PHYSICIAN LABELING 6065802

LEVLEN® 21 Tablets

(levonorgestrel and ethinyl estradiol tablets)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

LEVLEN® 21 tablets:
Each LEVLEN® 21 tablet (Levonorgestrel and Ethinyl Estradiol Tablets) contains 0.15 mg of levonorgestrel ((d(-)-13 beta-ethyl-17-alpha-ethinyl – 17 beta-hydroxygon-4-en-3-one) a totally synthetic progestogen, and 0.03 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol). The inactive ingredients present are cellulose, FD&C Yellow 6, lactose, magnesium stearate, and polacrilin potassium.

FPO

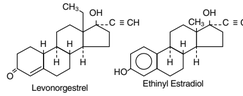
LEVLEN® 28 Tablets

(levonorgestrel and ethinyl estradiol tablets)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

LEVLEN® 28 tablets:
21 light-orange LEVLEN® (Levonorgestrel and Ethinyl Estradiol Tablets) tablets, each containing 0.15 mg of levonorgestrel ((d(-)-13 beta-ethyl – 17-alpha-ethinyl – 17 beta-hydroxygon-4-en-3-one) a totally synthetic progestogen, and 0.03 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol) and 7 pink inert tablets. The inactive ingredients present are cellulose, D&C Red 30, FD&C Yellow 6, lactose, magnesium stearate, and polacrilin potassium.



Levonorgestrel Ethinyl Estradiol

CLINICAL PHARMACOLOGY

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

INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.

Oral contraceptives are highly effective. Table I lists the typical accidental pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization and the IUD, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE I. LOWEST EXPECTED AND TYPICAL FAILURE RATES DURING THE FIRST YEAR OF CONTINUOUS USE OF A METHOD

	% of Women Experiencing an Accidental Pregnancy in the First Year of Continuous Use	
Method	Lowest Expected*	Typical**
(No contraception)	(89)	(89)
Oral contraceptives combined	0.1	3 N/A***
progestin only	0.5	N/A***
Diaphragm with spermicidal cream or jelly	3	18
Spermicides alone (foam, creams, jellies and vaginal suppositories)	3	21
Vaginal Sponge		
nulliparous	5	18
multiparous	>8	>28
IUD (medicated)	1	6#
Condom without spermicides	2	12
Periodic abstinence (all methods)	2-10	20
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15

Adapted from J. Trussell and K. Kost, Table II, Studies in Family Planning, *18(5)*, Sept.-Oct. 1987.

*The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year if they do not stop for any other reason.

**This term represents "typical" couples who initiate use of a method (not necessarily for the first time) who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

***N/A = Data not available

#Combined typical rate for both medicated and nonmedicated IUD. The rate for medicated IUD alone is not available.

CONTRAINDICATIONS

Oral contraceptives should not be used in women with any of the following conditions:

- Thrombophlebitis or thromboembolic disorders.
- A past history of deep-vein thrombophlebitis or thromboembolic disorders.
- Cerebral-vascular or coronary-artery disease.
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use.
- Hepatic adenomas or carcinomas.
- Known or suspected pregnancy.

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

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

Practitioners prescribing oral contraceptives should be familiar with the following information relating to these risks.

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined. Throughout this labeling, epidemiologic studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral-contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral-contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population. For further information, the reader is referred to a text on epidemiologic methods.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial infarction

An increased risk of myocardial infarction has been attributed to oral-contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary-artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral-contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

Smoking in combination with oral-contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (Table II) among women who use oral contraceptives.

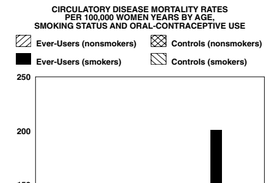


TABLE II (Adapted from P.M. Layde and V. Beral, Lancet, 1:541-546, 1981.)

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism. Oral contraceptives have been shown to increase blood pressure among users (see section 9 in "WARNINGS"). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

b. Thromboembolism

An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep-vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.

