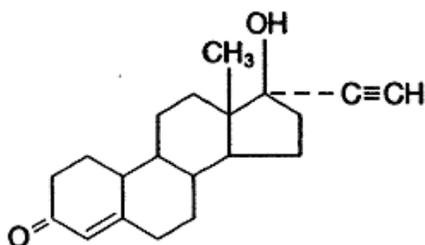




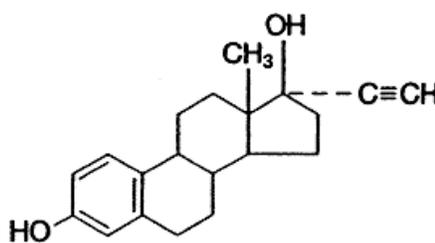
Patients should be counseled that this product does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.

DESCRIPTION

OVCON[®] 35 provides a regimen for oral contraception derived from 21 white tablets composed of norethindrone and ethinyl estradiol followed by 7 green tablets of inert ingredients. The chemical name for norethindrone is 17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one and for ethinyl estradiol the chemical name is 19-nor-17 α -pregna-1,3,5 (10)-trien-20-yn-3,17-diol. The structural formulas are:



NORETHINDRONE



ETHINYL ESTRADIOL

The active white OVCON[®] 35 tablets contain 0.4 mg norethindrone and 0.035 mg ethinyl estradiol. The green tablets contain inert ingredients.

OVCON[®] 35 contains the following inactive ingredients: dibasic calcium phosphate, D&C Yellow No. 10 (aluminum lake), FD&C Blue No. 1 (aluminum lake), FD&C Yellow No. 6 (aluminum lake), lactose, magnesium stearate, maltodextrin, povidone, sodium starch glycolate, spearmint flavor, starch (corn), sucralose and talc.

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).

PHARMACOKINETICS

Absorption

Ethinyl estradiol and norethindrone are rapidly absorbed with maximum plasma concentrations occurring within 2 hours after OVCON[®] 35 administration (see Table 1). Norethindrone appears to be completely absorbed following oral administration; however, it is subject to first-pass metabolism resulting in an absolute bioavailability of approximately 65%. Large intersubject variability is reflected in a 3- to 5-fold variation in norethindrone bioavailability. Ethinyl estradiol bioavailability is approximately 43% due to small-intestinal and hepatic first-pass metabolism.

Table 1. Mean \pm SD Pharmacokinetic Parameters Following Single Dose Administration of OVCON[®] 35 in Healthy Female Subjects Under Fasting Condition

Norethindrone/Ethinyl Estradiol	t _{max} (h)	C _{max} (pg/mL)	AUC _{0-∞} (pg•h/mL)	t _{1/2} (h)
Norethindrone 0.4 mg	1.24 \pm 0.40 ^a	4210.6 \pm 1628.8 ^a	18034.9 \pm 7852.9 ^b	8.6 \pm 3.7 ^b
Ethinyl estradiol 35 μ g	1.44 \pm 0.33 ^b	131.4 \pm 34.2 ^b	1065.8 \pm 276.2 ^b	17.1 \pm 4.4 ^b

^a n = 26

^b n = 25

Effect of Food. The food-effect on the rate and the extent of norethindrone and ethinyl estradiol absorption after OVCON[®] 35 administration has not been evaluated.

Distribution

Norethindrone is 36% bound to sex hormone-binding globulin (SHBG) and 61% bound to albumin. Ethinyl estradiol is not bound to SHBG but is highly (98.5%) bound to albumin. Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg.

Metabolism

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation; less than 5% of a norethindrone dose is excreted unchanged; greater than 50% and 20-40% of a dose is excreted in urine and feces, respectively. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol, and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy-ethinyl estradiol which is formed by the CYP3A4 isoform of cytochrome P450.

Excretion

Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Ethinyl estradiol and norethindrone are excreted in both urine and feces, primarily as metabolites. Ethinyl estradiol is excreted in urine and feces as glucuronides and sulfates, and about 28-43% undergoes enterohepatic circulation. The mean terminal elimination half-lives of norethindrone and ethinyl estradiol following single dose administration of OVCON[®] 35 are approximately 9 hours and 17 hours, respectively.

Special Populations

Race. The effect of race on the disposition of norethindrone and ethinyl estradiol after OVCON[®] 35 administration has not been evaluated.

