CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-653/S-017 & 19-697/S-012

Trade Name: Ortho-Cyclen 0.25mg/0.035mg

Ortho Tri-Cyclen 0.18mg/0.035mg, 0.215mg/0.035mg, 0.25mg/0.035mg

Generic Name: norgestimate/ethinyl estradiol tablets

Sponsor: Johnson RW

Approval Date: 04/20/1998

Indications: Ortho-Cyclen & Ortho Tri-Cyclen: For the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Ortho Tri-Cyclen: For the treatment of moderate acne vulgaris in females, greater than or equal to 15 years of age, who have no known contradictions to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-017 & 19-697/S-012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-017 & 19-697/S-012

APPROVAL LETTER

ORIGINAL APR 20 1998

NDA 19-653/S-017
NDA 19-697/S-012

The R.W. Johnson Pharmaceutical Research Institute
Attention: Ms. Isabel Drzewiecki
Senior Director, Regulatory Affairs
Route 202 South, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Drzewiecki:

Please refer to your supplemental new drug applications dated June 13, 1996, received June 14, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

ORTHO-CYCLEN (NDA 19-653); and
ORTHO TRI-CYCLEN (NDA 19-697)
(norgestimate/ethinyl estradiol) Tablets

We also refer to your submissions dated November 3, 1997, in which you respond to our approvable letter dated July 15, 1997.

These supplemental applications provide for the following labeling changes:

Prescribing Information

The order of the two products listed in the labeling has been changed such that Ortho-Tri Cyclen now appears before Ortho Cyclen.

CLINICAL PHARMACOLOGY section

"**Acne**" subsection,

This subsection has been added with the approval of acne as an indication on December 31, 1996. This section reads:

"Acne is a skin condition with a multifactorial etiology. The combination of ethinyl estradiol and norgestimate may increase sex hormone binding globulin (SHBG) and decrease free testosterone resulting in a decrease in the severity of facial acne in otherwise healthy women with this skin condition."

INDICATIONS AND USAGE section

A new second paragraph has been added with the approval of the acne indication which reads:

"Ortho Tri-Cyclen is indicated for the treatment of moderate acne vulgaris in females, ≥15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications."

WARNINGS section

"**1. Thromboembolic Disorders and Other Vascular Problems**" subsection

"*a. Myocardial Infarction*" subheading, the final paragraph has been revised to read:

> "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)."

"**3. Carcinoma of the Breast and Reproductive Organs**" subsection

A new second paragraph has been added that reads:

> "A meta-analysis of 54 studies reports that women who are currently using combined oral contraceptives or have used them in the past 10 years are at slightly increased risk of having breast cancer diagnosed although the additional cancers tend to be localized to the breast. There is no evidence of an increased risk of having breast cancer diagnosed 10 or more years after cessation of use."

Additionally, in this same section the first sentence of the last paragraph has been revised to delete the word "intraepithelial" from the phrase "cervical intraepithelial neoplasia."

[redacted]

Detailed Patient Labeling

[redacted]

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated November 3, 1997, with the revisions listed below. Accordingly, the supplemental application is approved. The revisions are as follows:

Prescribing Information

INDICATIONS AND USAGE section

Table 1 should be updated to the 1998 Trussell table, a copy is enclosed for your reference.

WARNINGS section

"1. Thromboembolic Disorders and Other Vascular Problems" subsection

"a. Myocardial Infarction" subheading, the final paragraph should be unbolded.

"3. Carcinoma of the Breast and Reproductive Organs" subsection

The new second paragraph should be revised to the read:

"A meta-analysis of 54 studies [redacted]

Additionally, in this same section the first sentence of the last paragraph, return the word "intraepithelial" to the phrase "cervical intraepithelial neoplasia".

[redacted]

These revisions are terms of the supplemental approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 19-653/S-017 and NDA 19-697/S-012. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Christina Kish, Project Manager, at (301) 827-4260.

