

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-626

Name: Norgestimate and Ethinyl Estradiol Tablets,
0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and
0.25/0.035 mg, respectively, packaged in a
28-day Cycle Regimen

Sponsor: Watson Laboratories, Inc.

Approval Date: August 17, 2006

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CONTENTS

Reviews / Information Included in this Review
--

Approval Letter	X
Tentative Approval Letter(s)	
Approved Labeling	X
Labeling Review(s)	X
Medical Review(s)	
Chemistry Reviews	X
Bioequivalence Reviews	X
Statistical Review(s)	
Microbiology Review(s)	
Administrative Documents	X
Correspondence	X

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APPROVAL LETTER

AUG 17 2006

Watson Laboratories, Inc.
Attention: Janie M. Gwinn
Associate Director of Regulatory Affairs
311 Bonnie Circle
Corona, CA 92880

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 30, 2002, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg, respectively, packaged in a 28-Day Cycle Regimen.

Reference is also made to your amendments dated January 28, February 24, May 15, June 30, July 31, and August 4, 2003, August 5, 2004, and February 24, and August 7, 2006.

We have completed the review of this ANDA and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved. The Division of Bioequivalence has determined your Norgestimate and Ethinyl Estradiol Tablets, 28-Day Cycle Regimen, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg, respectively, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ortho Tri-Cyclen® Tablets, 28-Day Cycle Regimen, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg, respectively, of RW Johnson Pharmaceutical Research Institute). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

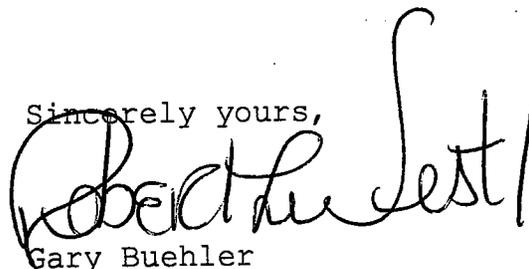
Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

 For
8/17/2006

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-626
Division File
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Endorsements:

HFD-630/N.Takiar/ *N. Takiar 8/10/06*
HFD-630/H.Khorshidi/ *H.Khorshidi 8/10/06*
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HFD-613/P.Birch/ via email
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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVED LABELING

TABLE I: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR, (UNITED STATES).

Method (1)	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year ³ (4)
	Typical Use ¹ (2)	Perfect Use ² (3)	
Chance ⁴	85	85	
Spermicides ⁵	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal ⁶		2	
Post-Ovulation		1	
Withdrawal	19	4	
Cap ⁷			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponges			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm ⁸	20	6	56
Condom ⁹			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combinaid		0.1	
IUD			
Progesterane T	2.0	1.5	81
Copper T380A	0.8	0.6	78
LMg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Adapted from Hatcher et al., 1998 Ref. #1.

¹Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

²Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

³Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.

⁴The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception, if they abandoned contraception altogether.

⁵foams, creams, gels, vaginal suppositories, and vaginal film.

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

⁷With spermicidal cream or jelly.

⁸Without spermicides.

In clinical trials with monophasic norgestimate and ethinyl estradiol tablets 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 tri-phasic norgestimate and ethinyl estradiol tablets 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 norgestimate and ethinyl estradiol tablets (tri-phasic), 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, tri-phasic norgestimate and ethinyl estradiol tablets showed a statistically significant decrease in inflammatory lesion count and total lesion count (Table II). The adverse reaction profile of norgestimate and ethinyl estradiol tablets (tri-phasic) from these two controlled clinical trials is consistent with what has been noted from previous studies involving norgestimate and ethinyl estradiol tablets (tri-phasic) 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

	Norgestimate and Ethinyl Estradiol Tablets (tri-phasic)		Placebo
	N = 163	N = 161	
Mean Age at Enrollment	27.3 years	28.0	
Inflammatory Lesions - Mean Percent Reduction	56.6	35.6	
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
- Migraine with focal aura
- 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
- Hypersensitivity to any component of this product

WARNINGS

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

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

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

The information contained in this package insert is principally based on studies carried out in patients who used oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestogens remains to be determined.

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk

does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

a. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six.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 WOMAN-YEARS BY AGE, SMOKING STATUS AND ORAL CONTRACEPTIVE USE

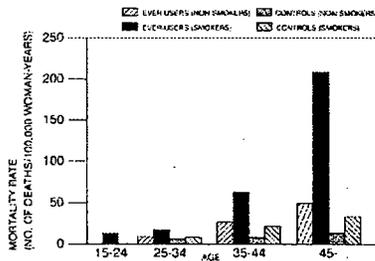


TABLE III. (Adapted from P.M. Layde and V. Beral, ref. #12.)

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.¹² In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.¹⁴⁻¹⁶ 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.

Norgestrel 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.¹⁷

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.^{2,21,22} 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.²³ 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.² The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.²⁴ 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.²⁹ The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.8 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.5 for normotensive users and 25.7 for users with severe hypertension.²⁹ 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 contraceptive. 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 recommendations involve 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	0.3	0.5	0.9	1.9	13.8	31.6
Non-smoker						
Oral contraceptives	2.2	3.4	5.6	13.5	51.1	117.2
Smoker**						
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, *et al.*, #25.

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, 73-83}

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 of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.⁹²

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.⁴⁵⁻⁴⁹ 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, 63} 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.⁶⁴ 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.^{66, 67} However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.⁶⁸ 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 1c), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

In clinical studies with monophasic norgestimate and ethinyl estradiol tablets 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 tri-phasic norgestimate and ethinyl estradiol tablets 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 contraceptives⁶⁹ and this increase is more likely in older oral contraceptive users⁶⁹ and with extended duration of use.⁶⁴ Data from the Royal College of General Practitioners⁷⁰ 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 disease⁷⁰ 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.^{69, 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 monophasic norgestimate and ethinyl estradiol tablets.

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 pre-existent.

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 ref-

4 of 12

to blood pressure, dizziness, bloating, and pelvic pressure, 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 progestagens 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, griseofulvin, topiramite, and possibly with ampicillin and tetracyclines.²²

8. INTERACTIONS WITH LABORATORY TESTS

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

- Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin III; increased norepinephrine-induced platelet aggregability.
- 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.
- Other binding proteins may be elevated in serum.
- Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels remain unchanged.
- 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.
- Glucose tolerance may be decreased.
- 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, combination oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use combination oral contraceptives but to use other forms of contraception until she has completely weaned her child.

12. PEDIATRIC USE

Safety and efficacy of norgestimate and ethinyl estradiol tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

13. 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
- Changes 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.^{7a-7c}

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, Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) and Norgestimate and Ethinyl Estradiol Tablets (monophasic) must be taken exactly as directed and at intervals not exceeding 24 hours. Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) and Norgestimate and Ethinyl Estradiol Tablets (monophasic) are available in a tablet dispenser which can be used for a Sunday Start or a Day 1 Start schedule.