A two- to four-fold increase in the relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued from at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four to six weeks after delivery in women who elect not to breast-feed, or a midtrimester pregnancy termination.

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (> 35 years) hypertensive women who also smoke. Hypertension was found to be a risk factor, for both users and nonusers, for both types of strokes, while smoking interacted to increase the risk for hemorrhagic strokes.

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension. The attributable risk is also greater in older women.

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing less than 50 micrograms of estrogen.

e. Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women aged 40 to 49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups. In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with older oral-contraceptive formulations containing 50 micrograms or higher of estrogens.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral-contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral-contraceptive users is based on data gathered in the 1970's – but not reported until 1983. However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral-contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular-disease risks may be increased with oral-contraceptive use after age 40 in healthy nonsmoking women (even with the newer low-dose formulations), there are greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception.

Therefore, the Committee recommended that the benefits of oral contraceptive use by healthy nonsmoking women over 40 may outweigh the possible risks. Of course, older women, as all women who take oral contraceptives, should take the lowest possible dose formulation that is effective.

TABLE III. ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth related
**Deaths are method related

Adapted from H.W. Ory, Family Planning Perspectives, *15*:57-63, 1983.

3. CARCINOMA OF THE REPRODUCTIVE ORGANS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. The overwhelming evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses. The Cancer and Steroid Hormone (CASH) study also showed no latent effect on the risk of breast cancer for at least a decade following long-term use. A few studies have shown a slightly increased relative risk of developing breast cancer; although the methodology of these studies, which included differences in examination of users and nonusers and differences in age at start of use, has been questioned.

Some studies suggest that oral-contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral-contraceptive use and breast and cervical cancers, a cause-and-effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral-contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use. Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral-contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral-contraceptive users approaches less than one per million users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL-CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

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

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral-contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral-contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral-contraceptive users may be minimal. The recent findings of minimal risk may be related to the use of oral-contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 micrograms of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see "WARNINGS" 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral-contraceptive users.

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral-contraceptive users and with continued use. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing quantities of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease should be encouraged to use another method of contraception. If women with hypertension elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension among ever- and never-users.

10. HEADACHE

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

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestogen may be important. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

1. PHYSICAL EXAMINATION AND FOLLOW-UP

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of oral contraceptives and at least annually during use of oral contraceptives. These physical examinations should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

2. LIPID DISORDERS

Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contraceptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult. (See "WARNINGS" 1d.)

3. LIVER FUNCTION

If jaundice develops in any woman receiving such drugs, the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

4. FLUID RETENTION

Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

5. EMOTIONAL DISORDERS

Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

6. CONTACT LENSES

Contact-lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, and possibly with griseofulvin, ampicillin and tetracyclines.

8. INTERACTIONS WITH LABORATORY TESTS

Certain endocrine-and liver-function tests and blood components may be affected by oral contraceptives:

a. Increased prothrombin and factors VII, VIII, IX and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

b. Increased thyroid-binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased reflecting the elevated TBG, free T4 concentration is unaltered.

c. Other binding proteins may be elevated in serum.

d. Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.

e. Triglycerides may be increased.

f. Glucose tolerance may be decreased.

g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. CARCINOGENESIS

See "WARNINGS" section.

10. PREGNANCY

Pregnancy Category X. See "CONTRAINDICATIONS" and "WARNINGS" sections.

11. NURSING MOTHERS

Small amounts of oral-contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

INFORMATION FOR THE PATIENT

See "Patient Labeling" printed below.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (see "WARNINGS" section).

- Thrombophlebitis.
- Arterial thromboembolism.
- Pulmonary embolism.
- Myocardial infarction.
- Cerebral hemorrhage.
- Cerebral thrombosis.
- Hypertension.
- Gallbladder disease.
- Hepatic adenomas or benign liver tumors.

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

- Mesenteric thrombosis.
- Retinal thrombosis.

