

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-653/S-027 & 19-697/S-024

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: 01/16/2001

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.

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APPROVAL LETTER



NDA 19-653/S-027
NDA 19-697/S-024

R.W. Johnson Pharmaceutical and Research Institute
Attention: William R. Sisco
Associate Director, Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

Dear Mr. Sisco:

Please refer to your supplemental new drug applications dated July 18, 2000, received July 19, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ORTHO-CYCLEN® (norgestimate/ethinyl estradiol) Tablets, ORTHO TRI-CYCLEN® (norgestimate/ethinyl estradiol) Tablets.

These "Changes Being Effected" supplemental new drug applications provide for revisions to the graphics and wording for points 4 and 5 of the "Instructions for using your Diapak® Tablet Dispenser" section of the Detailed Patient Labeling/Brief Summary Patient Package Insert, approved on November 22, 1999.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (patient package insert submitted July 18, 2000). Accordingly, these supplemental applications are approved effective on the date of this letter.

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is 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 20857

Please submit one market package of the drug product when it is available.

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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, call Jennifer Mercier, B.S., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Susan Allen

1/16/01 01:38:57 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-653/S-027 & 19-697/S-024

LABELING

DETAILED PATIENT LABELING

ORTHO TRI-CYCLEN® ORTHO-CYCLEN® 21/28 Day Regimen (norgestimate/ethinyl estradiol)

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

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 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%
IUD:	1 to 2%
Diaphragm with spermicides:	20%
Spermicides alone:	26%
Vaginal sponge:	20 to 40%
Female sterilization:	<1%
Male sterilization:	<1%
Cervical Cap with spermicides:	20 to 40%
Condom alone (male):	14%
Condom alone (female):	21%
Periodic abstinence:	25%
Withdrawal:	19%
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 CONTRAINDICATIONS 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 or physical illness
 - 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 vessels 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 to two 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 if you are not breast feeding or for two weeks after second trimester abortion. If you are breast feeding, you should not use oral contraceptives 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. A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of 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 CONTRACEPTION PER 100,000 MONSTERLE WOMEN, BY FERTILITY CONTROL METHOD, ACCORDING TO AGE	15-19		20-24		25-29		30-34		35-39		40-44	
	Method of control	Age	Method of control	Age	Method of control	Age	Method of control	Age	Method of control	Age	Method of control	Age
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 birth-related

In the above table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeded 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)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or faintness 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 the breast, ask your doctor or health care provider)

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

3. Laboratory tests

If you are scheduled for any laboratory tests, tell your 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

See reverse side for additional information.

DETAILED PATIENT LABELING (continued)

increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), anticonvulsants such as carbamazepine (Fegretol 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-TRICYCLLEN 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:**
Before you start taking your pills.
1. BE SURE TO READ THESE DIRECTIONS: Anyone 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).
3. ALSO FIND:
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.
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 DIAL PACK® 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. 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:

1. If you miss 1 white, light blue, or blue "active" pill: 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 or more "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:** Keep taking 1 pill every day until Sunday. On Sunday, 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:** Keep taking 1 pill every day until Sunday. On Sunday, 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.

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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.

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2. Then take 1 pill a day until you finish the pack.

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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:** Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pill pack and start a new pack that same day.

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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 are breast fed and the health care provider believes that it is a good clinical 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

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.

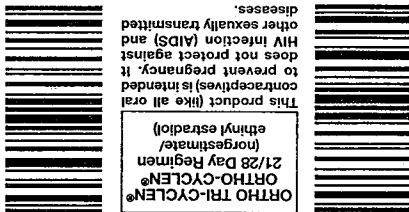
If you want more information about birth control pills, ask your doctor/health care provider or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read. The Professional Labeling also published in a book entitled *Physicians' Desk Reference*, available in many book stores and public libraries.

ORTHO-McNEIL

ORTHO-McNEIL PHARMACEUTICAL, INC.
Raritan, New Jersey 08869

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REVISED APRIL 2000 640-50-9003



Ortho Tri-Cylen
Ortho-Cylen
21/28 Day Regimen
(norgestimate/
ethinyl estradiol)

69-09-05-09



**ORTHO TRI-CYLEN® 21/28 Day Regimen
ORTHO-CYLEN® 21/28 Day Regimen
(norgestimate/ethinyl estradiol)**

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

ORTHO TRI-CYLEN® 21/28 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 contains inert ingredients. (Note: refills with 21 pills do not contain green tablets.)

ORTHO-CYLEN® 21/28 Day Regimen: Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each green tablet contains inert ingredients. (Note: refills with 21 pills do not contain green tablets.)

**BRIEF SUMMARY
PATIENT PACKAGE INSERT**

Oral contraceptives, also known as "birth control pills" or "the pill," are taken to prevent pregnancy. ORTHO TRI-CYLEN 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 Patient Labeling. 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 anticonvulsants 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 that 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. The Detailed Patient Labeling gives you further information which you should read and discuss with your health care provider.

ORTHO TRI-CYLEN and ORTHO-CYLEN (like all oral contraceptives) are intended to prevent pregnancy. ORTHO TRI-CYLEN 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 backup 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).
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 ON REVERSE SIDE.