Sincerely,

4/13/98

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-580/RBennett/MMann
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)
HFD-580/CKish/4.9.98/n19653ap.s17
concurrence:RBennett 4.13.98/LRarick 4.13.98

SUPPLEMENT APPROVAL (S/AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-017 & 19-697/S-012

APPROVABLE LETTER

ORIGINAL

NDA 19-653/S-017
NDA 19-697/S-012

JUL 15 1997

The R.W. Johnson Pharmaceutical Research Institute
Attention: Ms. Isabel Drzewiecki
Senior Director, Regulatory Affairs
Route 202 South, P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Drzewiecki:

Please refer to your supplemental new drug applications dated June 13, 1996, received June 14, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

ORTHO-CYCLEN (NDA 19-653); and
ORTHO TRI-CYCLEN (NDA 19-697)
(norgestimate/ethinyl estradiol) Tablets

These supplemental applications provide for the following labeling change to the Physician Package Insert, **WARNINGS** section, **"Thromboembolic Disorders and Other Vascular Problems"** subsection, **"a. Myocardial Infarction"** heading, new last paragraph:

"Norgestimate has minimal androgenic activity (see **CLINICAL PHARMACOLOGY**), and there is some evidence that the risk of myocardial infarction [ ] [ ]

We have completed the review of this supplemental application as submitted with draft labeling, and it is approvable with the following revisions. Before this application may be approved, it will be necessary for you to submit final printed labeling (FPL) revised as follows:

1. Revise the proposed paragraph listed above to read:

   "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." (Sponsor provide Spitzer reference).

2. Remove from both the Patient and Physician Package Inserts, [ ] [ ] section the claim of [ ] [ ], which is not currently part of the class labeling for oral contraceptives.

Please submit 20 copies of the printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Christina Kish, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

7-11-97

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Orig. NDA
HFD-580
HFD-92/DDM-DIAB
HFD-40/DDMAC (with draft labeling)
DISTRICT OFFICE
HFD-580/RBennett/HJolson/LRarick
HFD-580/CKish/6.26.97/n19653ae.s17
concurrence:LPauls 6.26.97/RBennett 6.27.97/HJolson 7.10.97

SUPPLEMENT APPROVABLE (S/AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-017 & 19-697/S-012

LABELING

Component #635-50-900-4

APPROVED

APR 20 1998

PHYSICIANS' PACKAGE INSERT

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.

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 ☐ 21 Tablets and ORTHO TRI-CYCLEN ☐ 28 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 lactose, magnesium stearate, and pregelatinized starch.

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, lactose, magnesium stearate, and pregelatinized starch.

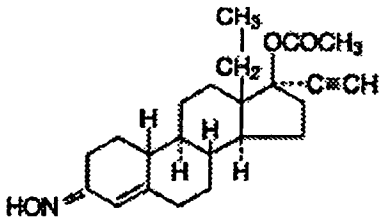
Each blue tablet contains 0.250 mg of the progestational compound norgestimate (18,19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch.

Each green tablet in the ORTHO TRI-CYCLEN ☐ 28 package contains only inert ingredients, as follows: D & C Yellow No. 10 Aluminum Lake, FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose and pregelatinized starch.

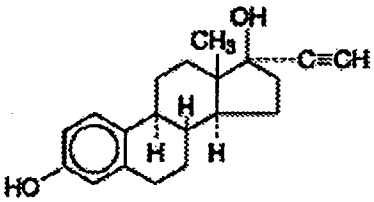
ORTHO-CYCLEN ☐ 21 Tablets and ORTHO-CYCLEN ☐ 28 Tablets.

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, lactose, magnesium stearate, and pregelatinized starch.

Each green tablet in the ORTHO-CYCLEN ☐ 28 package contains only inert ingredients, as follows: D & C Yellow No. 10 Aluminum Lake, FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose and pregelatinized starch.



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. The combination of ethinyl estradiol and norgestimate may increase sex hormone binding globulin (SHBG) and decrease free testosterone resulting in a decrease in the severity of facial acne in otherwise healthy women with this skin condition.

Norgestimate and ethinyl estradiol are well absorbed following oral administration of ORTHO-CYCLEN and ORTHO TRI-CYCLEN. On the average, peak serum concentrations of norgestimate and ethinyl estradiol are observed within two hours (0.5-2.0 hr for norgestimate and 0.75-3.0 hr for ethinyl estradiol) after administration followed by a rapid decline due to distribution and elimination. Although norgestimate serum concentrations following single or multiple dosing were generally below assay detection within 5 hours, a major norgestimate serum metabolite, 17-deacetyl norgestimate, (which exhibits a serum half-life ranging from 12 to 30 hours) appears rapidly in serum with concentrations greatly exceeding that of norgestimate. The 17-deacetylated metabolite is pharmacologically active and the pharmacologic profile is similar to that of norgestimate. The elimination half-life of ethinyl estradiol ranged from approximately 6 to 14 hours.

Both norgestimate and ethinyl estradiol are extensively metabolized and 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. Ethinyl estradiol is metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

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, ≥15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications.

