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10305001

ORTHO TRI-CYCLEN® TABLETS
ORTHO-CYCLEN® TABLETS
(norgestimate/ethinyl estradiol)

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

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DESCRIPTION

Each of the following products is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol.

ORTHO TRI-CYCLEN® Tablets.

Each white tablet contains 0.180 mg of the progestational compound, norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include carnauba wax, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, purified water and titanium dioxide.

Each light blue tablet contains 0.215 mg of the progestational compound norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD & C Blue No. 2 Aluminum Lake, carnauba wax, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, purified water and titanium dioxide.

Each blue tablet contains 0.250 mg of the progestational compound norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD & C Blue No. 2 Aluminum Lake, carnauba wax, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, purified water and titanium dioxide.

Each dark green tablet contains only inert ingredients, as follows: FD & C Blue No. 2 Aluminum Lake, ferric oxide, hypromellose, lactose, magnesium stearate, polyethylene glycol, pregelatinized corn starch, purified water, talc and titanium dioxide.

ORTHO-CYCLEN® Tablets.

Each blue tablet contains 0.250 mg of the progestational compound norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD & C Blue No. 2 Aluminum Lake, carnauba wax, croscarmellose sodium, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, purified water and titanium dioxide.

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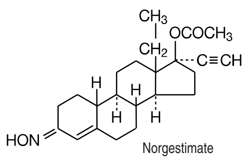
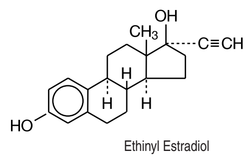


Norgestimate



Ethinyl Estradiol

CLINICAL PHARMACOLOGY

Oral Contraception

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

Receptor binding studies, as well as studies in animals and humans, have shown that norgestimate and 17-deacetyl norgestimate, the major serum metabolite, combine high progestational activity with minimal intrinsic androgenicity.[90-93] Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in sex hormone binding globulin (SHBG), resulting in lower serum testosterone.[90,91,94]

Acne

Acne is a skin condition with a multifactorial etiology, including androgen stimulation of sebum production. While the combination of ethinyl estradiol and norgestimate increases sex hormone binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established.

PHARMACOKINETICS

Absorption

Norgestimate (NGM) and ethinyl estradiol (EE) are rapidly absorbed following oral administration. Norgestimate is rapidly and completely metabolized by firstpass (intestinal and/or hepatic) mechanisms to norelgestromin (NGMN) and norgestrel (NG), which are the major active metabolites of norgestimate.

Peak serum concentrations of NGMN and EE are generally reached by 2 hours after administration of ORTHO-CYCLEN® or ORTHO TRI-CYCLEN®. Accumulation following multiple dosing of the 250 µg NGM / 35 µg dose is approximately 2-fold for NGMN and EE compared with single dose administration. The pharmacokinetics of NGMN is dose proportional following NGM doses of 180 µg to 250 µg. Steady-state concentration of EE is achieved by Day 7 of each dosing cycle. Steady-state concentrations of NGMN and NG are achieved by Day 21. Non-linear accumulation (approximately 8 fold) of norgestrel is observed as a result of high affinity binding to SHBG (sex hormone-binding globulin), which limits its biological activity.

TABLE I. Summary of norelgestromin, norgestrel and ethinyl estradiol pharmacokinetic parameters.