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

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. ORTHO TRI-CYLEN and ORTHO-CYLEN 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-CYLEN: 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-CYLEN: 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-CYLEN: Take the first "active" white pill of the first pack during the first 24 hours of your period.

ORTHO-CYLEN: 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 backup 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-CYLEN:

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 backup 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.

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

If you **MISS 2** 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 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. See reverse side for additional information.

Instructions for using your DIALPAK Tablet Dispenser on reverse side.

BRIEF SUMMARY PATIENT PACKAGE INSERT (continued)

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 backup for those 7 days.

ORTHO-CYCLER:

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 backup 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 backup 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 backup 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 backup 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 backup method.

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

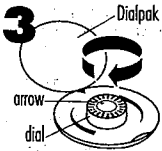
Use a **BACK-UP METHOD** anytime you have sex. **KEEP TAKING ONE "ACTIVE" PILL EACH DAY** until you can reach your doctor or clinic.

Instructions for using your Dialpak® Tablet Dispenser Please Read Me!

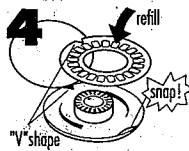
- Sunday Start
- or
- Day 1 Start

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

Save these instructions.



SET THE DAY:
 Sunday Start: the arrow on your empty Dialpak should point to SU (Sunday).
 Day 1 Start: turn the dial on your empty Dialpak until the arrow points to the first day of your period (if your period starts on Tuesday, the arrow will point to TU).



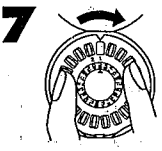
Insert the new refill by lining up the "V" shape on the refill with the "V" shape at the top of your Dialpak. Snap the refill in place. You are ready to take pill "1." You should always begin your pill cycle with pill "1," as shown on the inner part of the refill ring.



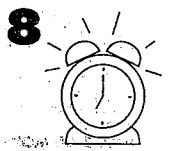
Remove pill "1" by pushing down on the pill. The pill will come out through a hole in the back of the Dialpak.



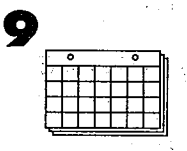
Swallow the pill. You will take one pill each day. If you use a Sunday Start and you are taking the pill for the **FIRST TIME**, YOU **MUST USE A BACK-UP METHOD OF BIRTH CONTROL FOR THE FIRST 7 DAYS**. If you use a Day 1 Start, you are protected from becoming pregnant as soon as you take your first pill.



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



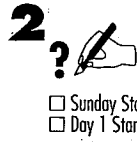
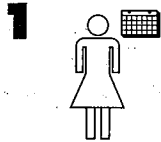
Take your pill at the same time every day. It is important to take the correct pill each day and not miss any pills. To help you remember, take your pill at the same time as another daily activity, like turning off your alarm clock or brushing your teeth.



When your refill is empty, keep your Dialpak case.
 • If your refill contained 21 pills, you will not take a pill on days 22 through 28, you must start a new refill on the day following day 28.
 • If your refill contained 28 pills, you will start a new refill on the day after pill "28."



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



- Sunday Start
- Day 1 Start

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

When you get your period:

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

If you miss one pill... take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in one day. You will not need a back-up method of birth control if you have sex.

If you miss two or more pills in a row... YOU **MAY BECOME PREGNANT** if you have sex during the next 7 days! YOU **MUST USE A BACK-UP METHOD OF BIRTH CONTROL** (condoms, foam, or sponge) for those 7 days and follow the instructions below. **LOOK AT THE PILL NUMBERS ON YOUR REFILL** — the instructions below depend on which pills you miss, and if you used a Sunday Start or Day 1 Start.

Sunday Start

- If you miss **two pills** in a row of pills **1 through 14:** Take two pills as soon as you remember and two pills the next day, then keep taking one pill each day as usual.
- If you miss pills **14 and 15** or if you miss **two pills** in a row of pills **15 through 21** or if you miss **three** or more pills in a row of pills **1 through 21:** Keep taking one pill each day until Sunday. On Sunday, **THROW OUT** the rest of the pills and start a new refill.

Day 1 Start

- If you miss **two pills** in a row of pills **1 through 14:** Take two pills as soon as you remember and two pills the next day, then keep taking one pill each day as usual.
- If you miss pills **14 and 15** or if you miss **two pills** in a row of pills **15 through 21** or if you miss **three** or more pills in a row of pills **1 through 21:** **THROW OUT** the rest of the pills and start a new refill that day.

If you miss pills 22 through 28...

Some refills contain 21 pills and some contain 28 pills. If your refill contains 28 pills, remember that pills 22 through 28 are "reminder" pills and do not contain active ingredients.
 • If you miss any of pills 22 through 28, you will still be protected. *Throw away the missed pills and keep taking one pill each day until you finish the refill. Start a new refill on the day after pill "28."*

Side effects:

Some side effects are normal and will go away after the first 1, 2 or 3 months as your body gets used to the pill. For more information on side effects see the Brief Summary on the other side of this page, the Detailed Patient Information Labeling that came with your pills, or ask your health care provider or pharmacist.