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug related:

- Nausea.
- Vomiting.
- Gastrointestinal symptoms (such as abdominal cramps and bloating).
- Breakthrough bleeding.
- Spotting.
- Change in menstrual flow.
- Amenorrhea.
- Temporary infertility after discontinuation of treatment.
- Edema.
- Melasma which may persist.
- Breast changes: tenderness, enlargement, secretion.
- Change in weight (increase or decrease).
- Change in cervical erosion and secretion.
- Diminution in lactation when given immediately postpartum.
- Cholestatic jaundice.
- Migraine.
- Rash (allergic).
- Mental depression.
- Reduced tolerance to carbohydrates.
- Vaginal candidiasis.
- Change in corneal curvature (steepening).
- Intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:

- Congenital anomalies.
- Pre-menstrual syndrome.
- Cataracts.
- Optic neuritis.
- Changes in appetite.
- Cystitis-like syndrome.
- Headache.
- Nervousness.
- Dizziness.
- Hirsutism.
- Loss of scalp hair.
- Erythema multiforme.
- Erythema nodosum.
- Hemorrhagic eruption.
- Vaginitis.
- Porphyria.
- Impaired renal function.
- Hemolytic uremic syndrome.
- Budd-Chiari syndrome.
- Acne.
- Changes in libido.
- Colitis.
- Sickle-cell disease.
- Cerebral-vascular disease with mitral valve prolapse.
- Lupus-like syndromes.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

NONCONTRACEPTIVE HEALTH BENEFITS

The following noncontraceptive health benefits related to the use of oral contraceptives are supported by epidemiological studies which largely utilized oral-contraceptive formulations containing doses exceeding 0.035 mg of ethinyl estradiol.

Effects on menses:

- increased menstrual cycle regularity.
- decreased blood loss and decreased incidence of iron-deficiency anemia.
- decreased incidence of dysmenorrhea.

Effects related to inhibition of ovulation:

- decreased incidence of functional ovarian cysts.
- decreased incidence of ectopic pregnancies.

Effects from long-term use:

- decreased incidence of fibroadenomas and fibrocystic disease of the breast.
- decreased incidence of acute pelvic inflammatory disease.
- decreased incidence of endometrial cancer.
- decreased incidence of ovarian cancer.

DOSAGE AND ADMINISTRATION

LEVLEN® 21 Tablets

To achieve maximum contraceptive effectiveness, LEVLEN® 21 Tablets (levonorgestrel and ethinyl estradiol tablets) should be taken exactly as directed at intervals not exceeding 24-hours.

The dosage of LEVLEN® 21 Tablets is **one tablet** daily for 21 consecutive days per menstrual cycle according to the prescribed schedule. Tablets are then discontinued for 7 days (three weeks on, one week off).

It is recommended that LEVLEN® 21 Tablets be taken at the same time each day. During the first cycle of medication, the patient should be instructed to take one LEVLEN® 21 Tablet daily for twenty-one (21) consecutive days, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) The tablets are then discontinued for one week (7 days). Withdrawal bleeding usually occurs within 3 days following discontinuation of LEVLEN® 21 Tablets. (If an alternate starting regimen is used [Sunday Start or postpartum], contraceptive reliance should not be placed on LEVLEN® 21 Tablets until after the first 7 consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.)

The patient begins her next and all subsequent 21-day courses of LEVLEN® 21 Tablets on the same day of the week that she began her first course, following the same schedule: 21 days on – 7 days off. She begins taking her light-orange tablets on the 8th day after discontinuance, regardless of whether or not a menstrual period has occurred or is still in progress. Any time the next cycle of LEVLEN® 21 Tablets is started later than the 8th day, the patient should be protected by another means of contraception until she has taken a tablet daily for seven consecutive days. If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if LEVLEN® 21 Tablets are taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

In the nonlactating mother, LEVLEN® 21 Tablets may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See "CONTRAINDICATIONS", "WARNINGS", and "PRECAUTIONS" concerning thromboembolic disease.)

LEVLEN® 28 Tablets

To achieve maximum contraceptive effectiveness, LEVLEN® 28 Tablets (levonorgestrel and ethinyl estradiol tablets) should be taken exactly as directed at intervals not exceeding 24-hours.