Renal Insufficiency. The effect of renal disease on the disposition of norethindrone and ethinyl estradiol after OVCON[®] 35 administration has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

Hepatic Insufficiency. The effect of hepatic disease on the disposition of norethindrone and ethinyl estradiol after OVCON[®] 35 administration has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function.

Drug-Drug-Interactions

See "Precautions" section—DRUG INTERACTIONS

INDICATIONS AND USAGE

OVCON[®] 35 is 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 2 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, the IUD, and the Norplant system, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

TABLE 2
Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception and the percentage continuing use at the end of the first year. United States.

Method (1)	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year ³
	Typical Use ¹ (2)	Perfect Use ² (3)	(4)
Chance ⁴	85	85	
Spermicides ⁵	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-thermal ⁶		2	
Post-Ovulation		1	
Cap ⁷			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm ⁷	20	6	56
Withdrawal	19	4	
Condom ⁸			
Female (reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant and Norplant 2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces risk of pregnancy by at least 75%⁹

Lactational Amenorrhea Method: LAM is a highly effective, *temporary* method of contraception¹⁰

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

- ¹ Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason
- ² Among couples who initiate use of a method (not necessarily for the first time) and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason
- ³ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year
- ⁴ The percentage of women becoming pregnant noted in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% became pregnant in one year. This estimate was lowered slightly (to 85%) to represent the percentage that would become pregnant within one year among women now relying on reversible methods of contraception if they abandon contraception altogether
- ⁵ Foams, creams, gels, vaginal suppositories and vaginal film
- ⁶ Cervical mucous (ovulation) method supplemented by calendar in the preovulatory and basal body temperature in the postovulatory phases
- ⁷ With spermicidal cream or jelly
- ⁸ Without spermicides
- ⁹ The treatment schedule is one dose within 72 hours after unprotected intercourse and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlen (1 dose is 2 light orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills)
- ¹⁰ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced or the baby reaches six months of age

CONTRAINDICATIONS

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

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders
- Cerebrovascular or coronary artery disease (current or history)
- Valvular heart disease with thrombogenic complications
- Uncontrolled hypertension
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- Known or suspected carcinoma of the breast or personal history of breast cancer
- 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, or active liver disease
- Known or suspected pregnancy
- Hypersensitivity to any component of this product

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) 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 risk of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and 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 certain inherited thrombophilias, 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, epidemiological 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 epidemiological methods.

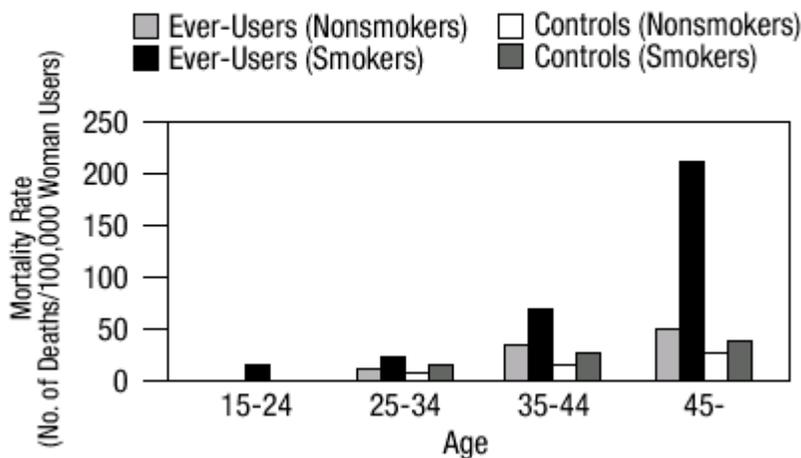
1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

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 (Figure 1) among women who use oral contraceptives.

FIGURE 1
CIRCULATORY DISEASE MORTALITY RATES PER 100,000
WOMEN-YEARS BY AGE, SMOKING STATUS AND
ORAL CONTRACEPTIVE USE



Layne PM, Beral V. *Lancet* 1981;1:541-546.

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**). Such increases in risk factors have been associated with an increased risk of heart disease and the risk increases with the number of risk factors present. 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 non-users 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 approximate incidence of deep-vein thrombosis and pulmonary embolism in users of low dose (<50 µg ethinyl estradiol) combination oral contraceptives is up to 4 per 10,000 woman-years compared to 0.5-3 per 10,000 woman-years for non-users. However, the incidence is substantially less than that associated with pregnancy (6 per 10,000 woman-years). 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 relative risk of postoperative 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 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 breastfeed.

c. Cerebrovascular diseases

Oral contraceptives have been shown to increase both the relative and attributable risk 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. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilias, hyperlipidemias, and obesity. Women with migraine (particularly migraine with aura) who take combination oral contraceptives may be at an increased risk of stroke.