28-Day Regimen (Sunday Start)

When taking Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) and Norgestimate and Ethinyl Estradiol Tablets (monophasic) 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 white 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 Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) and Norgestimate and Ethinyl Estradiol Tablets (monophasic) 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 white 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 Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) and Norgestimate and Ethinyl Estradiol Tablets (monophasic) 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.

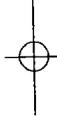
ACNE

The timing of initiation of dosing with Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) for acne should follow the guidelines for use of Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) as an oral contraceptive. Consult the DOSAGE AND ADMINISTRATION section for oral contraceptives. The dosage regimen for Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) for treatment of facial acne, as available in a tablet dispenser, utilizes a 21-day active and a 7-day placebo schedule. Take one active tablet daily for 21 days followed by one white tablet for 7 days. After 28 tablets have been taken, a new course is started the next day.

HOW SUPPLIED

Norgestimate and Ethinyl Estradiol Tablets (Tri-Phasic) are available in a 28 tablet dispenser containing 7 light orange active tablets, 7 orange active tablets, 7 peach active tablets, and 7 white placebo tablets.

Each light orange tablet is round, unscored, debossed with WATSON on one side and 524 on the other side and contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each orange tablet is round, unscored, debossed with WATSON on one side and 525 on



peach tablet is round, unscored, debossed with WATSON on one side and 526 on the other side, and contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. (Placebo tablets have a debossed WATSON on one side and P on the other side.)

Norgestimate and Ethinyl Estradiol Tablets (Tri-Phasic) are packaged in cartons of 6 tablet dispensers.

Norgestimate and Ethinyl Estradiol Tablets (Monophasic) are available in a 28 tablet dispenser containing 21 peach active tablets, and 7 white placebo tablets.

Each peach tablet is round, unscored, debossed with WATSON on one side and 526 on the other side, and contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. (Placebo tablets have a debossed WATSON on one side and P on the other side.)

Norgestimate and Ethinyl Estradiol Tablets (Monophasic) are packaged in cartons of 6 tablet dispensers.

Store at 20°-25°C (68°-77°F). [See USP controlled room temperature.]

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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. Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) 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 re-examined 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.

Norgestimate and ethinyl estradiol tablets (monophasic and tri-phasic), like all oral contraceptives, are intended to prevent pregnancy. Tri-phasic norgestimate and ethinyl estradiol tablets are 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.

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) - 28 Day Regimen

Each light orange tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each orange tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each peach tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

Norgestimate and Ethinyl Estradiol Tablets (monophasic) - 28 Day Regimen

Each peach tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

INTRODUCTION

Any woman who considers using oral contraceptives (the "birth control pill" or the "pill") should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your 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: 20%
- Spermicides alone: 28%
- 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 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, liver, 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 injury 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. 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 of stopping use, was generally accounted for by cancers 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.

Method of control and outcome	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					
	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	6.5	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	1.5	1.7	2.9	3.6

*Deaths are birth-related
**Deaths are method-related

In the above table, the risk of death from any birth control method is less than the risk of childbearing, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death was always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who 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 deter-

mine 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, combination oral contraceptives may decrease the amount and quality of your milk. If possible, do not use combination oral contraceptives while breast feeding. You should use another method of contraception since breast feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting combination oral contraceptives only after you have weaned your child completely.

3. Laboratory tests

If you are scheduled for any laboratory tests, tell your 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), anti-convulsants such as carbamazepine, phenytoin, phenylbutazone, 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

Norgestimate and ethinyl estradiol tablets (monophasic and tri-phasic), like all oral contraceptives, are intended to prevent pregnancy. Norgestimate and ethinyl estradiol tablets (tri-phasic) are 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 THAT IT HAS 28 PILLS:

The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 7 "reminder" white pills (without hormones).

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic): There are 7 light orange "active" pills, 7 orange "active" pills, and 7 peach "active" pills.

Norgestimate and Ethinyl Estradiol Tablets (monophasic): There are 21 peach "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 DETAILED PATIENT LABELING.

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. Norgestimate and Ethinyl Estradiol Tablets are available in a 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:

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic): Take the first "active" light orange pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack the same day.

Norgestimate and Ethinyl Estradiol Tablets (monophasic): Take the first "active" peach 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 the 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:

Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet dispenser. Note: if the first day of your period is a Sunday, you can skip this step.

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic): Take the first "active" light orange pill of the first pack during the first 24 hours of your period.

Norgestimate and Ethinyl Estradiol Tablets (monophasic): Take the first "active" peach pill of the first pack during the first 24 hours of your period.

You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:

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

WHAT TO DO IF YOU MISS PILLS

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic):

If you MISS 1 light orange, orange, or peach "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.

2. You do not need to use a back-up birth control method if you have sex.

If you MISS 2 light orange or orange "active" pills in a row in WEEK 1 OR WEEK 2 of your pack:

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

If you **MISS 2** peach "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** light orange, orange, or peach "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.

Norgestimate and Ethinyl Estradiol Tablets (monophasic):

If you **MISS 1** peach "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** peach "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** peach "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** peach "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 white "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 re-examined at least once a year. Be sure to inform your health care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health care provider, because this is a time to determine if there are any 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.

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CANADA

Issued: July 2004

12 OF 12

PATIENT INSERT

DETAILED PATIENT LABELING
Norgestimate and
Ethinyl Estradiol Tablets

Pa only

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.

Norgestimate and Ethinyl Estradiol Tablets (Tri-Minist)[®] - 28 Day Regimen

Each light orange tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each orange tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each peach tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

Morgestimate and Ethinyl Estradiol Tablets (non-norgestimate) - 28 Day Regimen

Each peach tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

INTRODUCTION

Any woman who considers using oral contraceptives (the "birth control pill" or "the pill") should understand the benefits and risks of using the 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 doctor's advice. The doctor who prescribes your pill should discuss the risks and benefits of the pill in his talking with him or her, both when you first start taking the pill and during your visits. 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). 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 spermicide: 20%
- Spermicide alone: 25%
- Female sterilization: 4%
- Male sterilization: 4%

General tip with spermicide: 20 to 40%.

Condom alone (male): 13%.

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 especially high for 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 (occurring 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 safe 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 epilepsies
- Mental depression
- Gallbladder, liver, heart or kidney disease
- History of scanty or irregular menstrual periods

Women with any of these conditions should be checked often by their 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 blockages 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 in 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 illness or injury 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 also not take oral contraceptives during the last two weeks 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 washed your child before using the pill. (See also the section on Breast Feeding in General Precautions.)