Analyte	Cycle	Day	C_{max}	t_{max} (h)	AUC_{0-24h}	$t_{1/2}$ (h)
Mean (SD) Pharmacokinetic Parameters of ORTHO TRI-CYCLEN During a Three Cycle Study						
NGMN	3	7	1.80 (0.46)	1.42 (0.73)	15.0 (3.88)	NC
		14	2.12 (0.56)	1.21 (0.26)	16.1 (4.97)	NC
		21	2.66 (0.47)	1.29 (0.26)	21.4 (3.46)	22.3 (6.54)
NG	3	7	1.94 (0.82)	3.15 (4.05)	34.8 (16.5)	NC
		14	3.00 (1.04)	2.21 (2.03)	55.2 (23.5)	NC
		21	3.66 (1.15)	2.58 (2.97)	69.3 (23.8)	40.2 (15.4)
EE	3	7	124 (39.5)	1.27 (0.26)	1130 (420)	NC
		14	128 (38.4)	1.32 (0.25)	1130 (324)	NC
		21	126 (34.7)	1.31 (0.56)	1090 (359)	15.9 (4.39)
Mean (SD) Pharmacokinetic Parameters of ORTHO-CYCLEN During a Three Cycle Study						
Analyte	Cycle	Day	C_{max}	t_{max} (h)	AUC_{0-24h}	$t_{1/2}$ (h)
NGMN	1	1	1.78 (0.397)	1.19 (0.250)	9.90 (3.25)	18.4 (5.91)
	3	21	2.19 (0.655)	1.43 (0.680)	18.1 (5.53)	24.9 (9.04)
NG	1	1	0.649 (0.49)	1.42 (0.69)	6.22 (2.46)	37.8 (14.0)
	3	21	2.65 (1.11)	1.67 (1.32)	48.2 (20.5)	45.0 (20.4)
EE	1	1	92.2 (24.5)	1.2 (0.26)	629 (138)	10.1 (1.90)
	3	21	147 (41.5)	1.13 (0.23)	1210 (294)	15.0 (2.36)

C_{max}= peak serum concentration, t_{max}= time to reach peak serum concentration, AUC_{0-24h}= area under serum concentration vs time curve from 0 to 24 hours, $t_{1/2}$= elimination half-life, NC = not calculated.

NGMN and NG: C_{max}= ng/mL, AUC_{0-24h}=h•ng/mL

EE: C_{max}=pg/mL, AUC_{0-24h}=h•pg/mL

The effect of food on the pharmacokinetics of ORTHO-CYCLEN or ORTHO TRI-CYCLEN has not been studied.

Distribution

Norelgestromin and norgestrel are highly bound (>97%) to serum proteins. Norelgestromin is bound to albumin and not to SHBG, while norgestrel is bound primarily to SHBG. Ethinyl estradiol is extensively bound (> 97%) to serum albumin and induces an increase in the serum concentrations of SHBG.

Metabolism

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

Excretion

The metabolites of norelgestromin and ethinyl estradiol are eliminated by renal and fecal pathways. Following administration of ^{14}C-norgestimate, 47% (45-49%) and 37% (16-49%) of the administered radioactivity was eliminated in the urine and feces, respectively. Unchanged norgestimate was not detected in the urine. In addition to 17-deacetyl norgestimate, a number of metabolites of norgestimate have been identified in human urine following administration of radiolabeled norgestimate. These include 18, 19-Dinor-17-pregn-4-en-20-yn-3-one,17-hydroxy-13-ethyl,(17α)-(-);18,19-Dinor-5β-17-pregnan-20-yn,3α,17β-dihydroxy-13-ethyl,(17α), various hydroxylated metabolites and conjugates of these metabolites.

Special Populations

The effects of body weight, body surface area or age on the pharmacokinetics of ORTHO-CYCLEN® or ORTHO TRI-CYCLEN® have not been studied.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of ORTHO-CYCLEN® or ORTHO TRI-CYCLEN® have not been studied. However, steroid hormones may be poorly metabolized in women with impaired liver function (see PRECAUTIONS).

Renal Impairment

The effects of renal impairment on the pharmacokinetics of ORTHO-CYCLEN® or ORTHO TRI-CYCLEN® have not been studied.

Drug-Drug Interactions

No formal drug-drug interaction studies were conducted with ORTHO-CYCLEN® or ORTHO TRI-CYCLEN®. Interactions between contraceptive steroids and other drugs have been reported in the literature (see PRECAUTIONS).

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

INDICATIONS AND USAGE

ORTHO-CYCLEN® and ORTHO TRI-CYCLEN® Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

ORTHO TRI-CYCLEN is indicated for the treatment of moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. ORTHO TRI-CYCLEN should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

Oral contraceptives are highly effective for pregnancy prevention. Table II 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 II: 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.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[3]
Method (1)	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 T380A	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

Hatcher et al, 1998, Ref. # 1.

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

Lactational Amenorrhea Method: LAM is highly effective, temporary method of contraception.[10]

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

[1] Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop 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 percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

[5] Foams, creams, gels, vaginal suppositories, and vaginal film.

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

[7] With spermicidal cream or jelly.

[8] Without spermicides.

[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.

ORTHO-CYCLEN and ORTHO TRI-CYCLEN have not been studied for and are not indicated for use in emergency contraception.