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 progestogens 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 the lowest estrogen content which is judged appropriate for the individual patient.

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 40-49 years old 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 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 3).

TABLE 3
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	AGE					
	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

Ory HW. *Family Planning Perspectives* 1983; 15:57-63.

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 risk. 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 low and below 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 1970s 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 risk 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.

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. Although the risk of breast cancer may be slightly increased among current users of oral contraceptives (RR = 1.24), this excess risk decreases over time after oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use, and no relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used oral contraceptives before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early oral contraceptive use is extremely small. Breast

cancers diagnosed in current or previous oral contraceptive users tend to be less advanced clinically than in never-users. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is a hormone-sensitive tumor.

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer 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 cancer 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 their occurrence 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 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 that may lead to partial or complete loss of vision. 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 in so far as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy (see "**Contraindications**" section).

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. 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 1.a.** and **1.d.**), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

9. ELEVATED BLOOD PRESSURE

Women with significant hypertension should not be started on hormonal contraceptive. 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 concentrations 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 elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see **Contraindications** section). 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 cause (see **WARNINGS 1.c.**).

11. BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. If bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy 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 (possibly with anovulation), especially when such a condition was preexistent.

PRECAUTIONS

1. SEXUALLY TRANSMITTED DISEASES

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

2. PHYSICAL EXAMINATION AND FOLLOW-UP

A periodic personal and family medical history and complete physical examination are appropriate for all women, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination 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 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.

3. 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 1.d.**).

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

4. 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.

5. 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.

6. EMOTIONAL DISORDERS

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. 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.

7. CONTACT LENSES

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

8. DRUG INTERACTIONS

Changes in contraceptive effectiveness associated with co-administration of other products:

a. Anti-infective agents and anticonvulsants

Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin. Several cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and tetracyclines. However, clinical pharmacology studies investigating drug interaction between combined oral contraceptives and these antibiotics have reported inconsistent results.

b. Anti-HIV protease inhibitors

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of combination oral contraceptive products may be affected with co-administration of anti-HIV protease inhibitors. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

c. Herbal products

Herbal products containing St. John's Wort (*hypericum perforatum*) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Increase in plasma levels of estradiol associated with co-administered drugs:

Co-administration of atorvastatin and certain combination oral contraceptives containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP 3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

Changes in plasma levels of co-administered drugs:

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of combination oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid,

morphine and clofibrac acid, due to induction of conjugation have been noted when these drugs were administered with combination oral contraceptives.

9. 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 hormone 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 and levels of various other lipids and lipoproteins may be affected.
- 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.

10. CARCINOGENESIS

See **WARNINGS** section.

11. PREGNANCY

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

12. NURSING MOTHERS

Small amounts of oral contraceptive steroids and/or metabolites 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, combination 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 combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

13. PEDIATRIC USE

Safety and efficacy of OVCON[®] 35 have been established in women of reproductive age. Safety and efficacy are expected to be the same in postpubertal adolescents under the age of 16 years and in users ages 16 years and older. Use of this product before menarche is not indicated.

14. GERIATRIC USE

This product has not been studied in women over 65 years of age and is not indicated in this population.

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:

- 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 pain, cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema/fluid retention
- Melasma/chloasma which may persist
- Breast changes: tenderness, pain, enlargement, and secretion
- Change in weight or appetite (increase or decrease)
- Change in cervical ectropion and secretion
- Possible diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine headache
- Rash (allergic)
- Mood changes, including depression
- Vaginitis, including candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses
- Decrease in serum folate levels.
- Exacerbation of systemic lupus erythematosus
- Exacerbation of porphyria
- Exacerbation of chorea
- Aggravation of varicose veins
- Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms

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

- Premenstrual syndrome
- Cataracts
- Optic neuritis, which may lead to partial or complete loss of vision
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Impaired renal function
- Hemolytic uremic syndrome
- Budd-Chiari syndrome
- Acne
- Changes in libido
- Colitis
- Pancreatitis

- Dysmenorrhea

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 or 0.05 mg of mestranol.