The risk of circulatory diseases 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. You may be at greater risk from oral contraceptives if you have had a blood clot in the past, if you are over 35 years of age, if you are a smoker, if you are a woman 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 (stopping 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 use of oral contraceptives greatly increase the risk of blood clots in the legs, which may lead to other complications 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 estrogen.

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, oral contraceptive use has been associated with 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 is thought to be related to duration of use. The employment of oral contraceptives has been associated with a decrease in the risk of developing breast cancer.

A meta-analysis of 54 studies found a small increase in the risk of breast cancer for oral contraceptive users. However, this increase in the frequency of breast cancer diagnosis, which has been reported in women who use oral contraceptives, was generally accounted for by cancers 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 CONTROL OF FERTILITY PER 100,000 WOMEN WHO USE A BIRTH CONTROL METHOD ACCORDING TO AGE

Method of control	15-19	20-24	25-29	30-34	35-39	40-44
Major deaths	15-19	20-24	25-29	30-34	35-39	40-44
Control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives	0.3	0.5	0.9	1.9	3.8	3.16
Other methods†	2.2	3.4	6.6	13.5	21.1	11.7
Nonusers	0.8	0.8	1.0	1.0	1.4	1.4
Diagnoses	1.8	1.5	1.2	0.7	0.3	0.4
Pregnancies	2.5	1.5	1.5	1.7	2.9	3.6

*Deaths are from heart disease.

†Deaths are from heart disease.

In the above table, the risk of death from any birth control method is less than the risk in childbearing women who are not using any method of birth control. It is women aged 15 to 35. The risk of death was highest for women aged 15 to 35. 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 (2.87 deaths per 100,000 women, depending on age). For 28 associated with pregnancy (3.16 deaths per 100,000 women), although the risk of death was higher than that associated with pregnancy (2.87 deaths per 100,000 women), the risk of death was lower than that associated with pregnancy (2.87 deaths per 100,000 women) for pill users who smoke and are over the age of 35. The estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (17.7/100,000 women) than the estimated risk associated with pregnancy (2.87/100,000 women) for 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 in 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 head pain, coupling 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)

- Stomach pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor)
- Severe pain or tenderness in the stomach area (possibly indicating 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 in taking your pills on schedule. If this bleeding continues in the 5th or 6th or later for more than 2 or 3 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. Menstrual changes

A spoty 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 two or three days. If you do not get your next period, you should be sure to inform your health care provider. If you have 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. If you are pregnant or think you are, you should check with your doctor about the use of any oral contraceptive while you are pregnant.

2. While breast feeding

If you are breast feeding, consult your doctor before starting oral contraceptives. Some of the drug will be on the milk. The effect on the infant is not known. A few adverse effects of the pill (gastrointestinal and breast-feeding problems) may be associated with oral contraceptives. The amount and quality of your milk. If possible, do not use combination oral contraceptives while breast feeding. You should use another method of contraception since breast feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breast feed for longer periods of time. You should consider starting combination oral contraceptives only after you have weaned your child completely.

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BRIEF SUMMARY PATIENT PACKAGE INSERT (continued)

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 re-examined 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.

Norgestimate and ethinyl estradiol tablets (monophasic and tri-phasic), like all oral contraceptives, are intended to prevent pregnancy. Tri-phasic norgestimate and ethinyl estradiol tablets are 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.

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Issued: July 2004

DETAILED PATIENT LABELING (continued)

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, phenytoin, phenylbutazone, 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

Norgestimate and ethinyl estradiol tablets (monophasic and tri-phasic), like all oral contraceptives, are intended to prevent pregnancy. Norgestimate and ethinyl estradiol tablets (tri-phasic) are 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 THAT IT HAS 28 PILLS:

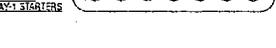
The 28-pill pack has 21 "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" white pills (without hormones).

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic): There are 7 light orange "active" pills, 7 orange "active" pills, and 7 peach "active" pills.

Norgestimate and Ethinyl Estradiol Tablets (monophasic): There are 21 peach "active" pills.

3. ALSO FIND:

- 1) where on the pack to start taking pills,
- 2) in what order to take the pills (follow the arrows).



4. BE SURE YOU HAVE READY AT ALL TIMES:

ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam, or sponge) to use as a back-up 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. Norgestimate and Ethinyl Estradiol Tablets are available in a 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:

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic): Take the first "active" light orange pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack the same day.

Norgestimate and Ethinyl Estradiol Tablets (monophasic): Take the first "active" peach 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 the 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:

Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) printed on the tablet dispenser. Note: If the first day of your period is a Sunday, you can skip this step.

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic): Take the first "active" light orange pill of the first pack during the first 24 hours of your period.

Norgestimate and Ethinyl Estradiol Tablets (monophasic): Take the first "active" peach pill of the first pack during the first 24 hours of your period.

You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.

Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).

Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:

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

WHAT TO DO IF YOU MISS PILLS

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic):

If you MISS 1 light orange, orange, or peach "active" pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.

2. You do not need to use a back-up birth control method if you have sex.

If you MISS 2 light orange or orange "active" pills in a row in WEEK 1 OR WEEK 2 of your pack:

1. Take 2 pills on the day you remember and 2 pills the next day.

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

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

If you MISS 2 peach "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 light orange, orange, or peach "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.

Norgestimate and Ethinyl Estradiol Tablets (monophasic):

If you MISS 1 peach "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 peach "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 peach "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 peach "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 white "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 re-examined at least once a year. Be sure to inform your health care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health care provider, because this is a time to determine if there are 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
- acne (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.

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Issued: July 2004

Issued: July 2004

**BRIEF SUMMARY
PATIENT PACKAGE INSERT**

Norgestimate and Ethinyl Estradiol Tablets

Rx only

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

Norgestimate and Ethinyl Estradiol Tablets (tri-phasic): Each light orange tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each orange tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each peach tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

Norgestimate and Ethinyl Estradiol Tablets (monophasic): Each peach tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

Oral contraceptives, also known as "birth control pills" or "the pill," are taken to prevent pregnancy. Norgestimate and Ethinyl Estradiol Tablets (tri-phasic) 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.