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

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

Method	% of Women Experiencing an Accidental Pregnancy in the First Year of Continuous Use: Lowest Expected*	Typical**
(No Contraceptive)	(85)	(85)
Oral contraceptives		3
combined	0.1	N/A***
progestin only	0.5	N/A***
Diaphragm with spermicidal cream or jelly	6	18
Spermicides alone (foam, creams, gels, jellies, vaginal suppositories, and vaginal film)	6	21
Vaginal sponge		
nulliparous	9	18
parous	20	36
Implant	0.09	0.09
Injection: depot medroxyprogesterone acetate	0.3	0.3
IUD		
progesterone	1.5	2.0
copper T 380A	0.6	0.8
Condom without spermicides		
female	5	21
male	3	12
Cervical Cap with spermicidal cream or jelly		
nulliparous	9	18
parous	26	36
Periodic abstinence (all methods)	1-9	20
Female sterilization	0.4	0.4
Male sterilization	0.10	0.15

Adapted from RA Hatcher et al, Table 5-2, (1994) ref. #1.

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

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

*** N/A - Data not available

In clinical trials with ORTHO-CYCLEN, 1,651 subjects completed 24,272 cycles and a total of 18 pregnancies were reported. This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 0.96 per 100 women-years. This rate includes patients who did not take the drug correctly.

In four clinical trials with ORTHO TRI-CYCLEN, the use-efficacy pregnancy rate ranged from 0.68 to 1.47 per 100 women-years. In total, 4,756 subjects completed 45,244 cycles and a total of 42 pregnancies were reported. This represents an overall use-efficacy rate of 1.21 per 100 women-years. One of these 4 studies was a randomized comparative clinical trial in which 4,633 subjects completed 22,312 cycles. Of the 2,312 patients on ORTHO TRI-CYCLEN, 8 pregnancies were reported. This represents an overall use-efficacy pregnancy rate of 0.94 per 100 women-years.

In two double-blind, placebo-controlled, six month, multicenter clinical trials, ORTHO TRI-CYCLEN showed a statistically significant decrease in inflammatory lesion count and total lesion count (Table II). The adverse reaction profile of ORTHO TRI-CYCLEN from these two controlled clinical trials is consistent with what has been noted from previous studies involving ORTHO TRI-CYCLEN and are the known risks associated with oral contraceptives.

Table II: Acne Vulgaris Indication
Combined Results: Two Multicenter, Placebo-Controlled Trials
Primary Efficacy Variables: Evaluable-for-Efficacy Population

	ORTHO TRI-CYCLEN®	Placebo
	N = 163	N = 161
Mean Age at Enrollment	27.3 years	28.0
Inflammatory Lesions Mean Percent Reduction	56.6	36.6
Total Lesions Mean Percent Reduction	49.6	30.3

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
- Known or suspected carcinoma of the breast
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Cholestatic jaundice of pregnancy or jaundice with prior pill use
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy

WARNINGS

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

The use of oral contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia, 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 among women who use oral contraceptives.

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

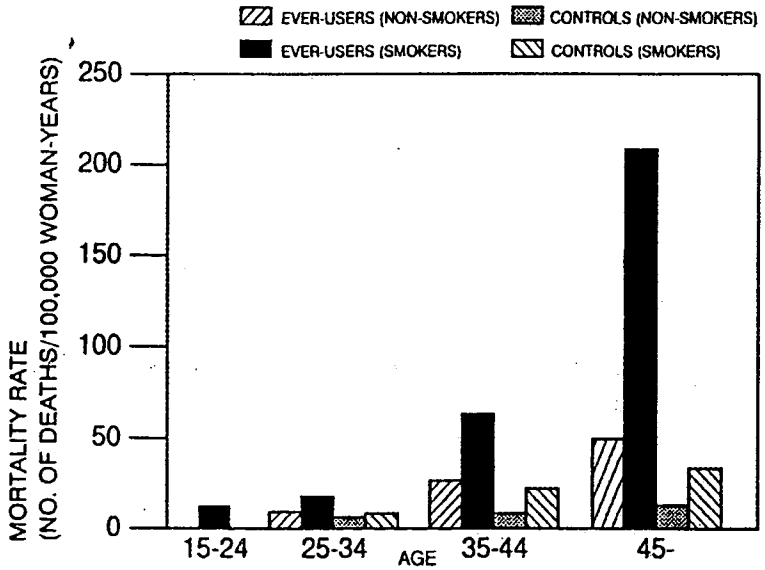


TABLE III. (Adapted from P.M. Layde and V. Beral, ref. #12.)

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). revised as requested weeks ago

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 or four weeks after a second trimester abortion.