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

To achieve maximum contraceptive effectiveness, OVCON[®] 35 must be taken exactly as directed and at intervals not exceeding 24 hours. The dosage of OVCON[®] 35 is one white tablet daily for 21 consecutive days, followed by one green inert tablet daily for 7 consecutive days. It is recommended that tablets be taken at the same time each day. The pill may be swallowed whole or chewed and swallowed. If the pill is chewed, the patient should drink a full glass (8 ounces) of liquid immediately after swallowing. During the first cycle of use, the patient is instructed to begin taking OVCON[®] 35 on either Day 1 or the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (white) is taken that day. One white tablet should be taken daily for 21 consecutive days followed by one green inert tablet daily for 7 consecutive days. Withdrawal bleeding should usually occur within three days following discontinuation of white tablets and may not have finished before the next pack is started. During the first cycle with a Sunday start, contraceptive reliance should not be placed on OVCON[®] 35 until a white tablet has been taken daily for 7 consecutive days and a non-hormonal back-up method of birth control (such as condoms or spermicide) should be used during those 7 days. 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 tablets on the same day of the week on which she began her first course, following the same schedule: 21 days on white tablets—7 days on green inert tablets. If in any cycle the patient starts tablets later than the proper day, she should protect herself against pregnancy by using a non-hormonal back-up method of birth control until she has taken a white tablet daily for 7 consecutive days.

When the patient is switching from a 21-day regimen of tablets, she should wait 7 days after her last tablet before she starts OVCON[®] 35. She will probably experience withdrawal bleeding during that week. She should be sure that no more than 7 days pass after her previous 21-day regimen. When the patient is switching from a 28-day regimen of tablets, she should start her first pack of OVCON[®] 35 on the day after her last tablet. She should not wait any days between packs. The patient may switch any day from a progestin-only pill and should begin OVCON[®] 35 the next day. If switching from an implant or injection, the patient should start OVCON[®] 35 on the day of implant removal or, if using an injection, the day the next injection would be due.

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 healthcare provider. Although pregnancy is unlikely if OVCON[®] 35 is 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. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. Hormonal contraceptives should be discontinued if pregnancy is confirmed.

For additional patient instructions regarding missed pills, see the “WHAT TO DO IF YOU MISS PILLS” section in the **DETAILED PATIENT LABELING**. Any time the patient misses two or more white tablets, she should also use another method of non-hormonal back-up contraception until she has taken a white tablet daily for seven consecutive days. If the patient misses one or more green tablets, she is still protected against pregnancy **provided** she begins taking white tablets again on the proper day. If breakthrough bleeding occurs following missed white tablets, it will usually be transient and of no consequence. The possibility of ovulation increases with each successive day that scheduled white tablets are missed. The risk of pregnancy increases with each active (white) tablet missed.

OVCON[®] 35 may be initiated no earlier than day 28 postpartum in the nonlactating mother due to the increased risk for thromboembolism. 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). The patient should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking. However, if intercourse has already occurred, the possibility of ovulation and conception prior to initiation of medication should be considered. OVCON[®] 35 may be initiated after a first-trimester abortion; if the patient starts OVCON[®] 35 immediately, additional contraceptive measures are not needed.

For additional patient instructions regarding complete dosing instructions, see the “HOW TO TAKE THE PILL” section in the **DETAILED PATIENT LABELING**.

HOW SUPPLIED

OVCON[®] 35 (norethindrone and ethinyl estradiol tablets, chewable) is available only in a 28-day regimen. Each package contains 21 round, white tablets of 0.4 mg norethindrone and 0.035 mg ethinyl estradiol, imprinted with **W|C** on one side and 581 on the other. Each capsule-shaped, green tablet contains inert ingredients and is imprinted with **W|C** on one side and 481 on the other.

OVCON[®] 35

N 0430-0582-14

Carton of 6 compacts

Store at 25° C (77° F); excursions permitted to 15°- 30° C (59°- 86° F) [see USP Controlled Room Temperature]

References are available upon request.

PATIENT PACKAGE INSERT BRIEF SUMMARY

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 without missing any pills, have a failure rate of about 1 % per year (1 pregnancy per 100 women per year of use). The typical failure rate of pill users is 5% per year when women who miss pills are included.

