated monkeys could not be differentiated from control on the basis of general health, alertness, and behaviour. Bleeding usually started on the third or fourth day after discontinuation of drug administration each month, lasted three or four days, and was never heavy.

Ovaries from animals treated for one or two years were small, whitish with only small follicles visible, and no sign of recent rupture or of corpora lutea. Germinal epithelium was intact, and the layer of primordial ovocytes and young follicles appeared normal. Inside this cortical layer were small and medium-sized vesicular follicles and many corpora atretica, remnants of old follicles. Follicles had developed normally until the vesicular stage and then degenerated before attaining their full preovulatory growth. Ovocytes appeared normal in all stages of development until the last pre-ovulatory step when maturation was inhibited.

Uteri of treated monkeys had proliferative endometria with no decidual changes in the stroma. The vaginal tracts exhibited moderate to considerable epithelial cornification. Mammary glands were in the resting stage. Pituitaries of treated monkeys showed a decrease of basophilic cells.

Normal ovulatory cycles resumed shortly after medication was stopped. The sexual skin increased in redness, the vaginal epithelium became highly carnified during ovulation, and corpora lutea developed in the ovaries. The number and appearance of ova were normal, as was the rate of atresia. Endometria were proliferative or secretory.

The ability to conceive also returned. The conception rate in the treated group compared favourably with that in the control group. Babies of treated animals were all normal at birth, and the females developed normally.

In summary, it was concluded from these studies that continuous administration of norethindrone for periods of one and two years suppressed ovulation without permanent effects on ovarian function and fertility of monkeys.

Chronic Oral Toxicities in Monkeys

Chronic oral toxicity studies were conducted in 8 immature rhesus monkeys – 4 males and 4 females. Norethindrone was administered in the amount of 2.5 mg per kg daily, five days a week for 183 days. No gross or microscopic signs of drug toxicity were found from blood studies, biopsies or at autopsy. As might be anticipated, testicular atrophy occurred in the males. There was also evidence of hormonal stimulation of the sexual skin and mammary glands of both sexes and of the uterine mucosa in females.

Long-Term Oral Studies of the Combination

A. Dogs

A combination of 50 parts norethindrone acetate to one part ethinyl estradiol was administered orally for 7 years at dosage levels of 0.051, 0.51, and 1.275 mg/kg/day (equivalent to 1, 10 and 25 times the human dose) in 28-day cycles (21 days of drug administration followed by 7 days of drug withdrawal). Sixteen dogs were initiated as controls and at each dosage level.

All dogs were observed daily. Body weights were recorded weekly. Mammary examinations were conducted once each month. Ophthalmoscopic examinations (indirect technique) were done every six months. Clotting studies were conducted for all dogs twice during the control period, six times during the first year, and semiannually thereafter. Urinary steroid outputs were done once during the control period and annually thereafter.

One control dog and 9 treated dogs died or were sacrificed in extremis during the study. At the end of 7 years of study, the number of dogs surviving in each group was 15, 15, 14 and 10 at the control, 0.051, 0.51, and 1.275 mg/kg/day dosage levels, respectively.

One dog at the 0.051 and 0.51 mg/kg/day dosage levels, and 2 dogs at the 1.275 mg/kg/day dose levels were hysterectomized during the study.

At the end of 7 years of study, nodules were palpated in the mammary tissue of 5 control dogs, 5 dogs at the 0.051 mg/kg/day dosage level, 6 dogs at the 0.51 mg/kg/day level and 6 dogs at the 1.275 mg/kg/day level. Frequently, nodules disappeared after variable periods of time. Only rarely did nodules reach or exceed 10 mm in diameter, and commonly the behaviour of these indicated that they were cystic in nature.

Alopecia was seen more frequently for treated dogs than for control dogs. Red or brown vaginal discharge was seen most frequently for control dogs and dogs at the 0.051 mg/kg/day dosage level. It was rarely noted for dogs at the 0.51 and 1.275 mg/kg/day dosage levels following 18 months of study.

Treated dogs showed greater body weight gains than control dogs.

No changes considered to be related to treatment were seen in the mammary development, behaviour or in urinary steroid output.

Fibrinogen concentrations were somewhat greater for treated dogs than for control dogs during the 6^{th} and 7^{th} years of study. No other unusual changes were noted in clotting studies.