The dosage of LEVLEN® 28 Tablets is one light-orange tablet daily for 21 consecutive days per menstrual cycle, followed by 7 pink inert tablets according to the prescribed schedule.

It is recommended that LEVLEN® 28 Tablets be taken at the same time each day. During the first cycle of medication, the patient should be instructed to take one LEVLEN® 28 Tablet daily in the order of 21 light-orange and then 7 pink inert tablets for twenty-eight (28) consecutive days, beginning on day one (1) of her menstrual cycle. (The first day of menstruation is day one.) Withdrawal bleeding usually occurs within 3 days following the last light-orange tablet. (If an alternate starting regimen is used [Sunday Start or postpartum], contraceptive reliance should not be placed on LEVLEN® 28 Tablets until after the first 7 consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered.)

The patient begins her next and all subsequent 28-day courses of LEVLEN® 28 Tablets on the same day of the week that she began her first course, following the same schedule. She begins taking her light-orange tablets on the next day after ingestion of the last pink tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of LEVLEN® 28 Tablets is started later than the next day, the patient should be protected by another means of contraception until she has taken a tablet daily for seven consecutive days.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. Although the occurrence of pregnancy is highly unlikely if LEVLEN® 28 Tablets are taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more active tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

Any time the patient misses two or more tablets, she should also use another method of contraception until she has taken a tablet daily for seven consecutive days. If breakthrough bleeding occurs following missed active tablets, it usually will be transient and of no consequence. If the patient misses one or more pink tablets, she is still protected against pregnancy provided she begins taking the light-orange tablets again on the proper day.

In the nonlactating mother, LEVLEN® 28 Tablets may be initiated postpartum, for contraception. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See "CONTRAINDICATIONS," "WARNINGS," and "PRECAUTIONS" concerning thromboembolic disease.)

HOW SUPPLIED

LEVLEN® 21 Tablets (levonorgestrel and ethinyl estradiol tablets), are available in packages of 3 SLIDECASE® dispensers. Each cycle contains 21 round tablets as follows:

NDC 50419-021, 21 active, light-orange tablets marked "B" on one side and "21" on the other side, each containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol;

In packages of:
3 SLIDECASE® dispensers . . . . . NDC 50419-410-21

LEVLEN® 28 Tablets (levonorgestrel and ethinyl estradiol tablets), are available in packages of 3 SLIDECASE® dispensers. Each cycle contains 28 round tablets as follows:

NDC 50419-021, 21 active, light-orange tablets marked "B" on one side and "21" on the other side, each containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol;

NDC 50419-028, 7 inert pink tablets marked "B" on one side and "28" on the other side.

In packages of:
3 SLIDECASE® dispensers . . . . . NDC 50419-411-28

REFERENCES

References furnished upon request.

BRIEF SUMMARY PATIENT PACKAGE INSERT

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Oral contraceptives, also known as "birth-control pills" or "the pill" are taken to prevent pregnancy and when taken correctly, have a failure rate of less than 1% per year when used without missing any pills. The typical failure rate of large numbers of pill users is less than 3% per year when women who miss pills are included. For most women oral contraceptives are also free of serious or unpleasant side effects. However, forgetting to take pills considerably increases the chances of pregnancy.

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be life-threatening or may cause temporary or permanent disability or death. The risks associated with taking oral contraceptives increase significantly if you:

- smoke.
- have high blood pressure, diabetes, high cholesterol.
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice or malignant or benign liver tumors.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may subside within the first three months of use.

The serious side effects of the pill occur very infrequently, especially if you are in good health and do not smoke. However, you should know that the following medical conditions have been associated with or made worse by the pill:

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.

2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or health-care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anti-convulsants and some antibiotics may decrease oral-contraceptive effectiveness.

Studies to date of women taking the pill have not shown an increase in the incidence of cancer of the breast or cervix. There is, however, insufficient evidence to rule out the possibility that pills may cause such cancers.

Taking the pill provides some important noncontraceptive benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections, and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your health-care provider. Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you.