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 0.035 mg or less of estrogen.

e.Persistence of risk of vascular disease

There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 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. While there are conflicting reports, most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk has been reported to be related to duration of use (36-44,79-89).

A meta-analysis of 54 studies reports that women who are currently using combined oral contraceptives or have used them in the past 10 years are at a slightly increased risk of having breast cancer diagnosed although the additional cancers tend to be localized to the breast. There is no evidence of an increased risk of having breast cancer diagnosed 10 or more years after cessation of use. (95)

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical 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.

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 have shown an increased risk of developing hepatocellular carcinoma (52-54, 96) in oral contraceptive users. However, these cancers are rare in the U.S.

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 before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

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

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.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.

2.LIPID DISORDERS

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

3.LIVER FUNCTION

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

4.FLUID RETENTION

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

5.EMOTIONAL DISORDERS

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

6.CONTACT LENSES

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

7.DRUG INTERACTIONS

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, carbamazepine, and possibly with griseofulvin, ampicillin and tetracyclines (72).

8.INTERACTIONS WITH LABORATORY TESTS

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

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

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

c.Other binding proteins may be elevated in serum.

d.Sex 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.High-density lipoprotein (HDL-C) and total cholesterol (Total-C) may be increased, low-density lipoprotein (LDL-C) may be increased or decreased, while LDL-C/HDL-C ratio may be decreased and triglycerides may be unchanged.

f.Glucose tolerance may be decreased.

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

9.CARCINOGENESIS

See WARNINGS Section.

10.PREGNANCY

Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS Sections.

11.NURSING MOTHERS

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

12.SEXUALLY TRANSMITTED DISEASES

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

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

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

•Nausea
•Vomiting
•Gastrointestinal symptoms (such as abdominal cramps and bloating)
•Breakthrough bleeding
•Spotting
•Change in menstrual flow
•Amenorrhea
•Temporary infertility after discontinuation of treatment
•Edema
•Melasma which may persist
•Breast changes: tenderness, enlargement, secretion

•Change in weight (increase or decrease)
•Change in cervical erosion and secretion
•Diminution in lactation when given immediately postpartum
•Cholestatic jaundice
•Migraine
•Rash (allergic)
•Mental depression
•Reduced tolerance to carbohydrates
•Vaginal candidiasis
•Change in corneal curvature (steepening)
•Intolerance to contact lenses

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

•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. 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.

21-Day Regimen (Sunday Start)

When taking ORTHO TRI-CYCLEN® 21 and ORTHO-CYCLEN® 21, the first tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first tablet is taken on that day. One tablet is taken daily for 21 days. For subsequent cycles, no tablets are taken for 7 days, then a tablet is taken 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 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).

21-Day Regimen (Day 1 Start)

The dosage of ORTHO TRI-CYCLEN® 21 and ORTHO-CYCLEN® 21, for the initial cycle of therapy is one 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". For subsequent cycles, no tablets are taken for 7 days, then a new course is started of one tablet a day for 21 days. The dosage regimen then continues with 7 days of no medication, followed by 21 days of medication, instituting a three-weeks-on, one-week-off dosage regimen.

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 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).

28-Day Regimen (Sunday Start)

When taking ORTHO TRI-CYCLEN® 28 and ORTHO-CYCLEN® 28 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 green 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 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).

28-Day Regimen (Day 1 Start)

The dosage of ORTHO TRI-CYCLEN® 28 and ORTHO-CYCLEN® 28, 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 green 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 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 FOR ALL DOSING REGIMENS

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 until pregnancy is ruled out.

2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

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 green tablet for 7 days. After 28 tablets have been taken, a new course is started the next day.

HOW SUPPLIED

ORTHO TRI-CYCLEN® 21 Tablets are available in a DIALPAK® Tablet Dispenser (NDC 0062-1902-15) containing 21 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.

The white tablets are unscored, with "Ortho" and "180" debossed on each side; the light blue tablets are unscored with "Ortho" and "215" debossed on each side; the blue tablets are unscored with "Ortho" and "250" debossed on each side.

ORTHO TRI-CYCLEN® 21 Tablets are available for clinic usage in a VERIDATE® Tablet Dispenser (unfilled) and VERIDATE Refills (NDC 0062-1902-20).

ORTHO TRI-CYCLEN® 28 Tablets are available in a DIALPAK® Tablet Dispenser (NDC 0062-1903-15) 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 green tablet contains inert ingredients.