Ophthalmological examinations revealed eye changes for several dogs in each group. No drug relationship was noted with respect to the occurrence of these changes.

Compound related gross lesions consisting of alopecia and enlarged and/or cystic uteri were observed in a number of dogs at terminal sacrifice. Organ weight effects were limited to increase in uterine weights of individuals in most experimental groups. Microscopically, drug related changes included absence of ovulation in all dogs in the high-dose group and most dogs in the mid-dose group, and increased incidence and severity of cystic endometrial hyperplasia and uterine adenomyosis in dogs in the high dose group.

The occurrence of benign tumors in vaginas and uteri of several dogs in the high dose group was considered drug related.

Hyperplastic nodules and benign tumors occurred in mammary glands of dogs both in control and treated groups, but the incidence at the high-dose level was somewhat greater. No malignant mammary neoplasm occurred in any of the dogs in this study.

Monkeys

A combination of 50 parts of norethindrone acetate to one part ethinyl estradiol was administered orally to mature female rhesus monkeys in a long-term study for a period of 10 years at dosage levels of 0.051, 0.51, and 2.55 mg/kg/day (1, 10, and 50 times the human dose). The dosing regimen consisted of consecutive cycles of 21 days of drug administration followed by 7 days of drug withdrawal. Sixteen monkeys were assigned to each treatment group; while an additional 16 animals received the food vehicle only.

Daily observations of general health revealed no evidence of overt effects of drug treatment or significant changes in behaviour. The percent body weight gain of surviving animals was comparable, although the body weights of the treated groups were less than controls at some intervals.

Red vaginal discharge occurred with greater frequency in control and low-dose groups and was usually observed in the withdrawal phase of the mid-and high-dose groups, reflecting the pharmacologic action of the drug combination. No drug related alterations were noted in vaginal cytology or mammary development.

A retinal macular granularity, with and without foci of altered reflectivity, was noted in both control and treated animals beginning at 6 years. Although the incidence and severity of these alterations appeared to be greater in treated animals, no definite relationship to drug administration was considered to have been established.

Reduced total platelet count and increased fibrinogen concentrations were noted more frequently for treated monkeys during the initial 90 months and 48 months of study, respectively. An occasional animal showed an elevated postprandial glucose concentration, but no treatment or dosage relationship was apparent. No drug related alteration in urinary steroid output was observed.

Small nodules were palpable in or near the mammary tissue of five, four, three, and two monkeys in the control, 0.051, 0.51, and 2.55 mg/kg/day dosage groups, respectively, at least at one examination. Detailed physical examinations also revealed an abdominal mass in 2 control monkeys, slight curvature of the spine in 2 low-dose animals, and a pulsating saphenous vein in a high-dose animal.

No drug-related gross lesions were seen in animals that died, were sacrificed *in extremis* during the study or were terminally sacrificed. A frequent cause of death in this study, which is a common occurrence in non-human primates, was acute gastric dilatation. The lesions observed at necropsy appeared spontaneous and unrelated to drug administration.

A statistically significant decrease ($p<0.05$) in the mean absolute uterine weight at the high-dose level was drug related.

Microscopically, drug related lesions included uterine atrophy, slightly increased incidence of occurrence of mucus and inflammatory cells in the cervical canal, and dilatation of acini and ducts in mammary glands of monkeys from the high-dose group, were considered to be related to the pharmacologic effect of the test combination.

No drug-related neoplasms were observed in the study. A low overall incidence of neoplasms was seen in all organs and tissues examined. A total of 6 neoplastic microscopic lesions were noted during this entire study; an adenoma (pancreatic duct origin) in a low-dose animal; a granulosa cell carcinoma (ovary) in a control animal with metastasis to liver, lymph node, and lung; and a leiomyoma (uterus) and 2 papillomas (skin) in high-dose animals. With the exception of the granulosa cell carcinoma, no malignant neoplasms were identified.

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PART III: CONSUMER INFORMATION

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

About this medication

What the medication is used for

LOESTRIN 1.5/30 is an oral contraceptive preparation, which contains two female sex hormones (1.5 mg Norethindrone Acetate and 30 mcg Ethinyl Estradiol). It has been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. The risk associated with taking birth control pills is generally lower than the risk associated with pregnancy, except in smokers over 35.