For the majority of women, oral contraceptives can be taken safely. But for some women oral contraceptive use is associated with 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, or are obese
- 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 are pregnant or have unexplained vaginal bleeding.

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

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 the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) 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 are nausea, vomiting, bleeding or spotting between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting, may decrease or 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. Women with migraine also may be at increased risk of stroke when taking the pill.
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 patient information leaflet given to you with your supply of pills. Notify your healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics, and herbal preparations containing St. John's Wort (*hypericum perforatum*), may decrease oral contraceptive effectiveness.

Breast cancer has been diagnosed slightly more often in women who use the pill than in women of the same age who do not use the pill. This very small increase in the number of breast cancer diagnoses

gradually disappears during the 10 years after stopping use of the pill. It is not known whether the difference is caused by the pill. It may be that women taking the pill are examined more often, so that breast cancer is more likely to be detected. You should have regular breast examinations by a healthcare provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use hormonal contraceptives because breast cancer is usually a hormone-sensitive tumor.

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

Taking the combination pill provides some important noncontraceptive health 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 healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your healthcare provider.

DOSAGE AND ADMINISTRATION

HOW TO TAKE OVCON 35

IMPORTANT POINTS TO REMEMBER

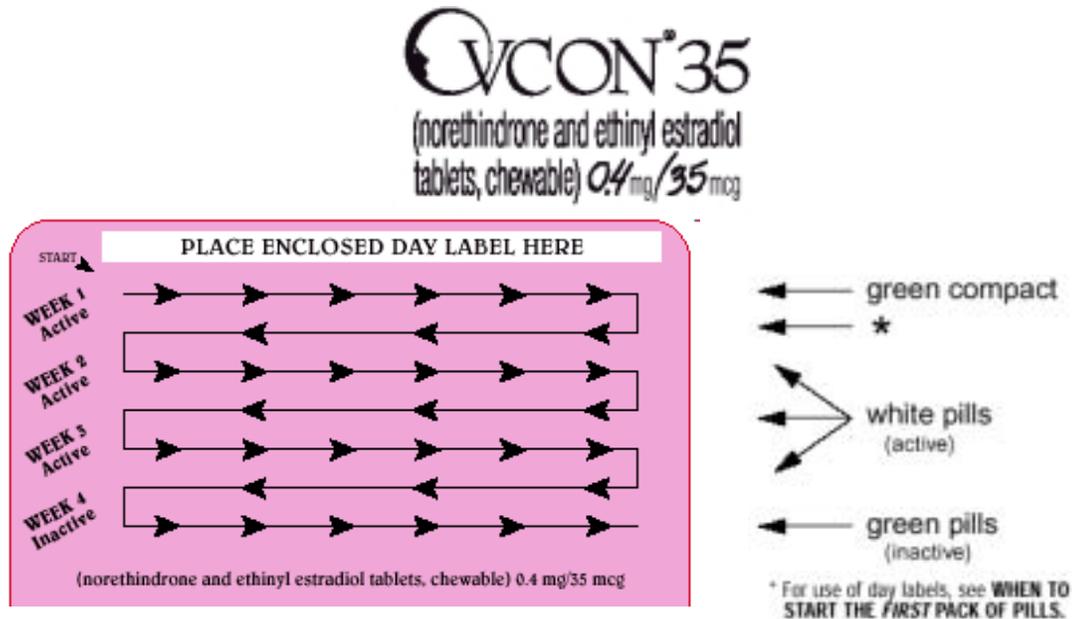
BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
 - Before you start taking your pills
 - Anytime you are not sure what to do
2. THE PILL MAY BE SWALLOWED WHOLE OR CHEWED AND SWALLOWED. IF THE PILL IS CHEWED, YOU SHOULD DRINK A FULL GLASS (8 OUNCES) OF LIQUID IMMEDIATELY AFTER SWALLOWING.
3. 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.
4. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS.
If you have spotting or light bleeding or 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 healthcare provider.
5. 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.
6. IF YOU HAVE VOMITING (within 3 to 4 hours after you take your pill), you should follow the instructions for WHAT TO DO IF YOU MISS PILLS. IF YOU HAVE DIARRHEA or IF YOU TAKE CERTAIN MEDICINES, including some antibiotics, or the herbal supplement St. John's Wort, your pills may not work as well. Use a back-up method of birth control (such as condoms or spermicide) until you check with your healthcare provider.
7. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

8. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your healthcare provider.