The white tablets are unscored, with "Ortho" and "180" debossed on each side; the light blue tablets are unscored with "Ortho" and "215" debossed on each side; the blue tablets are unscored with "Ortho" and "250" debossed on each side.

ORTHO TRI-CYCLEN® 28 Tablets are available for clinic usage in a VERIDATE® Tablet Dispenser (unfilled) and VERIDATE Refills (NDC 0062-1903-20).

ORTHO-CYCLEN® 21 Tablets are available in a DIALPAK® Tablet Dispenser (NDC 0062-1900-15) containing 21 tablets. Each blue tablet contains 0.250 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol which are unscored with "Ortho" and "250" debossed on each side.

ORTHO-CYCLEN® 21 Tablets are available for clinic usage in a VERIDATE® Tablet Dispenser (unfilled) and VERIDATE Refills (NDC 0062-1900-20).

ORTHO-CYCLEN® 28 Tablets are available in a DIALPAK® Tablet Dispenser (NDC 0062-1901-15) containing 28 tablets as follows: 21 blue tablets as described under ORTHO-CYCLEN 21 Tablets, and 7 green tablets containing inert ingredients.

ORTHO-CYCLEN® 28 Tablets are available for clinic usage in a VERIDATE® Tablet Dispenser (unfilled) and VERIDATE Refills (NDC 0062-1901-20).

Caution: Federal law prohibits dispensing without prescription.

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BRIEF SUMMARY PATIENT PACKAGE INSERT

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

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be 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 doctor or health care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anti-convulsants and some antibiotics may decrease oral contraceptive effectiveness.

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. 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 pills 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 health care provider. Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. Your pharmacist should have given you the detailed patient information labeling which gives you further information which you should read and discuss with your health care provider.

ORTHO-CYCLEN and ORTHO TRI-CYCLEN (like all oral contraceptives) are intended to prevent pregnancy. ORTHO TRI-CYCLEN is also used to treat moderate acne in females who are able to take oral contraceptives. 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.

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.

ORTHO TRI-CYCLEN ☐ 21 Day Regimen and
ORTHO TRI-CYCLEN ☐ 28 Day 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 green tablet in the ORTHO TRI-CYCLEN ☐ 28 Day Regimen contains inert ingredients.

ORTHO-CYCLEN ☐ 21 Day Regimen and
ORTHO-CYCLEN ☐ 28 Day Regimen

Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each green tablet in ORTHO-CYCLEN ☐ 28 Day Regimen 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 health care provider. 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 health care provider'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 other non-surgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. 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%
Injection: <1%
IUD: 1 to 2%
Diaphragm with spermicides: 18%
Spermicides alone: 21%
Vaginal sponge: 18 to 36%
Cervical Cap: 18 to 36%
Condom alone (male): 12%
Condom alone (female): 21%
Periodic abstinence: 20%
No methods: 85%

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 are pregnant or think you may be pregnant. You should also not use 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 doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

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

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health care provider 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, heart or kidney disease
- History of scanty or irregular menstrual periods

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

Also, be sure to inform your doctor or health care provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of developing blood clots

Blood clots and blockage of blood vessels are 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 have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor 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 or four weeks after a second trimester abortion. 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

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer.

An analysis of 54 studies reports that women who are currently using combined oral contraceptives or have used them in the past 10 years are at a slightly increased risk of having breast cancer diagnosed although the additional cancers tend to be localized to the breast. There is no evidence of an increased risk of having breast cancer diagnosed 10 or more years after stopping use.

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 pills 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 (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceed 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.

WARNING SIGNALS

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

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

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. Vaginal bleeding

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

2. Contact lenses

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

3. Fluid retention

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

4. Melasma

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

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

GENERAL PRECAUTIONS

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

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

are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

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

2. While breast feeding

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

3. Laboratory tests

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

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), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually transmitted diseases

ORTHO-CYCLEN and ORTHO TRI-CYCLEN (like all oral contraceptives) are intended to prevent pregnancy. ORTHO TRI-CYCLEN is also used to treat moderate acne in females who are able to take oral contraceptives. 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, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
   On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.
   Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
   It is important to take it at about the same time every day.

2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:
   The 21-pill pack has 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week without pills.

   The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" green pills (without hormones).

   ORTHO TRI-CYCLEN: There are 7 white "active" pills, 7 light blue "active" pills, and 7 blue "active" pills.

   ORTHO-CYCLEN: There are 21 blue "active" 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, foam, or sponge) 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 doctor or clinic 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 "active" white pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

ORTHO-CYCLEN: Take the first "active" blue 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 as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:

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

ORTHO-CYCLEN: Take the first "active" blue 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:**

   21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.