In clinical trials with ORTHO-CYCLEN, 1,651 subjects completed 24,272 cycles and the overall use-efficacy (typical user efficacy) pregnancy rate was approximately 1 pregnancy per 100 women-years. This rate includes patients who did not take the drug correctly.

In four clinical trials with ORTHO TRI-CYCLEN, a total of 4,756 subjects completed 45,244 cycles, and the use-efficacy pregnancy rate was approximately 1 pregnancy per 100 women-years.

ORTHO TRI-CYCLEN was evaluated for the treatment of acne vulgaris in two randomized, double-blind, placebo-controlled, multicenter, Phase 3, six (28 day) cycle studies. 221 patients received ORTHO TRI-CYCLEN and 234 patients received placebo. Mean age at enrollment for both groups was 28 years. At the end of 6 months, the mean total lesion count changes from 55 to 31 (42% reduction) in patients treated with ORTHO TRI-CYCLEN and from 54 to 38 (27% reduction) in patients similarly treated with placebo. Table III summarizes the changes in lesion count for each type of lesion in the ITT population. Based on the investigator's global assessment conducted at the final visit, patients treated with ORTHO TRI-CYCLEN showed a statistically significant improvement in total lesions compared to those treated with placebo.

Table III: Acne Vulgaris Indication. Combined Results: Two Multicenter, Placebo-Controlled Trials. Observed Means at Six Months (LOCF)* and at Baseline. Intent-to-Treat Population.

	ORTHO TRI-CYCLEN (N=221)		Placebo (N=234)		Difference in Counts between ORTHO TRI-CYCLEN and Placebo at 6 Months
# of Lesions	Counts	% Reduction	Counts	% Reduction	
INFLAMMATORY LESIONS					
Baseline Mean	19		19		
Sixth Month Mean	10	48%	13	30%	3 (95% CI: -1.2, 5.1)
NON-INFLAMMATORY LESIONS					
Baseline Mean	36		35		
Sixth Month Mean	22	34%	25	21%	3 (95% CI: -0.2, 7.8)
TOTAL LESIONS					
Baseline Mean	55		54		
Sixth Month Mean	31	42%	38	27%	7 (95% CI: 2.0, 11.9)

*LOCF: Last Observation Carried Forward

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
- Cerebral vascular or coronary artery disease (current or past history)
- Valvular heart disease with complications
- Severe 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
- Acute or chronic hepatocellular disease with abnormal liver function
- Hepatic adenomas or carcinomas
- 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 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, and gallbladder disease, 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, 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 (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

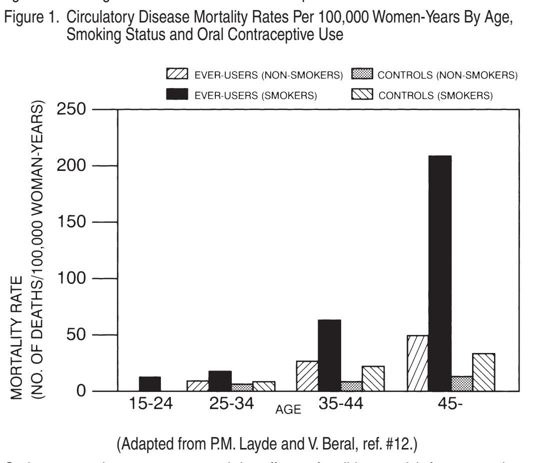
1. Thromboembolic Disorders and Other Vascular Problems

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.[4-10] 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.[11] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older and in nonsmokers over the age of 40 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



(Adapted from P.M. Layde and V. Beral, ref. #12.)

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[14-18] 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.

Norgestimate has minimal androgenic activity (see CLINICAL PHARMACOLOGY), and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater [97].

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.[2,3,19-24] 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.[25] The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.[2]

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.[9] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[26] 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 weeks after delivery in women who elect not to breast feed.

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, and smoking interacted to increase the risk of stroke.[27-29]

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.[30] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers 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.[30] The attributable risk is also greater in older women.[3]

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.[31-33] A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents.[14-16] 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 activity of the progestogen used in the contraceptives. The activity and 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 who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups.[8] 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.[34] 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 IV). 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 low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data

gathered in the 1970's.[35] Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. The Committee concluded that 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 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. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

Of course, older women, as all women, who take oral contraceptives, should take an oral contraceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

Table IV: Annual Number of Birth-Related or Method-Related Deaths Associated With Control of Fertility Per 100,000 Non-Sterile 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, ref. #35.