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:
The pill pack has 21 "active" white pills (with hormones) to take for 3 weeks, followed by 7 "reminder" green pills (without hormones) to take for 1 week.



3. ALSO FIND:
 - where on the pack to start taking pills,
 - in what order to take the pills (follow the arrows), and
 - the week numbers as shown in the picture above.
4. BE SURE YOU HAVE READY AT ALL TIMES:
 - ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicide) 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 2 choices of which day to start taking your first pack of pills. (See DAY 1 START or SUNDAY START directions below.) Decide with your healthcare provider which is the best day for you. Once you have decided which day you will begin taking your pills, immediately do the following: remove the Brief Summary from inside the compact and look for the attached day label sheet; peel the label from the sheet which has the start day printed on the left hand side; place the label on the blister card in the designated location. Take your pill daily in the order indicated by the arrows on the blister card. Pick a time of day which will be easy to remember and take your pill at the same time each day.

DAY 1 START:

1. Take the first "active" white 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" white 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 or spermicide 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 of YOUR OVCON[®] 35:
Start the next pack on the day after your last green "reminder" pill. Do not wait any days between packs.
3. WHEN YOU SWITCH FROM A DIFFERENT BRAND OF PILLS:
If your previous brand had 21 pills, wait 7 days before starting OVCON[®] 35.
If your previous brand had 28 pills, start taking OVCON[®] 35 on the day after the last pill.

WHAT TO DO IF YOU MISS PILLS

The pill may not be as effective if you miss white "active" pills, and particularly if you miss the first few or the last few white "active" pills in a pack.

If you MISS 1 white "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 white "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 COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills.

You MUST use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for those 7 days.

If you MISS 2 white "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 healthcare provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for those 7 days.

If you MISS 3 OR MORE white "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 healthcare provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex on the days when you missed pills or during the first 7 days after restarting your pills. You MUST use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for the first 7 days after you restart your pills.

If you forget any of the 7 green "reminder" pills in Week 4:

1. THROW AWAY the pills you missed.
2. Keep taking 1 pill each day until the pack is empty.
3. You do not need a back-up method.

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

1. Use a BACK-UP METHOD anytime you have sex.
2. KEEP TAKING ONE "ACTIVE" (WHITE) PILL EACH DAY until you can reach your healthcare provider.

DETAILED 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.

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.

Although oral contraceptives have important advantages over other methods of contraception, they have certain risks that no other method has, and some of these risks may continue after you have stopped using the oral contraceptive. 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 Ovcon 35 properly so that it will be as effective as possible. However, this booklet is not a replacement for a careful discussion between you and your healthcare provider. You should discuss the information provided in this booklet with your healthcare provider, both when you first start taking the pill and during your revisits. You should also follow your healthcare provider's advice with regard to regular check-ups while you are on Ovcon 35.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth control pill" or "the pill" are used to prevent pregnancy and are more effective than most other nonsurgical methods of birth control. The chance of becoming pregnant is approximately 1% per year (1 pregnancy per 100 women per year of use) when the pills are used correctly, and no pills are missed. Typical failure rates are 5% per year when women who miss pills are included. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

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

No methods: 85%
Vaginal sponge: 20 to 40%
Cervical cap: 20 to 40%
Spermicides alone: 26%
Periodic abstinence: 25%
Condom (female): 21%
Diaphragm with spermicides: 20%
Withdrawal: 19%
Condom (male): 14%
Female sterilization: 0.5%
IUD: 0.1 to 2.0%
Injectable progestogen: 0.3%
Male sterilization: 0.15%
Norplant system: 0.05%

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 the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) 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. You should not use the pill if you have or have ever had any of the following conditions:

- A history of heart attack or stroke
- A history of blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), or eyes

- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix, vagina, or certain hormonally-sensitive cancers
- Unexplained vaginal bleeding (until a diagnosis is reached by your healthcare provider)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy
- Heart valve or heart rhythm disorders that may be associated with formation of blood clots
- Diabetes affecting your circulation
- Uncontrolled high blood pressure
- Active liver disease with abnormal liver function tests
- Allergy or hypersensitivity to any of the components of OVCON® 35
- A need for surgery with prolonged bedrest

Tell your healthcare provider if you have any of the above conditions. Your healthcare provider can recommend a safer method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your healthcare provider if you or any family member has ever had:

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

Women with any of these conditions should be checked often by their healthcare provider if they choose to use oral contraceptives.