   28 pills: Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

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 MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up 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 doctor or clinic because you might be pregnant.

3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up 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 doctor or clinic because you might be pregnant.

3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up 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 MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up 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 doctor or clinic because you might be pregnant.

3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up 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 doctor or clinic because you might be pregnant.

3. You MAY BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:
If you forget any of the 7 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 doctor or clinic.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are about 3%. 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 health care provider or pharmacist.

OTHER INFORMATION

Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your health care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health care provider, because this is a time to determine if there are 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 doctor/health care provider 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.

ORTHO PHARMACEUTICAL
CORPORATION
Raritan, New Jersey 08869

Revised July 1997

635-50-900-4

a:\63550900.4/44

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-017 & 19-697/S-012

MEDICAL REVIEW(S)

JUN 16 1997

ORIGINAL

NDA 19-653/SLR-017
Ortho-Cyclen

NDA 19-697/SLR-012
Ortho Tri-Cyclen

The R.W. Johnson Pharmaceutical
Research Institute

Medical Officer's Review of Revised Draft Labeling
Dated June 13, 1997

Background: The Division of Metabolism and Endocrine Drug Products wrote the sponsor of Orthocept (desogestrel and ethinyl estradiol) tablets March 26, 1996. The letter stated in part:

> We have recently reviewed the article entitled (Lewis M.A., Spitzer W.O., Heinemann L.A.J., et. al., "Third Generation Oral Contraceptives and Risk of Myocardial Infarction: an International Case-Controlled Study" BMJ, 1996; 312:88-90) and believe that the following statement would be appropriate for your physician insert. This change may be made to your approved physician insert at your option.
>
> In the Physicians insert, WARNINGS section, "Thromboembolic Disorders and Other Vascular Problems" subsection, "a. Myocardial Infarction" heading, following the last paragraph add:
>
> "Desogestrel 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". (Sponsor provide Spitzer reference).

Final printed labeling for Orthocept was revised in August, 1996 exactly as suggested as above.

Current Submission: The sponsor feels that the revision described above is also relevant to Ortho-Cyclen and Ortho Tri-Cyclen because of the minimal androgenic activity of norgestimate, the progestogen present in Ortho-Cyclen and Ortho Tri-Cyclen. The sponsor wishes to add the following to the Ortho-Cyclen and Ortho Tri-Cyclen combined PHYSICIANS INSERT WARNINGS section, "Thromboembolic Disorders and Other Vascular Problems" subsection, "a. Myocardial Infarction" heading, following the last paragraph:

> "Norgestimate has minimal androgenic activity (see CLINICAL PHARMACOLOGY), and there is some evidence that the risk of myocardial infarction [ ]

Comment and Recommendation: Since norgestimate has minimal intrinsic androgenicity, the sponsor may revise the labeling for Ortho-Cyclen and Ortho Tri-Cyclen, but it is recommended that the exact wording incorporated into the Orthocept labeling be incorporated into the labeling for Ortho-Cyclen and Ortho Tri-Cyclen.

It is noted that the sponsor has also added "[ ]" to the list of "[ ] [ ]." It is recommended that the sponsor also remove this statement from the physician and patient labeling as it is not incorporated into class labeling for oral contraceptives.

Ridgely C. Bennett 6/5/97
Ridgely C. Bennett, M.D., M.P.H.

agree Marcellus
6/16/97

ORIGINAL MAR 23 1998

NDA 19-653
Ortho Cyclen (S017)
NDA 19-697
Ortho Tri-Cyclen (S012)
The R.W. Johnson Pharmaceutical Research Institute

March 16, 1998

Medical Officer's Review of Draft Labeling Dated Nov. 3, 1997

Background:
This draft labeling contains four groups of revisions:

1. Changes to the labeling that were submitted to NDA 20-681 for Ortho Tri-Cyclen Tablets for acne and approved by the Division of Dermatologic and Dental Drug Products on December 31, 1996.
2. An editorial change with regard to the order of appearance of these two products in the labeling. Ortho Tri-Cyclen now appears first in the text followed by Ortho-Cyclen.
3. Changes to the labeling as requested in our approval letter to the sponsor July 15, 1997 regarding the warning concerning myocardial infarction and our request to the sponsor to remove "[ ]" from the [ ] [ ] section. (Please refer to Attachment 1.)
4. Changes to the labeling concerning breast and [ ] cancers. These changes were previously submitted to NDA 16-954 (S-083) for Micronor where they were reviewed and an approval to the sponsor issued November 25, 1997 which requested three revisions. (Please refer to Attachment 2.)