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. The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives (COCs). However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use COCs before age 20. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history.

Breast cancers diagnosed in current or previous oral contraceptive users tend to be less clinically advanced than nonusers. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormonally-sensitive tumor.

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[45-48]. 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 especially with oral contraceptives of higher dose.[49] Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.[50,51]

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.[56,57] The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned,[55,56,58,59] 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. 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.[60,61] More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.[62-64] 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 a decrease in glucose tolerance in a significant percentage of users.[17] This effect has been shown to be directly related to estrogen dose.[65] Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[17,66] However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.[67] Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored 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.

In clinical studies with ORTHO-CYCLEN® there were no clinically significant changes in fasting blood glucose levels. No statistically significant changes in mean fasting blood glucose levels were observed over 24 cycles of use. Glucose tolerance tests showed minimal, clinically insignificant changes from baseline to cycles 3, 12, and 24.

In clinical studies with ORTHO TRI-CYCLEN® there were no clinically significant changes in fasting blood glucose levels. Minimal statistically significant changes were noted in glucose levels over 24 cycles of use. Glucose tolerance tests showed no clinically significant changes from baseline to cycles 3, 12, and 24.

9. Elevated Blood Pressure

Women with significant hypertension should not be started on hormonal contraception[98]. An increase in blood pressure has been reported in women taking oral contraceptives[68] and this increase is more likely in older oral contraceptive users[69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

Women with a history of hypertension or hypertension-related diseases, or renal disease[70] 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. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.[68-71] It should be noted that in two separate large clinical trials (N=633 and N=911), no statistically significant changes in mean blood pressure were observed with ORTHO-CYCLEN®.

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.

11. Bleeding Irregularities

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal 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 preexistent.

12. Ectopic Pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS

1. General

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

It is good medical practice for all women to have annual history and physical examinations, 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.

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.

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

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, griseofulvin and bosentan.

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 oral contraceptive products may be affected with co-administration of anti-HIV protease inhibitors. Healthcare professionals should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

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.

Concurrent use of bosentan and ethinyl estradiol containing products may result in decreased concentrations of these contraceptive hormones thereby increasing the risk of unintended pregnancy and unscheduled bleeding.

Increase in plasma levels associated with co-administered drugs

Co-administration of atorvastatin and certain 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 cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid, due to induction of conjugation, have been noted when these drugs were administered with oral contraceptives.

Combined hormonal contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.[101]

Healthcare professionals are advised to also refer to prescribing information of co-administered drugs for recommendations regarding management of concomitant therapy.

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; however, free or biologically active levels either decrease or 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 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 ORTHO TRI-CYCLEN® Tablets and ORTHO-CYCLEN® Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. There was no significant difference between ORTHO TRI-CYCLEN Tablets and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineral density between baseline and Cycle 13 in 123 adolescent females with anorexia nervosa in a double-blind, placebo-controlled, multicenter, one-year treatment duration clinical trial for the Intent To Treat (ITT) population. 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 and venous thrombosis with or without embolism
- 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 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
- Allergic reaction, including rash, urticaria, angioedema
- 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 a causal association has been neither confirmed nor refuted:

- Pre-menstrual syndrome
- Cataracts
- 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
- Acne
- Changes in libido
- Colitis
- Budd-Chiari Syndrome

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.

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.[73-78]

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

Other effects:

- 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

Oral Contraception

To achieve maximum contraceptive effectiveness, ORTHO TRI-CYCLEN® Tablets and ORTHO-CYCLEN® Tablets must be taken exactly as directed and at intervals not exceeding 24 hours. The possibility of ovulation and conception prior to initiation of medication should be considered. ORTHO TRI-CYCLEN and ORTHO-CYCLEN are available in the DIALPAK® Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided.

Sunday Start

When taking ORTHO TRI-CYCLEN® and ORTHO-CYCLEN® the first tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first tablet should be taken that day. Take one active tablet daily for 21 days followed by one dark green inactive tablet daily for 7 days. After 28 tablets have been taken, a new course is started the next day (Sunday). For the first cycle of a Sunday Start regimen, another method of contraception should be used until after the first 7 consecutive days of administration.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control such as condoms or spermicide if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should continue taking one tablet every day until Sunday. On Sunday the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling ("How to Take the Pill" section).