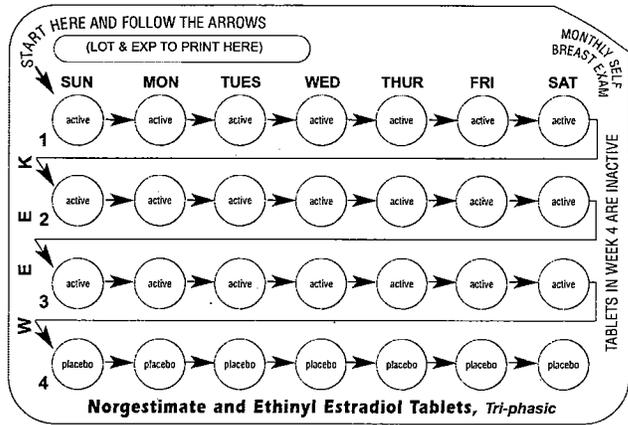
The serious side effects of the pill occur very infrequently, especially if you are in good health and are young. However, you should know that the following medical conditions have been associated with or made worse by the pill:

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.

CONTINUED ON PAGE 2



MON	TUE	WED	THU	FRI	SAT	SUN
TUE	WED	THU	FRI	SAT	SUN	MON
WED	THU	FRI	SAT	SUN	MON	TUE
THU	FRI	SAT	SUN	MON	TUE	WED
FRI	SAT	SUN	MON	TUE	WED	THU
SAT	SUN	MON	TUE	WED	THU	FRI

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



Rx only
6 Tablet Dispensers
28 Tablets Each

IMPORTANT: Each dispenser contains a combined Brief Summary, Patient Package Insert and Detailed Patient Labeling. This should be included with each package dispensed to the patient.

Norgestimate and Ethinyl Estradiol Tablets



NDC 0591-3134-28

Rx only
6 Tablet Dispensers
28 Tablets Each

Norgestimate and Ethinyl Estradiol Tablets



NDC 0591-3134-28

28-DAY REGIMEN

Each light orange tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each orange tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each peach tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

Rx only
6 Tablet Dispensers
28 Tablets Each



7/04

Norgestimate and Ethinyl Estradiol Tablets



NDC 0591-3134-28

28-DAY REGIMEN

Each light orange tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each orange tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each peach tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

Rx only
6 Tablet Dispensers
28 Tablets Each



NDC 0591-3134-28

Norgestimate and Ethinyl Estradiol Tablets



28-DAY REGIMEN

Each light orange tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each orange tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each peach tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

Rx only
6 Tablet Dispensers
28 Tablets Each



3 059131342817

Norgestimate and Ethinyl Estradiol Tablets



NDC 0591-3134-28

Dosage: One tablet daily as prescribed. See package insert.

Store at 20°-25°C (68°-77°F). [See USP controlled room temperature.]

Mfd. for: Watson Laboratories, Inc.
Corona, CA 92680 USA
Mfd. by: Pathon, Inc.
Mississauga, Ontario L5N 7K9
CANADA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-626

LABELING REVIEW(S)

**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number:	76-626	Date of Submission:	December 30, 2002
Applicant's Name:	Watson Laboratories, Inc.		
Established Name:	Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.25 mg/0.035 mg (Multi-Strength) (28 day regimen)		

Labeling Deficiencies:

1. GENERAL COMMENTS:

- a. Revise the storage temperature statements on all labels and labeling to read:
Store at 20-25° C (68 - 77° F) [see USP Controlled Room Temperature]
- b. Revise "—————" to "monophasic" and "—————" to "tri-phasic" on all affected labeling pieces.
- c. Your proposed proprietary name "TriNessa™" is under review.

2. BLISTER PACK DISPENSER

Satisfactory in final print labeling.

3. BLISTER PACK DISPENSER OUTER CONTAINER

We note your application does not mention an outer container for the blister pack dispenser. If you plan to use such an outer container i.e. compact, vinyl pouch, cardboard sleeve, etc., please provide its specifications.

4. START DAY STICKERS

Your application does not include day stickers for patients who choose to follow the "Day 1 Start" regimen, instead of the "Sunday Start" regimen. Please provide stickers or some other method to accommodate both regimens.

5. CARTON

- a. See GENERAL COMMENTS 1a and 1b.
- b. Please increase the prominence and readability of the tablet strength statements by increasing the font and choosing an alternative contrasting color.
- c. See the attached mocked-up copy of your carton for requested revisions.

6. PHYSICIAN INSERT

- a. See GENERAL COMMENT 1a and 1b.
- b. See the attached mocked-up copy of your insert for requested revisions.

7. DETAIL PATIENT LABELING AND BRIEF SUMMARY INSERTS

Your application did not include and patient inserts (single or combined). Please submit the DETAILED PATIENT LABELING and BRIEF SUMMARY PATIENT inserts.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.



Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Mocked-up copy of package insert

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Ortho Tri-Cyclen® Tablets

NDA Number: 19-697

NDA Drug Name: Ortho Tri-Cyclen® Tablets

NDA Firm: Ortho-McNeil Pharmaceuticals, Inc.

Date of Approval of NDA Insert and supplement #: NDA 19-697/S-022; revised January 2000 and approved June 5, 2000; and S-024, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with innovation label in jacket.

Basis of Approval for the Carton Labeling: Side-by-side comparison with innovation label in jacket.

Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X

Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by..." statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

- This review was based on the labeling for Ortho Tri-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-697/S-022; revised January 2000 and approved June 5, 2000; and S-024, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENT/ EXCLUSIVITIES

Patent Data -

No	Expiration	Use Code	Use	File
None	None	None	There are no unexpired patents for this product in the Orange Book Database	N/A

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	None

3. MANUFACTURING FACILITY

Patheon Inc.
Toronto Region Operations
2100 Syntex Court
Mississauga, Ontario, L5N 7K9
Canada
CFN#: 9690045
FEI#: 300264888

(Vol. 1.1, p. 0555)

4. STORAGE CONDITIONS:

NDA - None

ANDA - Store at _____ (revision requested)

USP - Preserve in well-closed containers

5. DISPENSING RECOMMENDATIONS:

NDA - To the dispenser: This carton contains three foil pouches each containing two pieces of information intended for the patient. Both informational pieces are to be provided to the patient with each prescription.

ANDA - IMPORTANT: Each _____ contains a combined _____ should be included with each package dispensed to the patient.

USP - None

6. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 0157-0160 (Volume 1.1).

7. PACKAGING CONFIGURATIONS:

RLD: Cartons of 6 x 21-Day and 6 x 28-Day Dialpak® Tablet Dispensers.

1 x 21-Day and 1 x 28-Day Veridate® Tablet Dispensers (unfilled) for clinic use.

ANDA: Cartons of 6 x 28-Day Blister Pack Tablet Dispenser.

9. CONTAINER/CLOSURE SYSTEM:

Blister: 145mm, _____

Backing: 135mm, aluminum foil, _____

(Vol. 1.2, p. 1090)

10. The tablet debossings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

21 active tablets:

7 of the 0.18 mg/0.035 mg active tablets are light orange, round, unscored, debossed with "WATSON" on one side and "524" on the other side.