Review and Comments:
Revisions mentioned under Background points 1,2, and 3 are acceptable. Revisions mentioned under Background point 4 are acceptable except as follows:

Physician's Package Insert

1. In the INDICATIONS AND USAGE section, Table 1 should be updated to the 1998 Trussell table.
2. In Warning number 1a. the bold lettering of the last paragraph should be unbolded.
3. In Warning number 3, "cervical intraepithelial neoplasia" is preferable to "cervical neoplasia".
4. [ ]

Recommendation:
Approval with the above requested revisions.

Ridgely C. Bennett

Ridgely C. Bennett, MD, MPH

Agree Marcellus
3/23/17

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-653/S-017 & 19-697/S-012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

NDA SUPP AMEND
SUR-018 BL

NOV. 0 3 1997

Lisa Rarick, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II, HFD-580
Attn: Document Control Room
5600 Fishers Lane
Rockville, MD 20857-1706

NDA 19-653 (S017)
ORTHO-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Please Cross refer to:

NDA 19-697 (S012)
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS | DATE 9/17/97

AMENDMENT TO SUPPLEMENT
DRAFT LABELING

Dear Dr. Rarick:

Reference is made to our approved New Drug Applications 19-653 and 19-697 for ORTHO-CYCLEN and ORTHO TRI-CYCLEN Tablets, respectively, and more specifically to our June 13, 1996 labeling supplement which provided for changes to our Physicians Insert regarding the risk of myocardial infarction with oral contraceptives containing progestogens with minimal androgenic activity. Further reference is made to the approvable letter received from the Agency dated July 15, 1997 requesting that we revise the text of the draft labeling as follows:

1. **WARNINGS** section, "**Thromboembolic Disorders and Other Vascular Problems**" subsection, "**a. Myocardial Infarction**" heading, new last paragraph:

   "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." (Sponsor provide Spitzer reference.)

2. Remove from both the Patient and Physician Package Inserts, [ ] section the claim of [ ], which is not currently part of the class labeling for oral contraceptives.

We wish to note that we were aware that we had inadvertently included the claim of [ ] in the draft labeling submitted on June 13, 1996. We had discussed this error with Ms. Christina Kish of your Division on October 11, 1996 and provided assurance at that time that the change had never been implemented and that the information would be deleted from the draft labeling.

At this time, we are amending this supplement to provide draft labeling which has been revised to incorporate the changes requested in the Agency's letter. In addition, the draft labeling contains the following revisions which had been previously submitted. These revisions were made after the submission of June 13, 1996 and prior to this submission:

- Changes to the labeling that were submitted to NDA 20-681 for ORTHO TRI-CYCLEN® Tablets for acne and approved by the Division of Dermatologic and Dental Drug Products on December 31, 1996.

- An editorial change was made with regard to the order of appearance of our products, i.e. ORTHO TRI-CYCLEN® now appears first in the text followed by ORTHO-CYCLEN®.

- Updated breast and [ ] information as provided in our June 12, 1997 Special Supplement - Changes Being Effected for this product and June 23, 1997 Special Supplement for NDA 19-697, ORTHO TRI-CYCLEN. Similar changes for our norethindrone-only containing product, MICRONOR®, NDA 16-954, were the topic of a teleconference held with the Agency on August 1, 1997. We are awaiting information from the Agency regarding their recommendations for modifications to the WARNINGS sections which we had submitted. Once these comments are received, they will be incorporated into the labeling.

With respect to the Agency's request that we submit final printed labeling, we wish to advise the Agency that final printed labeling is not available at this time. We, therefore, are providing draft labeling with this submission and will submit final printed labeling as soon as it becomes available.

If you have any questions, please do not hesitate to contact me directly at (908) 218-6140, or at (908) 704-4600, our number designated only for FDA use.

Sincerely,

The R. W. Johnson
Pharmaceutical Research Institute

Donna Panasewicz
Manager
Regulatory Affairs

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JUN 2 8 1996

NDA No. 19-697

THE R.W. JOHNSON PHARMACEUTICAL RESEARCH
INSTITUTE
Division of Ortho Pharmaceutical Corporation
U.S. Route 202, P.O. Box 300
Raritan, New Jersey 08869-0602

Attention: Isabel Drzewieki, Senior Director, Regulatory Affairs

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: ORTHO TRI-CYCLEN(Norgestimate + Ethinyl Estradiol)