Day 1 Start

The dosage of ORTHO TRI-CYCLEN® and ORTHO-CYCLEN®, for the initial cycle of therapy is one active tablet administered daily from the 1st day through the 21st day of the menstrual cycle, counting the first day of menstrual flow as "Day 1" followed by one dark green inactive tablet daily for 7 days. Tablets are taken without interruption for 28 days. After 28 tablets have been taken, a new course is started the next day.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control such as condoms or spermicide if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling ("How to Take the Pill" section).

The use of ORTHO TRI-CYCLEN and ORTHO-CYCLEN for contraception may be initiated 4 weeks postpartum in women who elect not to breast feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for "Nursing Mothers.") The possibility of ovulation and conception prior to initiation of medication should be considered.

(See Discussion of Dose-Related Risk of Vascular Disease from Oral Contraceptives.)

ADDITIONAL INSTRUCTIONS

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of oral contraceptives in the event of a missed menstrual period:

1. 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 and oral contraceptive use should be discontinued if pregnancy is confirmed.
2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out.

ACNE

The timing of initiation of dosing with ORTHO TRI-CYCLEN® for acne should follow the guidelines for use of ORTHO TRI-CYCLEN as an oral contraceptive. **Consult the DOSAGE AND ADMINISTRATION section for oral contraceptives.** The dosage regimen for ORTHO TRI-CYCLEN for treatment of facial acne, as available in a DIALPAK® Tablet Dispenser, utilizes a 21-day active and a 7-day placebo schedule. Take one active tablet daily for 21 days followed by one dark green inactive tablet for 7 days. After 28 tablets have been taken, a new course is started the next day.

HOW SUPPLIED

ORTHO TRI-CYCLEN® Tablets are available in a DIALPAK® Tablet Dispenser (NDC 0062-1910-15) containing 28 tablets. Each white tablet contains 0.180 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each light blue tablet contains 0.215 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each blue tablet contains 0.250 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each dark green tablet contains inert ingredients.

0.180/0.035 mg tablets - White, round, biconvex, coated tablet imprinted "O 180" on one side and "35" on the other side of the tablet.

0.215/0.035 mg tablets - Light blue, round, biconvex, coated tablet imprinted "O 215" on one side and "35" on the other side of the tablet.

0.250/0.035 mg tablets - Blue, round, biconvex, coated tablet imprinted "O 250" on one side and "35" on the other side of the tablet.

Each dark green reminder pill is a round, biconvex, coated tablet imprinted "O-M" on one side and "P" on the other side.

ORTHO TRI-CYCLEN® Tablets are available for clinic usage in a VERIDATE® Tablet Dispenser (unfilled) and VERIDATE Refills (NDC 0062-1910-20).

ORTHO-CYCLEN® Tablets are available in a DIALPAK® Tablet Dispenser (NDC 0062-1907-15) containing 28 tablets as follows: 21 blue tablets containing 0.250 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol, and 7 dark green tablets containing inert ingredients.

ORTHO-CYCLEN® Tablets are available for clinic usage in a VERIDATE® Tablet Dispenser (unfilled) and VERIDATE Refills (NDC 0062-1907-20).

Keep out of reach of children.

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Protect from light.

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BRIEF SUMMARY PATIENT PACKAGE INSERT

This product (like all oral contraceptives) 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. When taken correctly to prevent pregnancy, oral contraceptives have a failure rate of approximately 1% per year (1 pregnancy per 100 women per year of use) when used without missing any pills. The typical failure rate is approximately 5% per year (5 pregnancies per 100 women per year of use) 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.

ORTHO TRI-CYCLEN® may also be taken to treat moderate acne in females at least 15 years of age, who have started having menstrual periods, are able to take the pill and want to use the pill for birth control.

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 fatal or may cause temporary or permanent disability. 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

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.

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

> **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 are strongly advised not to 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 are young. 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. 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, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.
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 healthcare professional 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 may decrease oral contraceptive effectiveness.

Oral contraceptives may interact with lamotrigine (LAMICTAL®), an anticonvulsant used for epilepsy. This may increase the risk of seizures so your healthcare professional may need to adjust the dose of lamotrigine.