Also, be sure to inform your healthcare 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 cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Either of these can cause death or disability. 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 injury, or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your healthcare provider about stopping oral contraceptives three to four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for at least four weeks after delivery if you are not breastfeeding. If you are breastfeeding, you should wait until you have weaned your child before using the pill (see the section on **breastfeeding** in **GENERAL PRECAUTIONS**).

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills (containing 50 micrograms or higher of ethinyl estradiol) and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after

stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

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 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.

Women with migraine (especially migraine with aura) who take oral contraceptives also may be at higher risk of stroke.

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 in general are extremely rare and the chance of developing liver cancer from using the pill is thus even rarer.

5. Cancer of the breast and reproductive organs

Breast cancer has been diagnosed slightly more often in women who use the pill than in women of the same age who do not use the pill. This small increase in the number of breast cancer diagnoses gradually disappears during the 10 years after stopping use of the pill. It is not known whether the difference is caused by the pill. It may be that women taking the pill are examined more often, so that breast cancer is more likely to be detected. You should have regular breast examinations by a healthcare provider and examine your own breasts monthly. Tell your healthcare provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone-sensitive tumor.

Some studies have found an increase in the incidence of cancer or precancerous lesions of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that the pill may cause such cancers.

6. Lipid metabolism and inflammation of the pancreas

In patients with inherited defects of lipid metabolism, there have been reports of significant elevations of plasma triglycerides during estrogen therapy. This has led to pancreatitis in some cases.

ESTIMATED RISK OF DEATH FROM A 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.

Method of control and outcome	AGE					
	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 was 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, although over the age of 40, the risk increases to 32 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. 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. Older women, as all women who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestin that is compatible with the individual patient needs.

WARNING SIGNALS

If any of these adverse conditions occur while you are taking oral contraceptives, call your healthcare provider 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 healthcare provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (possibly indicating a 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

In addition to the risks and more serious side effects discussed above (see **RISKS OF TAKING ORAL CONTRACEPTIVES, ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY** and **WARNING SIGNALS** sections), the following may also occur:

1. Irregular Vaginal bleeding

Irregular vaginal bleeding or spotting may occur while you are taking Ovcon 35. 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 healthcare provider.

2. Contact lenses

If you wear contact lenses and notice a change in vision or an inability to wear your lenses, contact your healthcare 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 healthcare provider.

4. Melasma

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

5. Other side effects

Other side effects may include nausea and vomiting, change in appetite, breast tenderness, headache, nervousness, depression, dizziness, loss of scalp hair, rash, vaginal infections, and allergic reactions.

If any of these side effects bother you, call your healthcare provider.

GENERAL PRECAUTIONS

1. 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 healthcare provider. 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 healthcare provider immediately to determine whether you are pregnant. Stop taking Ovcon 35 if you are pregnant.

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 should not be used during pregnancy. You should check with your healthcare provider about risks to your unborn child of any medication taken during pregnancy.

On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

6. IF YOU HAVE VOMITING (within 3 to 4 hours after you take your pill), you should follow the instructions for WHAT TO DO IF YOU MISS PILLS. IF YOU HAVE DIARRHEA or IF YOU TAKE CERTAIN MEDICINES, including some antibiotics, or the herbal supplement St. John's Wort, your pills may not work as well. Use a back-up method of birth control (such as condoms or spermicide) until you check with your healthcare provider.
7. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.
8. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your healthcare provider.