NDA Number: 19-697

Supplement Number: S-012

Date of Supplement: JUNE 13, 1996

Date of Receipt: JUNE 14, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on AUG 1 2 1996 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office Drug Evaluation II
Center for Drug Evaluation and Research

ORIGINAL

NEW SUPPLEMENT

NDA NO. 19697 012

NDA SUPPL NO. SLR

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE
ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602

JUN 13 1996

Solomon Sobel, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II, HFD-510
Attn: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857-1706

NDA 19-653
ORTHO-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

Please Cross Refer to:

NDA 19-697
ORTHO TRI-CYCLEN® Tablets
(norgestimate/ethinyl estradiol)

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED-DRAFT LABELING

CENTER FOR DRUG REC'D JUN 14 1996 HFD-510 EVALUATION AND RESEARCH

Dear Dr. Sobel,

Reference is made to our approved New Drug Applications for ORTHO-CYCLEN Tablets (NDA 19-653) and for ORTHO TRI-CYCLEN Tablets (NDA 19-697). Reference is also made to your March 26, 1996 letter (**Attachment I**) which provided for an optional labeling change to our approved ORTHO-CEPT® Tablets (NDA 20-301) Physicians Insert regarding the risk of myocardial infarction with oral contraceptives containing progestogens with minimal androgenic activity.

We have evaluated the suggested change to our ORTHO-CEPT Tablets Physicians Insert described in your March 26, 1996 letter and feel it is also relevant to our ORTHO-CYCLEN Tablets and ORTHO TRI-CYCLEN Tablets Physicians Insert. Therefore, we wish to add the following to the ORTHO-CYCLEN/ORTHO TRI-CYCLEN combined Physicians Insert Warnings section, "Thromboembolic Disorders and Other Vascular Problems" subsection, "a. Myocardial Infarction" heading, following the last paragraph:

> "Norgestimate has minimal androgenic activity (see Clinical Pharmacology), and there is some evidence that the risk of myocardial infarction[ ]
> [ ]

This statement is predicated on the minimal androgenic activity of the progestogen norgestimate. The most recent approved labeling for ORTHO-CYCLEN and ORTHO TRI-CYCLEN (S-012 and S-005 respectively, filed November 3, 1994, approved January 29, 1996, **Attachment II)** addresses this in the Clinical Pharmacology section, stating, "Receptor binding studies, as well as studies in animals and humans, have shown that

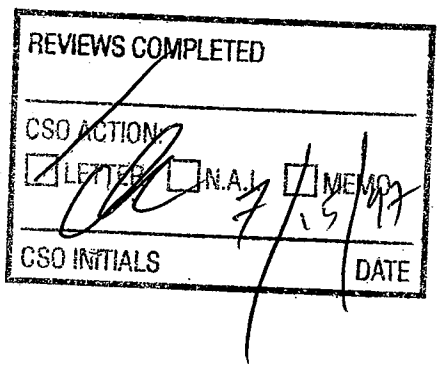
norgestimate and 17-deacetyl norgestimate, the major serum metabolite, combine high progestational activity with minimal intrinsic androgenicity (90-93). Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in sex hormone binding globulin (SHBG), resulting in lower serum testosterone (90,91,94)."

Additionally, in the "Precautions" section under subheading "8.d Interactions with Laboratory Tests", it states, "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." In subsection "e" it states, "High-density lipoprotein (HDL-C) and total cholesterol (Total-C) may be increased, low-density lipoprotein (LDL-C) may be increased or decreased, while LDL-C/HDL-C ratio may be decreased and triglycerides may be unchanged."

The addition of these approved changes makes our ORTHO-CYCLEN/ORTHO TRI-CYCLEN "Clinical Pharmacology" sections identical to that in the same section for ORTHO-CEPT Tablets, except for the name of the progestin. Final printed labeling containing these previously appproved changes is in the process of being printed. We will submit twenty copies of the final printed labeling as soon as it is available as requested in your January 29, 1996 approval letter.

We are also in the process of updating our labeling to provide for the additional change proposed in this letter (**Attachment III, page 6**) and plan to implement this change thirty (30) days from the date of this letter. Fifteen (15) copies of final printed labeling containing the additional paragraph, with ten (10) mounted on heavy weight paper, will be submitted when available as requested in your March 26, 1996 letter for ORTHO-CEPT.

Should you have any questions, you may contact me directly at (908) 218-6140 or at (908) 704-4600, our number designated for FDA use only.



Sincerely,

The R.W. Johnson
Pharmaceutical Research Institute

p.p. Isabel Drzewiecki

Isabel Drzewiecki
Senior Director
Regulatory Affairs

Attachments