You should be reexamined at least once a year while taking oral contraceptives. The "Detailed Patient Labeling" gives you further information which you should read and discuss with your health-care provider.

DETAILED PATIENT LABELING

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

INTRODUCTION

Any woman who considers using oral contraceptives (the birth-control pill or "the pill") should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this leaflet is not a replacement for a careful discussion between you and your health-care provider. You should discuss the information provided in this leaflet with him or her, both when you first start taking the pill and during your revisits. You should also follow your health-care provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% when used perfectly, without missing any pills. Typical failure rates are less than 3.0% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

In comparison, typical failure rates for other nonsurgical methods of birth control during the first year of use are as follows:

IUD	6%
Diaphragm with spermicides	18%
Spermicides alone	21%
Vaginal sponge	18%-30%
Condom alone	12%
Periodic abstinence	20%
No methods	89%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have had any of the following conditions:

- Heart attack or stroke.
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes.
- Blood clots in the deep veins of your legs.
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina.
- Liver tumor (benign or cancerous).

Or if you have any of the following:

- Chest pain (angina pectoris).
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor).
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill.
- Known or suspected pregnancy.

Tell your health-care provider if you have ever had any of these conditions. Your health-care provider can recommend another method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health-care provider if you or any family member has ever had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram.
- Diabetes.
- Elevated cholesterol or triglycerides.
- High blood pressure.
- Migraine or other headaches or epilepsy.
- Mental depression.
- Gallbladder, heart or kidney disease.
- History of scanty or irregular menstrual periods.

Women with any of these conditions should be checked often by their health-care provider if they choose to use oral contraceptives. Also, be sure to inform your doctor or health-care provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. RISK OF DEVELOPING BLOOD CLOTS

Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives and can be fatal. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives three to four weeks before surgery and not taking oral contraceptives for 2 weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby or a midtrimester pregnancy termination. It is advisable to wait for at least 4 weeks after delivery if you are not breast-feeding. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast-Feeding in "GENERAL PRECAUTIONS.")

2. HEART ATTACKS AND STROKES

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.

Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. GALLBLADDER DISEASE

Oral-contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. LIVER TUMORS

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in two studies, in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

5. CANCER OF THE REPRODUCTIVE ORGANS

There is, at present, no confirmed evidence that oral contraceptives increase the risk of cancer of the reproductive organs in human studies. Several studies have found no overall increase in the risk of developing breast cancer. However, women who use oral contraceptives and have a strong family history of breast cancer or who have breast nodules or abnormal mammograms should be closely followed by their doctors.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives.

ESTIMATED RISK OF DEATH FROM BIRTH-CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives nonsmoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

*Deaths are birth related
**Deaths are method related

In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral- contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death is highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, except for those women over the age of 40, when the risk increases to 3 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who don't smoke should not take oral contraceptives is based on information from older high-dose pills and on less-selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral-contraceptive use by healthy, nonsmoking women over 40 years of age may outweigh the possible risks. However, all women, especially older women, are cautioned to use the lowest-dose pill that is effective.

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung).
- Pain in the calf (indicating a possible clot in the leg).
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack).
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke).
- Sudden partial or complete loss of vision (indicating a possible clot in the eye).
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or health-care provider to show you how to examine your breasts).
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor).
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression).
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems).

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. VAGINAL BLEEDING

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

2. CONTACT LENSES

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your doctor or health-care provider.

3. FLUID RETENTION

Oral contraceptives may cause edema (fluid retention) with swelling of the fingers or ankles and may raise your blood pressure. If you experience fluid retention, contact your doctor or health-care provider.

4. MELASMA

A spotty darkening of the skin is possible, particularly of the face.

5. OTHER SIDE EFFECTS

Other side effects may include change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections.

If any of these side effects bother you, call your doctor or health-care provider.