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go back down. You should have regular breast examinations by a healthcare professional and examine your own breasts monthly. Tell your healthcare professional 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 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.

Taking the combination pill provides some important non-contraceptive 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 professional. Your healthcare professional 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 professional believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. Your pharmacist should have given you the detailed patient information labeling which gives you further information which you should read and discuss with your healthcare professional.

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 feel sick to your stomach or have spotting or light bleeding, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your healthcare professional.
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, OR IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
   Use a back-up method (such as condoms or spermicide) until you check with your healthcare professional.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your healthcare professional 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 healthcare professional.

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" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" dark green pills (without hormones).
   ORTHO TRI-CYCLEN®: There are 7 white "active" pills, 7 light blue "active" pills, 7 blue "active" pills, and 7 dark green "reminder" pills.
   ORTHO-CYCLEN®: There are 21 blue "active" pills, and 7 dark green "reminder" pills.
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills.
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 method in case you miss pills.
   AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. ORTHO TRI-CYCLEN® and ORTHO-CYCLEN® are available in the DIALPAK® Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your healthcare professional which is the best day for you. Pick a time of day which will be easy to remember.

Sunday Start:

ORTHO TRI-CYCLEN®: Take the first white "active" 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.

ORTHO-CYCLEN®: Take the first blue "active" 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.

Use another method of birth control such as condoms or spermicide as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

Day 1 Start:

ORTHO TRI-CYCLEN®: Take the first white "active" pill of the first pack during the first 24 hours of your period.

ORTHO-CYCLEN®: Take the first blue "active" pill of the first pack during the first 24 hours of your period.

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.

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:**
   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

ORTHO TRI-CYCLEN®:

If you **MISS 1** white, light blue or blue "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 or light blue "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 in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3RD WEEK**:

1. **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.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack 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 professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** white, light blue or blue "active" pills in a row (during the first 3 weeks):

1. **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.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack 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 professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

ORTHO-CYCLEN®:

If you **MISS 1** blue "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** blue "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 in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3RD WEEK**:

1. **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.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack 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 professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** blue "active" pills in a row (during the first 3 weeks):

1. **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.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack 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 professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

A REMINDER:

If you forget any of the 7 dark green "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.

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 healthcare professional.

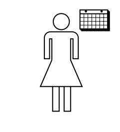
INSTRUCTIONS FOR USING YOUR DIALPAK® TABLET DISPENSER

PLEASE READ ME!

☐ **Sunday Start**
or
☐ **Day 1 Start**

There are two ways to start taking birth control pills,
Sunday Start or Day 1 Start.
Your healthcare professional will tell you which to use.

SAVE THESE INSTRUCTIONS.



1. If this is the first time you are taking birth control pills, or if you have not taken birth control pills for 10 days or more, your first step is to **wait until the first day you get your menstrual period**. Then, follow these instructions for either Sunday Start or Day 1 Start.

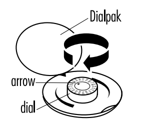
☐ **Sunday Start**
☐ **Day 1 Start**

2. When you get your period:

- You will use a **Sunday Start** if your doctor told you to take your first pill on a Sunday. Take pill "1" on the Sunday after your period starts.

If your period starts on a Sunday, take pill "1" that day.

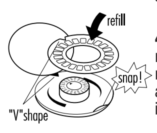
- You will use a **Day 1 Start** if your doctor told you to take pill "1" on the first day of your period.



3. SET THE DAY:

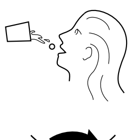
☐ **Sunday Start:** the arrow on your *empty* Dialpak should point to SU (Sunday).

☐ **Day 1 Start:** turn the dial on your *empty* Dialpak until the arrow points to the first day of your period (if your period starts on Tuesday, the arrow will point to TU).

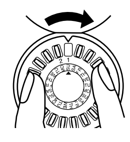


4. Insert the new refill by lining up the "V" shape on the refill with the "V" shape at the top of your Dialpak. Snap the refill in place. You are ready to take pill "1." You should always begin your pill cycle with pill "1," as shown on the inner part of the refill ring.

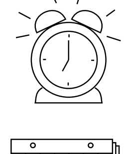
5. Remove pill "1" by pushing down on the pill. The pill will come out through a hole in the back of the Dialpak.