7 of the 0.215 mg/0.035 mg active tablets are orange, round, unscored, debossed with "WATSON" on one side and "525" on the other side.

7 of the 0.25 mg/0.035 mg active tablets are peach, round, unscored, debossed with "WATSON" on one side and "526" on the other side.

7 inert tablets: white, round debossed with "WATSON" on one side and "P=" on the other side

Date of Review: May 6, 2004

Date of Submission: December 30, 2002

Primary Reviewer: Postelle Birch

Date: 5/17/04

Team Leader: John Grace

Date: 5/17/04

cc: ANDA:76-626
DUP/DIVISION FILE
HFD-613/PBirchforOCatterson/JGrace (no cc)
V:\FIRMSNZWATSON\LTRS&REV\76-626na1.label.DOC
Review

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	None

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?	X		
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)			
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)			X
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	

Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

- This review was based on the labeling for Ortho Tri-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-697/S-022; revised January 2000 and approved June 5, 2000; and S-024, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. **PATENT/ EXCLUSIVITIES**

Patent Data -

No	Expiration	Use Code	Use	File
None	None	None	There are no unexpired patents for this product in the Orange Book Database	N/A

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
None			There is no unexpired exclusivity for this product	None

3. **MANUFACTURING FACILITY**

Patheon Inc.
 Toronto Region Operations
 2100 Syntex Court
 Mississauga, Ontario, L5N 7K9
 Canada
 CFN#: 9690045
 FEI#: 300264888

(Vol. 1.1, p. 0555)

4. **STORAGE CONDITIONS:**

NDA - None
 ANDA - Store at _____ (revision requested)
 USP- Preserve in well-closed containers

5. **DISPENSING RECOMMENDATIONS:**

NDA - To the dispenser: This carton contains three foil pouches each containing two pieces of information intended for the patient. Both informational pieces are to be provided to the patient with each prescription.
 ANDA - IMPORTANT: Each _____ contains a combined _____ should be included with each package dispensed to the patient.
 USP - None

6. **INACTIVE INGREDIENTS:**

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 0157-0160 (Volume 1.1).

7. **PACKAGING CONFIGURATIONS:**

RLD: Cartons of 6 x 21-Day and 6 x 28-Day Dialpak® Tablet Dispensers.
1 x 21-Day and 1 x 28-Day Veridate® Tablet Dispensers (unfilled) for clinic use.
ANDA: Cartons of 6 x 28-Day Blister Pack Tablet Dispenser.

9. CONTAINER/CLOSURE SYSTEM:

Blister: 145mm, _____
Backing: 135mm, aluminum foil, _____
(Vol. 1.2, p. 1090)

10. The tablet debossings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

21 active tablets:

7 of the 0.18 mg/0.035 mg active tablets are light orange, round, unscored, debossed with "WATSON" on one side and "524" on the other side.

7 of the 0.215 mg/0.035 mg active tablets are orange, round, unscored, debossed with "WATSON" on one side and "525" on the other side.

7 of the 0.25 mg/0.035 mg active tablets are peach, round, unscored, debossed with "WATSON" on one side and "526" on the other side.

7 inert tablets: white, round debossed with "WATSON" on one side and "P" on the other side

11. Watson submitted the name TriNessa for this product. The following is DMETS May 12, 2004 response to the name:

1. DMETS has no objections to the use of the proprietary name, TriNessa, provided that only one name TriNessa or _____ is approved. These names should not co-exist in the marketplace due to their similarity. Additionally, DMETS is aware of the sponsor's proposals for naming multiple oral contraceptive products with the suffix "nessa" or "nezza" and is concerned about the possibility of errors resulting from confusion from the proliferation of those suffixes. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the ANDA. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

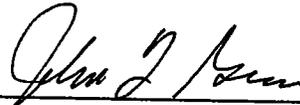
2. DDMAC finds the proprietary name TriNessa acceptable from a promotional perspective.

3. The Division of Reproductive and Urologic Drug Products had no concerns with the use of the proprietary name, TriNessa.

Date of Review: September 20, 2004

Date of Submission: August 5, 2004

Primary Reviewer: Postelle Birch  Date: 9/21/04

Team Leader: John Grace  Date: 9/22/04

cc: ANDA:76-626
DUP/DIVISION FILE
HFD-613/PBirchforDCatterson/JGrace (no cc)
V:\FIRMSNZWATSON\LTRS&REV\76-626ap.label.DOC
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-626

CHEMISTRY REVIEW(S)

#1



Chemistry Review Data Sheet

ANDA 76-626

**Norgestimate and Ethinyl Estradiol Tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg
(28-day regimen)**

Watson Laboratories, Inc.

**Neeru B. Takiar
Office of Generic Drugs, Division of Chemistry I**



Chemistry Review Data Sheet

Table of Contents

Table of Contents2

Chemistry Review Data Sheet.....2

The Executive Summary.....7

I. Recommendations 7

 A. Recommendation and Conclusion on Approvability 7

 B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable..... 7

II. Summary of Chemistry Assessments 7

 A. Description of the Drug Product(s) and Drug Substance(s)..... 7

 B. Description of How the Drug Product is Intended to be Used 9

 C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 9

 A. Reviewer’s Signature..... 9

 B. Endorsements:..... 9

 C. cc: ANDA 76-626 9

Chemistry Assessment9

Chemistry Review Data Sheet



Chemistry Review Data Sheet

1. ANDA 76-626
2. REVIEW #: 1
3. REVIEW DATE: May 15, 2003 REVISION DATE: June 19, 2003
4. REVIEWER: Neeru B. Takiar
5. PREVIOUS DOCUMENTS: None

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

December 30, 2002

New Correspondence (Minor Amendment)

January 28, 2003

Telephone Amendment

February 24, 2003

New Correspondence (Bio)

May 15, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Watson Laboratories Inc.

Address: 311 Bonnie Circle
Corona, CA 92880

Representative: Margaret Choy

Telephone: (909)-493-5475

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: : TriNessa™ (Proposed)

Non-Proprietary Name (USAN): Norgestimate and Ethinyl Estradiol Tablets

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: OrthoTri-Cyclen®

Innovator Company: Ortho-McNeil Pharmaceutical, Inc.