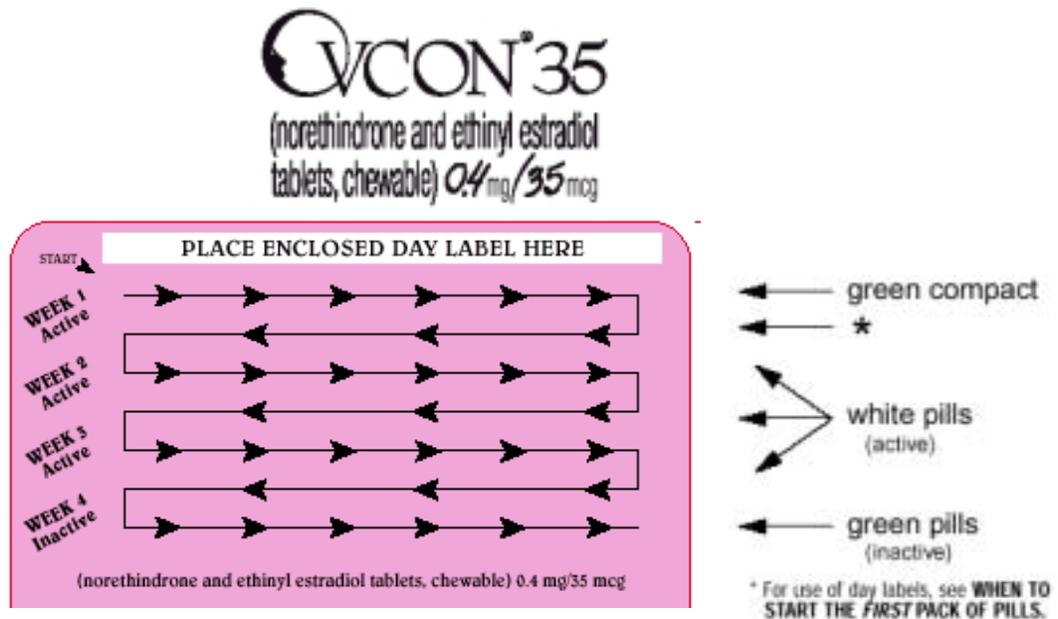
BEFORE YOU START TAKING YOUR PILLS

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:

The pill *pack* has 21 "active" white pills (with hormones) to take for 3 weeks, followed by 7 "reminder" green pills (without hormones) to take for 1 week.



3. ALSO FIND:

- where on the pack to start taking pills,
- in what order to take the pills (follow the arrows), and
- the week numbers as shown in the picture above.

4. BE SURE YOU HAVE READY AT ALL TIMES:

- ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicide) 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 2 choices of which day to start taking your first pack of pills. (See DAY 1 START or SUNDAY START directions below.) Decide with your healthcare provider which is the best day for you. Once you have decided which day you will begin taking your pills, immediately do the following: remove the Brief Summary from inside the compact and look for the attached day label sheet; peel the label from the sheet which has the start day printed on the left hand side; place the label on the blister card in the designated location. Take your pill daily in the order indicated by the arrows on the blister card. Pick a time of day which will be easy to remember and take your pill at the same time each day.

DAY 1 START:

1. Take the first "active" white 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" white 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 or spermicide 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 of YOUR OVCON[®] 35:**
Start the next pack on the day after your last green "reminder" pill. Do not wait any days between packs.
3. **WHEN YOU SWITCH FROM A DIFFERENT BRAND OF PILLS:**
If your previous brand had 21 pills, wait 7 days before starting OVCON[®] 35.
If your previous brand had 28 pills, start taking OVCON[®] 35 on the day after the last pill.

WHAT TO DO IF YOU MISS PILLS

The pill may not be as effective if you miss white "active" pills, and particularly if you miss the first few or the last few white "active" pills in a pack.

If you MISS 1 white "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 white "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 **COULD BECOME PREGNANT** if you have sex during the 7 days after you restart your pills. You **MUST** use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for those 7 days.

If you MISS 2 white "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 healthcare provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for those 7 days.

If you MISS 3 OR MORE white "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 healthcare provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex on the days when you missed pills or during the first 7 days after restarting your pills. You MUST use a non-hormonal birth control method (such as condoms or spermicide) as a back-up for the first 7 days after you restart your pills.

If you forget any of the 7 green "reminder" pills in Week 4:

1. THROW AWAY the pills you missed.
2. Keep taking 1 pill each day until the pack is empty.
3. You do not need a back-up method of birth control.

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

1. Use a BACK-UP METHOD anytime you have sex.
2. KEEP TAKING ONE "ACTIVE" (WHITE) PILL EACH DAY until you can reach your healthcare provider.

GENERAL

1. Pregnancy due to pill failure

If taken every day as directed, the incidence of pill failure resulting in pregnancy is approximately 1% per year (one pregnancy per 100 women per year), but more typical failure rates are about 5% per year. If pregnancy does occur, the risk to the fetus is minimal.

2. 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.

3. 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 healthcare provider or pharmacist.

4. Other information

Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your healthcare 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 healthcare provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.

Do not use this 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 healthcare provider or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read.

Manufactured by: Bristol-Myers Squibb Co.
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Rockaway, NJ 07866



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