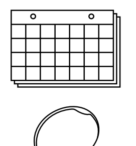
6. Swallow the pill. You will take one pill each day. If you use a Sunday Start and you are taking the pill for the FIRST TIME, YOU MUST USE A BACK-UP METHOD OF BIRTH CONTROL FOR THE FIRST 7 DAYS. If you use a Day 1 Start, you are protected from becoming pregnant as soon as you take your first pill.



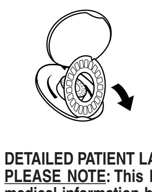
7. Wait 24 hours to take your next pill. To take pill "2," **turn the dial on your Dialpak** to the next day. Continue to take one pill each day until all the pills have been taken.



8. Take your pill at the same time every day. It is important to take the correct pill each day and not miss any pills. To help you remember, take your pill at the same time as another daily activity, like turning off your alarm clock or brushing your teeth.



9. When your refill is empty, keep your Dialpak case. You will start a new refill on the day after pill "28."



10. Turn the dial to the pill "1" position to remove the empty refill and insert a new refill. THE FIRST PILL IN EVERY REFILL WILL ALWAYS BE TAKEN ON THE SAME DAY OF THE WEEK, NO MATTER WHEN YOUR NEXT PERIOD STARTS.

DETAILED PATIENT LABELING

PLEASE NOTE: This labeling is revised from time to time as important new medical information becomes available. Therefore, please review this labeling carefully.

This product (like all oral contraceptives) does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

ORTHO TRI-CYCLEN® Regimen

Each white tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each dark green tablet contains inert ingredients.

ORTHO-CYCLEN® Regimen

Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each dark green tablet contains inert ingredients.

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 patient labeling 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 labeling is not a replacement for a careful discussion between you and your healthcare professional. You should discuss the information provided in this labeling with him or her, both when you first start taking the pill and during your revisits. You should also follow your healthcare professional's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES FOR CONTRACEPTION

Oral contraceptives or "birth control pills" or "the pill" are used to prevent pregnancy and are more effective than most other non-surgical methods of birth control. When they are

taken correctly without missing any pills, the chance of becoming pregnant is approximately 1% per year (1 pregnancy per 100 women per year of use). Typical failure rates, including women who do not always take the pill correctly, are approximately 5% per year (5 pregnancies per 100 women per year of use). The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

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

Implant: <1%	Male sterilization: <1%
Injection: <1%	Cervical Cap with spermicides: 20 to 40%
IUD: 1 to 2%	Condom alone (male): 14%
Diaphragm with spermicides: 20%	Condom alone (female): 21%
Spermicides alone: 26%	Periodic abstinence: 25%
Vaginal sponge: 20 to 40%	Withdrawal: 19%
Female sterilization: <1%	No methods: 85%

ORTHO TRI-CYCLEN® may also be taken to treat moderate acne if *all* of the following are true:

- You have started having menstrual cycles
- You are at least 15 years old
- Your healthcare professional says it is safe for you to use the pill
- You want to use the pill for birth control

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

> **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 are strongly advised not to smoke.**

Some women should not use the pill. For example, you should not take the pill if you have any of the following conditions:

- A history of heart attack or stroke
- 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 or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your healthcare professional)
- 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) or active liver disease
- Known or suspected pregnancy
- Valvular heart disease with complications
- Severe hypertension
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- Hypersensitivity to any component of this product

Tell your healthcare professional if you have had any of these conditions. Your healthcare professional can recommend a safer method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your healthcare professional if you have or have 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, 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 professional if they choose to use oral contraceptives.

Also, be sure to inform your healthcare professional 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 one of 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. 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 professional about stopping oral contraceptives 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 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.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills 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 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, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

5. Cancer of the Reproductive Organs and Breasts

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go back down. You should have regular breast examinations by a healthcare professional and examine your own breasts monthly. Tell your healthcare professional 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 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.

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.

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, ref. #35.

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 to 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 less than 40. Over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy in that age group. 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 do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking 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 progestogen that is compatible with the individual patient needs.

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your healthcare professional 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 professional 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

In addition to the risks and more serious side effects discussed above, the following may also occur:

1. Irregular 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 healthcare professional.

2. Contact Lenses

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

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 professional.

4. Melasma

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

5. Other Side Effects

Other side effects may include nausea and vomiting, change in appetite, 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 professional.