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

Who should not use birth control pills

You should not use birth control pills if you have 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 tumor associated with the use of the pill or other estrogen-containing products
- Jaundice or liver disease if still present

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

Warnings and Precautions

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:

Serious Warnings and Precautions

What is the most important information I should know about LOESTRIN 1.5/30 (a combination of estrogen and progestin hormones)?

- 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.

- 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.

1. 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.

2. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.

3. 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. These symptoms could indicate a possible blood clot in the eye.
    - Severe pain or lumps in the abdomen. These symptoms could indicate a possible tumor of the liver.
    - Severe depression.
    - Yellowing of the skin (jaundice).
    - Unusual swelling of the extremities.
    - Breast lumps. **ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.**

4. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing.

5. 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 alternate methods of contraception during this time.

6. Your doctor will advise you of the appropriate time to start the use of birth control pills after childbirth, miscarriage, or therapeutic abortion.

7. 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.

8. Should you require **MAJOR** surgery, inform your surgeon that you are using birth control pills.

9. **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 LOESTRIN 1.5/30.

10. **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**.

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

Usual Dose

HOW TO TAKE BIRTH CONTROL PILLS

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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) for one week.

ALSO CHECK: The pill pack for instructions on 1) WHERE TO START, and 2) DIRECTION TO TAKE PILLS IN.

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
   - 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 HAVE 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.

A. 21-DAY COMBINATION

With this type of birth control pill, you are 21 days on pills with seven days off pills. 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.

   LOESTRIN 1.5/30 (21's) is recommended for a Day 1 start.

   - Label the pack by selecting the appropriate day label strip that starts with Day 1 of your menstrual period (counting the first day of menstrual flow as Day 1). Place the strip in the space where you see the words "Place Day Label Here". Having the compact dispenser labeled with the correct day of the week will help remind you to take your tablet every day.

   - On Day 1 of your menstrual cycle, take your first tablet, beginning with the first tablet in the top row (where you see the word "start"). This tablet should correspond to the day of the week that you are taking your first tablet. To remove the tablet, push it through the back of the compact dispenser.

   - On the following day, take the next tablet in the row, always proceeding from left to right. Each new row will always begin on the same day of the week.

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.) Always have a new compact dispenser ready to start each cycle (refills may be obtained by giving a pharmacist the number on the prescription label).

B. 28-DAY COMBINATION

With this type of birth control pill, you take 21 pills, which contain hormones, and seven pills, which 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.

   LOESTRIN 1.5/30 (28's) is recommended for a Day 1 start.

   - Label the pack by selecting the appropriate day label strip that starts with Day 1 of your menstrual period (counting the first day of menstrual flow as Day 1). Place the strip in the space where you see the words "Place Day Label Here". Having the compact dispenser labeled with the correct day of the week will help remind you to take your tablet every day.

   - On Day 1 of your menstrual cycle, take your first tablet, beginning with the first tablet in the top row (where you see the word "start"). This tablet should correspond to the day of the week that you are taking your first tablet. To remove the tablet, push it through the back of the compact dispenser.

   - On the following day, take the next tablet in the row, always proceeding from left to right. Each new row will always begin on the same day of the week.

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 ON THE PILLS.** Your period should occur during the last seven days of using that pill pack. Always have a new compact dispenser ready to start each cycle (refills may be obtained by giving a pharmacist the number on the prescription label).

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 like 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 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.

Missed Dose

WHAT TO DO IF YOU MISS PILLS

The following chart outlines the actions you should take if you miss one or more of your birth control pills on a Day 1 start. If you are not using a Day 1 start, check with your doctor or clinic.

DAY 1 START
MISS 1 PILL
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 pills in one day.
MISS 2 PILLS IN A ROW
First 2 Weeks: 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the 7 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 7 days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS 2 PERIODS IN A ROW, CALLYOUR DOCTOR OR CLINIC.**

MISS 3 OR MORE PILLS IN A ROW

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 7 days after you miss the pills.
3. You may not have a period this month.

IF YOU MISS 2 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 missed 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. Talk about ways to make pill taking easier or about using another method of birth control.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

This document plus the full product monograph, prepared for health professionals is available by contacting Warner Chilcott Canada Co. at 1-800-521-8813.

This leaflet was prepared by Warner Chilcott Canada Co.

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

Read this booklet carefully and discuss its contents with your doctor

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.

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 vary from one preparation to another. The amount of estrogen is most 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	l 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 than many couples undertake successfully.