ORTHO-McNEIL PHARMACEUTICAL, INC.
 Raritan, New Jersey 08869

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
19-653/S-027 & 19-697/S-024

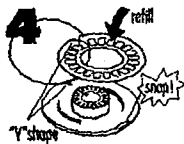
**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

NDA 19-653/S-027
ORTHO-CYCLEN® (norgestimate/ethinyl estradiol) Tablets
NDA 19-697/S-024
ORTHO TRI-CYCLEN® (norgestimate/ethinyl estradiol) Tablets

CSO Labeling Review

This supplement, the sponsor has made revisions to the “instructions for using your Dialpak® Tablets Dispenser” section of the insert.

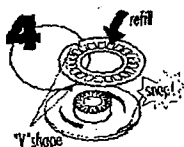
Original:



Insert the new refill by lining up the “V” shape on the refill with the “V” shape of the top of your Dialpak. Snap the refill in place. You are ready to take pill “1.”



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



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



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

Changed to above.

- The sponsor has updated the graphics and the instructions for points 4 and 5 of the instructions. This change was done to ensure better patient compliance and proper insertion of the refill ring.

Recommendation:

The changes are acceptable and should ensure better patient compliance and proper insertion of the refill ring.

Jennifer Mercier

Terri Rumble

Ridgely Bennett, M.D.

Dena Hixon, M.D.

Susan Allen, M.D.

/s/

Jennifer L. Mercier
1/16/01 11:13:21 AM
CSO

Labeling [patient]

Terri F. Rumble
1/16/01 12:54:05 PM
CSO

Ridgely C. Bennett
1/26/01 09:14:28 AM
MEDICAL OFFICER

Dena Hixon
1/26/01 11:53:59 AM
MEDICAL OFFICER

Susan Allen
1/26/01 02:37:52 PM
MEDICAL OFFICER

NDA 19-697/S-024

CBE-0 SUPPLEMENT

The R.W. Johnson Pharmaceutical Research Institute
Attention: William R. Sisco
Associate Director Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, NJ 08869-0602

JUL 31 2000

Dear Mr. Sisco:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: ORTHO TRI-CYCLEN (norgestimate/ethinyl estradiol) tablets

NDA Number: 19-697

Supplement Number: S-024

Date of Supplement: July 18, 2000

Date of Receipt: July 19, 2000

This supplemental application, submitted as a "Supplement - Changes Being Effected" supplement, proposes the following changes: revisions to the graphics and wording for points 4 and 5 of the "Instructions for using your Dialpak® Tablet Dispenser" section of the Detailed Patient Labeling/Brief Summary Patient Package Insert, approved on November 22, 1999.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 17, 2000 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

NDA 19-697/S024

Page 2

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble
for *Donnette Spell-lesane*
7/28/00

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 19-697/S024

Page 3

cc:

Archival NDA 19-653

HFD-580/Div. Files

HFD-580/Moore

HFD-580/Allen/Mann/Shames/Bennett

DISTRICT OFFICE

Drafted by: erf/July 26, 2000

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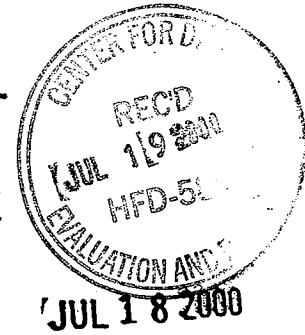
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CBE-30 SUPPLEMENT ACKNOWLEDGEMENT (AC)

ORIGINAL

THE R.W. JOHNSON
PHARMACEUTICAL RESEARCH INSTITUTE

ROUTE 202, P.O. BOX 300, RARITAN, NEW JERSEY 08869-0602



Susan Allen, M. D. Acting Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation III
Attn: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 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)

NDA NO. 19697 REF. NO. 024
NDA SUPPL FOR Labeling

CHANGES BEING EFFECTED
FINAL PRINTED LABELING

Dear Dr. Allen:

Reference is made to our approved New Drug Applications 19-653 and 19-697 for ORTHO-CYCLEN® and ORTHO TRI-CYCLEN® Tablets. At this time we are submitting a Changes Being Effected Final Printed Labeling supplement for the combination Detailed Patient Labeling/Brief Summary Patient Package Insert, which the Agency initially approved on November 22, 1999.

The changes made to this component are in the "Instructions for using your Dialpak® Tablet Dispenser" section of the insert. The graphics and wording for points 4 and 5 of this section have been revised to ensure better patient compliance and proper insertion of the refill ring.

At this time we are submitting 20 copies (12 on heavy-weight paper) of the Final Printed Labeling of the combination Detailed Patient Labeling and Brief Summary Patient Package Insert (component code 640-50-900-3) for ORTHO-CYCLEN® and ORTHO TRI-CYCLEN® Tablets

If you have any questions, please do not hesitate to contact me directly at (908) 704-4301 or at (908) 704-4600, our number designated only for FDA use.

Sincerely,

Deborah A. Sarau
for

William R. Sisco
Associate Director
Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
<input checked="" type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS <i>WRS</i> DATE <i>7/18/00</i>

Enclosures