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 professional. 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 professional immediately to determine whether you are pregnant. Stop taking your pills 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 findings have not been seen in more recent studies. Nevertheless, oral contraceptives should not be used during pregnancy. You should check with your healthcare professional about risks to your unborn child of any medication taken during pregnancy.

2. While Breast Feeding

If you are breast feeding, consult your healthcare professional 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, combination oral contraceptives may decrease the amount and quality of your milk. If possible, do not use combination 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 combination oral contraceptives only after you have weaned your child completely.

3. Laboratory Tests

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

4. 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), topiramate (Topamax®), carbamazepine (Tegretol® is one brand of

this drug), or phenytoin (Dilantin® is one brand of this drug), phenylbutazone (Butazolidin® is one brand), certain drugs used in the treatment of HIV or AIDS, and possibly certain antibiotics. Medicine for pulmonary hypertension, such as bosentan (Tracleer®). Pregnancies and breakthrough bleeding have been reported by women who also used some form of the herbal supplement St. John's Wort while using combined hormonal contraceptives. Hormonal contraceptives may interact with lamotrigine (LAMICTAL®), an anticonvulsant used for epilepsy. This may increase the risk of seizures so your healthcare professional may need to adjust the dose of lamotrigine. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective. Be sure to tell your healthcare professional if you are taking or start taking any medications while taking birth control pills.

5. Sexually Transmitted Diseases

ORTHO-CYCLEN® and ORTHO TRI-CYCLEN® (like all oral contraceptives) are intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

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 feel sick to your stomach or have spotting or light bleeding, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your healthcare professional.
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, OR IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
   Use a back-up method (such as condoms or spermicide) until you check with your healthcare professional.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your healthcare professional 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 healthcare professional.

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" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" dark green pills (without hormones).
   ORTHO TRI-CYCLEN®: There are 7 white "active" pills, 7 light blue "active" pills, 7 blue "active" pills, and 7 dark green "reminder" pills.
   ORTHO-CYCLEN®: There are 21 blue "active" pills and 7 dark green "reminder" pills.
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills.

CHECK PICTURE OF PILL PACK AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE IN THE BRIEF SUMMARY PATIENT PACKAGE INSERT.

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 method in case you miss pills.
   AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. ORTHO TRI-CYCLEN® and ORTHO-CYCLEN® are available in the DIALPAK® Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your healthcare professional which is the best day for you. Pick a time of day which will be easy to remember.

Sunday Start:

ORTHO TRI-CYCLEN®: Take the first white "active" 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.

ORTHO-CYCLEN®: Take the first blue "active" 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.

Use another method of birth control such as condoms or spermicide as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

Day 1 Start:

ORTHO TRI-CYCLEN®: Take the first white "active" pill of the first pack during the first 24 hours of your period.

ORTHO-CYCLEN®: Take the first blue "active" pill of the first pack during the first 24 hours of your period.

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.

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:**
   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

ORTHO TRI-CYCLEN®:

If you **MISS 1** white, light blue, or blue "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 or light blue "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 in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3RD WEEK**:

1. **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.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack 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 professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** white, light blue or blue "active" pills in a row (during the first 3 weeks):

1. **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.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack 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 professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

ORTHO-CYCLEN®:

If you **MISS 1** blue "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** blue "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 in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

If you **MISS 2** blue "active" pills in a row in **THE 3RD WEEK**:

1. **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.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack 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 professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** blue "active" pills in a row (during the first 3 weeks):

1. **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.
   If you are a Day 1 Starter:
   THROW OUT the rest of the pill pack and start a new pack 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 professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up method for those 7 days.

A REMINDER:

If you forget any of the 7 dark green "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.

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 healthcare professional.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately 5%, including women who do not always take the pills exactly as directed. If failure does occur, the risk to the fetus is minimal.

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 healthcare professional or pharmacist.

OTHER INFORMATION

Your healthcare professional 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 professional 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 professional 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 professional, because this is a time to determine if there are 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 combination 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
- 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 professional or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The professional labeling is also published in a book entitled *Physicians' Desk Reference,* available in many book stores and public libraries.

Keep out of reach of children.

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

Protect from light.

ORTHO WOMEN'S HEALTH & UROLOGY™
DIVISION OF ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC.

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