Who should not use birth control pills

You should not use birth control pills if you 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 tumor associated with the use of the pill or other estrogen-containing products
- 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
    1. A strong history of breast cancer
    2. 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
- Mental depression
- Fibroid tumors of the uterus
- Gallbladder or pancreatic disease
- Plans for forthcoming surgery
- History of jaundice or other liver disease

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

The risks of birth control pills

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

- Blood clots are the most common serious side effects 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 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 thickening
- 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 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 tumors**

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 tumors. Such tumors 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 tumors of the uterus
- Mental depression
- Liver problems with jaundice (yellowing of the skin)

- An increase or decrease in hair growth, sex drive, and appetite
- Skin pigmentation
- Headaches
- Rash
- 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 controls 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 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 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 tumor of the liver.
- Severe depression.
- Yellowing of the skin (jaundice).
- Unusual swelling of the extremities.
- Breast lumps. **ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.**

5. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing.

6. You will have a menstrual period when you stop taking birth control pills. You should delay pregnancy until another menstrual period occurs within four to six weeks. Contact your doctor for recommendation 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, 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 LOESTRIN 1.5/30.

11. Inform your doctor if you are taking or if you start to take other medication. 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

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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 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 taken daily for one week.

   - **ALSO CHECK:** The pill pack for instructions on 1) WHERE TO START, and 2) DIRECTION TO TAKE PILLS IN.

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
- 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 HAVE 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 spemicidal 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 <u>FIRST</u> 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 28-day type.

A. **21-DAY COMBINATION**

With this type of birth control pill, you are 21 days on pills with seven days off pills. 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.

   LOESTRIN 1.5/30 (21's) is recommended for a Day 1 start.

   - Label the pack by selecting the appropriate day label strip that starts with Day 1 of your menstrual period (counting the first day of menstrual flow as Day 1). Place the strip in the space where you see the words "Place Day Label Here." Having the compact dispenser labeled with the correct day of the week will help remind you to take your tablet every day.

   - On Day 1 of your menstrual cycle, take your first tablet, beginning with the first tablet in the top row (where you see the word "start"). This tablet should correspond to the day of the week that you are taking your first tablet. To remove the tablet, push it through the back of the compact dispenser.

   - On the following day, take the next tablet in the row, always proceeding from left to right. Each new row will always begin on the same day of the week.

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). Always have a new compact ready to start each cycle (refills may be obtained by giving a pharmacist the number on the prescription label).

B. 28-DAY COMBINATION

With this type of birth control pill, you take 21 pills, which contain hormones and seven pills, which 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.

   LOESTRIN 1.5/30 (28's) is recommended for a Day 1 start.

   - Label the pack by selecting the appropriate day label strip that starts with Day 1 of your menstrual period (counting the first day of menstrual flow as Day1). Place the strip in the space where you see the words "Place Day Label Here." Having the compact dispenser labeled with the correct day of the week will help remind you to take your tablet every day.

   - On Day 1 of your menstrual cycle, take your first tablet, beginning with the first tablet in the top row (where you see the word "start"). This tablet should correspond to the day of the week that you are taking your first tablet. To remove the tablet, push it through the back of the compact dispenser.

   - On the following day, take the next tablet in the row, always proceeding from left to right. Each new row will always begin on the same day of the week.

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 ON THE PILLS**. Your period should occur during the last seven days of using that pill pack. Always have a new compact dispenser ready to start each new cycle (refills may be obtained by giving a pharmacist the number on the prescription label).

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 like eating a meal or going to bed.
   - Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).

- Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK:**

- **21-PILLS**

WAIT SEVEN DAYS to start the next pack. You will have your period during that week.

- **28-PILLS**

Start the next pack **ON THE NEXT DAY**. Take one pill every day. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

The following chart outlines the actions you should take if you miss one or more of your birth control pills on a Day 1 start. If you are not using a Day 1 start, check with your doctor or clinic.

DAY 1 START
MISS 1 PILL
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 pills in one day.
MISS 2 PILLS IN A ROW
First 2 Weeks: 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back up method of birth control if you have sex in the 7 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 7 days after you miss

the pills. 3. You may not have a period this month. **IF YOU MISS 2 PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC**
MISS 3 OR MORE PILLS IN A ROW
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 7 days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS 2 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. Talk about ways to make pill taking easier or about using another method of birth control.