Chemistry Review Data Sheet

(Norgestimate and ethinyl estradiol tablets; Oral-28, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)
NDA #19-697; Approved July 03, 1992

Patent Certification: V1.1, Page 0017

U.S. Patent 4,530,839 (Paragraph III):	Expire on September 26, 2003
U.S. Patent 4,544,554 (Paragraph III):	Expire on September 26, 2003
U.S. Patent 4,616,006 (Paragraph III):	Expire on September 26, 2003
U.S. Patent 4,628,051 (Paragraph III):	Expire on September 26, 2003

Exclusivity: None

10. PHARMACOL. CATEGORY: Contraceptive

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg (28-Day Regimen)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

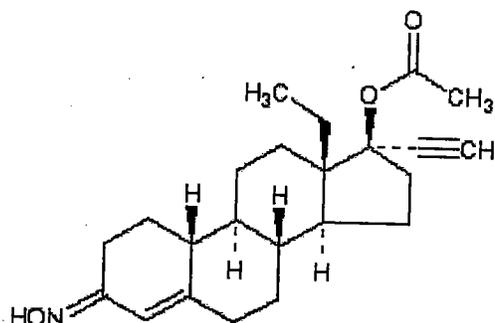
SPOTS product – Form Completed

Not a SPOTS product

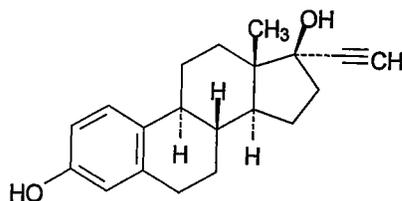
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Norgestimate: 18,19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α)-(+)-. C₂₃H₃₁NO₃, Molecular Weight: 369.51, USP

Chemistry Review Data Sheet



Ethinyl Estradiol. 19-Norpregna-1, 3, 5(10)-trien-20-yne-3,17-diol, (17 α)-. C₂₀H₂₄O₂. 296.40. 57-36-6. USP



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Inadequate	04-29-2003	Original Reviewed
	II			3	Adequate	05-07-2002	Reviewed previously
	III			4	N/A	-	-
	III			4	N/A	-	-

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted



Chemistry Review Data Sheet

- 6 – DMF not available
- 7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	Pending (product)	-	N.B.Takiar
Labeling	Pending		
Bioequivalence	Pending		
EA	Satisfactory (See #35)	-	N.B.Takiar
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
 Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Assessment Section

The Chemistry Review for ANDA 76-626

The Executive Summary

Review: #1

DMF for Drug Substance/Holder: # _____

Product: Norgestimate and Ethinyl Estradiol Tablets (28), 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)

Firm: Watson Laboratories Inc.

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not Approvable, MINOR will issue [Method Validation]

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: Norgestimate and Ethinyl Estradiol Tablets are non-sterile and non-compensial drug product intended solely for oral administration. The combination oral contraceptives act by the suppression of gonadotropins. The primary mechanism of this action is inhibition of ovulation. The proposed drug product is Norgestimate and Ethinyl Estradiol Tablets (28), 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg. The Reference Listed Drug is Ortho-Tri Cyclen® (NDA# 19-697) approved for Ortho-McNeil Pharmaceutical, Inc. The product will be packaged in a container/closure system consisting of blisters, (28) to be administered orally.

Drug Substance: The active ingredients for this product are Norgestimate and Ethinyl Estradiol, USP. Norgestimate USP is white or almost white fine crystalline powder with the following chemical name/formula/MW: 18,19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α)- (+)-. C₂₃H₃₁NO₃, 369.51. It is sparingly soluble in ethanol and freely soluble in chloroform. In addition to current USP tests and specifications, the firm will test for particle size. The key physicochemical properties that influence batch-to-batch reproducibility are specific rotation, residual solvents, particle size, and chromatographic purity.

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CHEMISTRY REVIEW #1 (P. 8 of 44)

Chemistry Assessment Section

Method Validation: Both Norgestimate and Ethinyl Estradiol drug substances are compendial items. Therefore, evaluation of firm's validated analytical methods for drug substances from the FDA District Laboratory is not required. However, evaluation of firm's validated analytical methods for drug product from the FDA District Laboratory is being submitted to the MV Coordinator. The analytical methods and validation data for the in-house methods submitted by the firm in this ANDA have been reviewed and found satisfactory.

B. Description of How the Drug Product is Intended to be Used

Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg, are intended for oral administration.

C. Basis for Approvability or Not-Approval Recommendation

The CMC review of this ANDA has identified the key deficiencies in the following areas, components, drug substance, container/closure, in-process, drug product release, method validation, and stability.

The firm should resolve all of the issues listed in the deficiency letter, section #36, as the deficiencies described indicate the proposed drug product can not be classified as safe and effective in this (1st) review cycle.

In addition to the chemistry, manufacturing, and controls issues, the labeling and bio review and status on EER are pending.

III. Administrative

A. Reviewer's Signature

B. Endorsements:

HFD-623/N.B.Takiar/

HFD-623/D.S.Gill, Ph.D./

HFD-617/S.KIM/

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F/T by:

C. cc: ANDA 76-626

Division File

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Field Copy

Chemistry Assessment

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confidential commercial

information from

CHEMISTRY REVIEW #1 (pages 10-42)



Chemistry Assessment Section

4. The review of the Bioequivalency section of this application is pending. Any deficiencies found will be sent to you under separate cover.
5. The review of the Labels and Labeling of this application is pending. Any deficiencies found will be sent to you under separate cover.

Sincerely yours,

Paul Schwager 6/24/03

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**



Chemistry Assessment Section

cc: ANDA 76-626
Division File
Field Copy

Endorsements:

HFD-623/N.B.Takiar/6/19/03 *N. Takiar 6/23/03*
HFD-623/D.Gill, Ph.D./6/19/03 *Method 6/23/03 for*
HFD-617/S.Kim/6/23/03 *S.K. 6/23/03*

V:\FIRMSNZ\WATSON\LTRS&REV\76626RV1.doc
F/T by:ard/6/23/03

TYPE OF LETTER: NOT APPROVABLE - MINOR [Method Validation]

**APPEARS THIS WAY
ON ORIGINAL**

#2



Chemistry Review Data Sheet

ANDA 76-626

**Norgestimate and Ethinyl Estradiol Tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg
(28-day regimen)**

Watson Laboratories, Inc.

**Neeru B. Takiar
Office of Generic Drugs, Division of Chemistry III**



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary.....	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s).....	7
B. Description of How the Drug Product is Intended to be Used	9
C. Basis for Approvability or Not-Approval Recommendation	9
III. Administrative	9
A. Reviewer's Signature.....	9
B. Endorsements:.....	9
C. cc: ANDA 76-626	9
Chemistry Assessment	10



Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. ANDA 76-626

2. REVIEW #: 2

3. REVIEW DATE: April 8, 2004

REVISION DATE: April 15, 2004

4. REVIEWER: Neeru B. Takiar

5. PREVIOUS DOCUMENTS:

Previous Documents

Original

New Correspondence (Minor Amendment)

Telephone Amendment

New Correspondence (Bio)

Document Date

December 30, 2002

January 28, 2003

February 24, 2003

May 15, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Telephone Amendment

Minor Amendment

Bio Amendment

CMC Amendment

Document Date

June 30, 2003

July 31, 2003

August 4, 2003

November 6, 2003

7. NAME & ADDRESS OF APPLICANT:

Name: Watson Laboratories Inc.