GENERAL PRECAUTIONS

1. Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

2. Missed periods and use of oral contraceptives before or during early pregnancy.

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your health-care provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, or if you missed two consecutive menstrual periods, you may be pregnant. Check with your health-care provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

There is no conclusive evidence that oral-contraceptive use is associated with an increase in birth defects, when taken inadvertently during early pregnancy. Previously, a few studies had reported that oral contraceptives might be associated with birth defects, but these studies have not been confirmed. Nevertheless, oral contraceptives or any other drugs should not be used during pregnancy unless clearly necessary and prescribed by your doctor. You should check with your doctor about risks to your unborn child of any medication taken during pregnancy.

3. While breast feeding

If you are breast feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, do not use oral contraceptives while breast-feeding. You should use another method of contraception since breast-feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast-feed for longer periods of time. You should consider starting oral contraceptives only after you have weaned your child completely.

4. Laboratory tests

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

5. Drug Interactions

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital) and phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use an additional method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective.

HOW TO TAKE THE PILL

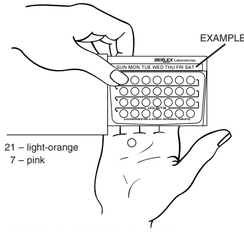
IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking your pills.
   Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late.
   The more pills you miss the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
   On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
   Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.
8. THIS PRODUCT (LIKE ALL ORAL CONTRACEPTIVES) IS INTENDED TO PREVENT PREGNANCY. IT DOES NOT PROTECT AGAINST TRANSMISSION OF HIV (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES SUCH AS CHLAMYDIA, GENITAL HERPES, GENITAL WARTS, GONORRHEA, HEPATITIS B, AND SYPHILIS.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
   It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IT HAS 21 OR 28 PILLS:
   The 21-pill pack has 21 "active" (light-orange) pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
   The 28-pill pack has 21 "active" (light-orange) pills (with hormones) to take for 3 weeks, followed by 1 week of reminder (pink) pills (without hormones).
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills (follow the arrows)



4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up in case you miss pills.
   AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START:

1. Take the first "active" (light-orange) pill of the first pack during the first 24 hours of your period.
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:

1. Take the first "active" (light-orange) pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
   Do not skip pills even if you are spotting or 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 OR SWITCH YOUR BRAND OF PILLS:**
   21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.
   28 pills: Start the next pack on the day after your last "reminder" pill.
   Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** (light-orange) "active" pill:

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

If you **MISS 2** (light-orange) "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 2** (light-orange) "active" pills in a row in **THE 3rd WEEK:**

1. ***If you are a Day 1 Starter:***
   THROW OUT the rest of the pill pack and start a new pack that same day.
   If you are a Sunday Starter:
   Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 3 OR MORE** (light-orange) "active" pills in a row (during the first 3 weeks).

1. ***If you are a Day 1 Starter:***
   THROW OUT the rest of the pill pack and start a new pack that same day.
   If you are a Sunday Starter:
   Keep taking 1 pill every day until Sunday. On Sunday THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:

If you forget any of the 7 (pink) "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method if you start your next pack on time.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately less than 1.0% if taken every day as directed, but more typical failure rates are less than 3.0%. If failure does occur, the risk to the fetus is minimal.

RISKS TO THE FETUS

If you do become pregnant while using oral contraceptives the risk to the fetus is small, on the order of no more than one per thousand. You should, however, discuss the risks to the developing child with your doctor.

PREGNANCY AFTER STOPPING THE PILL

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health-care provider or pharmacist.

OTHER INFORMATION

Your health-care provider will take a medical and family history before prescribing oral contraceptives and will examine you. You should be re-examined at least once a year. Be sure to inform your health-care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health-care provider, because this is a time to determine if there are any early signs of side effects of oral contraceptive use.

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:

- Menstrual cycles may become more regular.
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently.
- Ovarian cysts may occur less frequently.
- Ectopic (tubal) pregnancy may occur less frequently.
- Noncancerous cysts or lumps in the breast may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.
- Oral-contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your doctor or pharmacist. They have a more technical leaflet called the "Professional Labeling," which you may wish to read.

Manufactured for:
BERLEX Laboratories Inc., Wayne, NJ 07470

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