Address: 311 Bonnie Circle
Corona, CA 92880

Representative: Margaret Choy

Telephone: (909)-493-5475

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: : TriNessa™ (Proposed)

Non-Proprietary Name (USAN): Norgestimate and Ethinyl Estradiol Tablets



Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: OrthoTri-Cyclen®

Innovator Company: Ortho-McNeil Pharmaceutical, Inc.

(Norgestimate and ethinyl estradiol tablets; Oral-28, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)

NDA #19-697; Approved July 03, 1992

Patent Certification: V1.1, Page 0017

U.S. Patent 4,530,839 (Paragraph III):

Expire on September 26, 2003

U.S. Patent 4,544,554 (Paragraph III):

Expire on September 26, 2003

U.S. Patent 4,616,006 (Paragraph III):

Expire on September 26, 2003

U.S. Patent 4,628,051 (Paragraph III):

Expire on September 26, 2003

Exclusivity: None

10. PHARMACOL. CATEGORY: Contraceptive

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg (28-Day Regimen)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

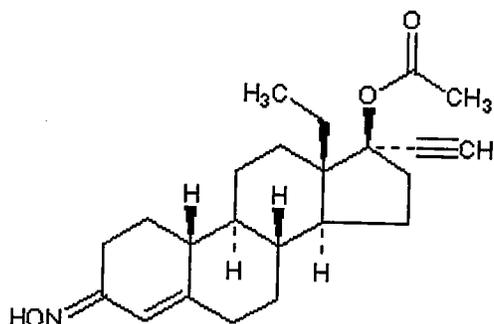
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

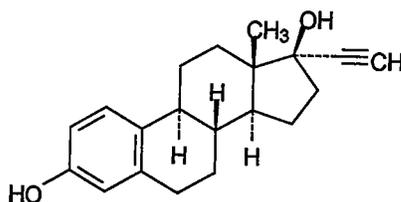
Norgestimate: 18, 19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α) - (+)-. C₂₃H₃₁NO₃, Molecular Weight: 369.51, USP



Chemistry Review Data Sheet



Ethynyl Estradiol: 19-Norpregna-1, 3, 5(10)-trien-20-yne-3, 17-diol, (17 α) - C₂₀H₂₄O₂. 296.40. 57-36-6. USP



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	1	Inadequate	04-07-2004	Reviewed by this reviewer
	II			3	Adequate	07-18-2003	Reviewed previously
	III			4	N/A	-	-
	III			4	N/A	-	-

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet



² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	2-4-2004	
Methods Validation	Pending	-	N.B.Takiar
Labeling	Pending		
Bioequivalence	Acceptable	8-18-03	P. Nwakama
EA	Satisfactory (See #35)	-	N.B.Takiar
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
 Yes No If no, explain reason(s) below:

**APPEARS THIS WAY
ON ORIGINAL**

The Chemistry Review for ANDA 76-626

The Executive Summary

Review: #2

DMF for Drug Substance/Holder: # _____

Product: Norgestimate and Ethinyl Estradiol Tablets (28), 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)

Firm: Watson Laboratories Inc.

I. Recommendations

- A. **Recommendation and Conclusion on Approvability**
Not Approvable, MINOR will issue
- B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: Norgestimate and Ethinyl Estradiol Tablets are non-sterile and non-compendial drug product intended solely for oral administration. The combination oral contraceptives act by the suppression of gonadotropins. The primary mechanism of this action is inhibition of ovulation. The proposed drug product is Norgestimate and Ethinyl Estradiol Tablets (28), 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg. The Reference Listed Drug is Ortho-Tri Cyclen® (NDA# 19-697) approved for Ortho-McNeil Pharmaceutical, Inc. The product will be packaged in a container/closure system consists of blisters, (28) to be administered orally.

Drug Substance: The active ingredients for this product are Norgestimate and Ethinyl Estradiol, USP. Norgestimate USP is white or almost white fine crystalline powder with the following chemical name/formula/MW: 18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α) - (+)-. C₂₃H₃₁NO₃. 369.51. It is sparingly soluble in ethanol and freely soluble in chloroform. In addition to current USP tests and specifications, the firm will test for particle size. The key physicochemical properties that influence batch-to-batch reproducibility are specific rotation, residual solvents, particle size, and chromatographic purity.

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information from

CHEMISTRY REVIEW #2 (P. 8 OF 40)

Chemistry Assessment Section

Method Validation: Both Norgestimate and Ethinyl Estradiol drug substance are compendial items. Request to evaluate firm's DP methods was submitted on April 21, 2004. Firm's in-house analytical methods and the corresponding validation data was reviewed and found satisfactory.

B. Description of How the Drug Product is Intended to be Used

Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg, are intended for oral administration.

C. Basis for Approvability or Not-Approval Recommendation

This application is not approvable (CMC including DMF # _____ is currently deficient. MV and labeling are pending).

III. Administrative

A. Reviewer's Signature

New B. Lalor

B. Endorsements:

HFD-623/N.B.Takiar/4-8-04; Revised on 4-15-04

HFD-623/D.S.Gill, Ph.D., TL/

HFD-617/S.Park, PM/

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F/T by: EW 4/20/04

C. cc: ANDA 76-626

Division File

DUP Jacket

Field Copy

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confidential commercial

information from

CHEMISTRY REVIEW #2 (pages 10-39)



Chemistry Assessment Section

cc: ANDA 76-626
Division File
Field Copy

Endorsements:

HFD-623/N.Takiar/4-8-04; Revised on 4-15-04 *N. Takiar 4/21/04*
HFD-623/D.Gill, Ph.D., TL/4-16-04 *DSG:DL 4-21-04*
HFD-617/S.Park, PM/4-19-04 *OK 4/23/04*

V:FIRMSNZ\WATSON\LTRS&REV\76626.RV2.doc

F/T by: EW 4-20-04

TYPE OF LETTER: NOT APPROVABLE - MINOR

**APPEARS THIS WAY
ON ORIGINAL**

#3

CHEMISTRY REVIEW



Chemistry Review Data Sheet

ANDA 76-626

**Norgestimate and Ethinyl Estradiol Tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg
(28-day regimen)**

Watson Laboratories, Inc.

**Neeru B. Takiar
Office of Generic Drugs, Division of Chemistry III**

Chemistry Review Data Sheet

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
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A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation	9
Chemistry Assessment	10

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. ANDA 76-626

2. REVIEW #: 3

3. REVIEW DATE: July 26, 2006

REVISION DATE:

4. REVIEWER: Neeru B. Takiar

5. PREVIOUS DOCUMENTS:

Previous Documents

Original

New Correspondence (Minor Amendment)

Telephone Amendment

New Correspondence (Bio)

New Correspondence

New Correspondence (Minor Amendment)

Bio Telephone Amendment

Minor Amendment

Document Date

December 30, 2002

January 28, 2003

February 24, 2003

May 15, 2003

June 30, 2003

July 31, 2003

August 4, 2003

November 6, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Minor Amendment

Document Date

February 24, 2006

7. NAME & ADDRESS OF APPLICANT:

Name: Watson Laboratories, Inc.

Address: 311 Bonnie Circle
Corona, CA 92880

Representative: Janie M. Gwinn

Telephone: (951)-493-4543

Fax: (951)-493-4581

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

Non-Proprietary Name (USAN): Norgestimate and Ethinyl Estradiol Tablets

Chemistry Review Data Sheet



9. LEGAL BASIS FOR SUBMISSION:

Innovator Product: OrthoTri-Cyclen®

Innovator Company: Ortho-McNeil Pharmaceutical, Inc.

(Norgestimate and ethinyl estradiol tablets; Oral-28, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)

NDA #19-697; Approved July 03, 1992

Patent Certification: V1.1, Page 0017

U.S. Patent 4,530,839 (Paragraph III):

Expired on September 26, 2003

U.S. Patent 4,544,554 (Paragraph III):

Expired on September 26, 2003

U.S. Patent 4,616,006 (Paragraph III):

Expired on September 26, 2003

U.S. Patent 4,628,051 (Paragraph III):

Expired on September 26, 2003

Exclusivity: None

10. PHARMACOL. CATEGORY: Contraceptive

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg (28-Day Regimen)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

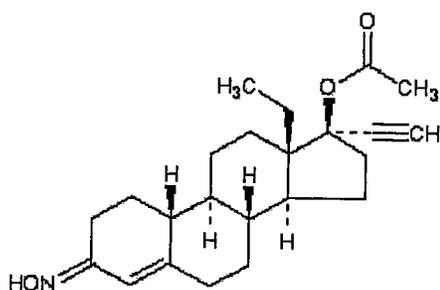
SPOTS product – Form Completed

Not a SPOTS product

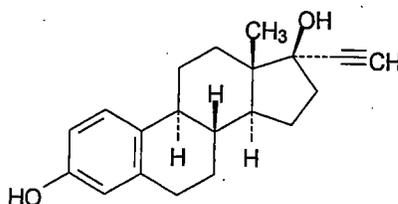
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Norgestimate: 18, 19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α) - (+)-. C₂₃H₃₁NO₃, Molecular Weight: 369.51, USP

Chemistry Review Data Sheet



Ethinyl Estradiol: 19-Norpregna-1, 3, 5(10)-trien-20-yne-3, 17-diol, (17 α) - C₂₀H₂₄O₂. 296.40. 57-36-6. USP



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II	/	/	1	Adequate	07/26/2006	Reviewed by this reviewer
	II			3	Adequate	02/13/2006	Reviewed previously
	III			4	N/A	-	-
	III			4	N/A	-	-

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)



Chemistry Review Data Sheet

B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending <i>Acceptable</i>	<i>8/17/06</i>	<i>S. Adams</i>
Methods Validation	N/A (non-complex DP)		
Labeling	Acceptable	9/22/04	PBirch
Bioequivalence	Acceptable	8/18/03	PNwakama
EA	Satisfactory (See #35)	-	NTakiar
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
 Yes No If no, explain reason(s) below:

APPEARS THIS WAY
 ON ORIGINAL



The Chemistry Review for ANDA 76-626

The Executive Summary

Review: #3

DMF for Drug Substance/Holder: # _____

Product: Norgestimate and Ethinyl Estradiol Tablets (28), 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg)

Firm: Watson Laboratories Inc.

I. Recommendations

A. **Recommendation and Conclusion on Approvability**
Approvable

B. **Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable**
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product: Norgestimate and Ethinyl Estradiol Tablets are non-sterile and non-compensial drug product intended solely for oral administration. The combination oral contraceptives act by the suppression of gonadotropins. The primary mechanism of this action is inhibition of ovulation. The proposed drug product is Norgestimate and Ethinyl Estradiol Tablets (28), 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg. The Reference Listed Drug is Ortho-Tri Cyclen® (NDA# 19-697) approved for Ortho-McNeil Pharmaceutical, Inc. The product will be packaged in a container/closure system consists of blisters, (28) to be administered orally.

Drug Substance: The active ingredients for this product are Norgestimate and Ethinyl Estradiol, USP. Norgestimate USP is white or almost white fine crystalline powder with the following chemical name/formula/MW: 18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α)-(+)-. C₂₃H₃₁NO₃, 369.51. It is sparingly soluble in ethanol and freely soluble in chloroform. In addition to current USP tests and specifications, the firm tests the DS for particle size. The key physicochemical properties that influence batch-to-batch reproducibility are specific rotation, residual solvents, particle size, and chromatographic purity.

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CHEMISTRY REVIEW #3 (P. 8 OF 28)

Chemistry Assessment Section

Method Validation: Both Norgestimate and Ethinyl Estradiol drug substance are compendial items. Firm's in-house analytical methods and the corresponding validation data was reviewed and found satisfactory.

B. Description of How the Drug Product is Intended to be Used

Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg, are intended for oral administration.

C. Basis for Approvability or Not-Approval Recommendation

The CMC for this application is approvable.

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Chemistry Assessment Section

cc: ANDA 76-626
Division File
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Endorsements:

HFD-630/NTakiar/7/26/06 *N. Takiar 7/26/06*
HFD-630/HKhorshidi/ *H. Khorshidi 7/28/06*
HFD-617/JSkanchy/ *J. Skanchy 8/2/06*

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F/T by:

TYPE OF LETTER: APPROVABLE

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-626

BIOEQUIVALENCE REVIEW(S)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No. 76626
Drug Product Name Norgestimate and Ethinyl Estradiol Tablets
Strength 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
Applicant Name Watson Laboratories, Inc.
Address 311 Bonnie Circle, Corona, California 92880
Submission Date(s) December 30, 2002

Amendment Date(s) July 30, 2003 (Telephone Amendment)

Reviewer Patrick Nwakama

First Generic No

File Location V:\firmsNZ\Watson\ltrs&rev\76626SDW.1202.doc

I. Executive Summary

This submission consisted of one fasting bioequivalence (BE) study on the Ethinyl Estradiol / Norgestimate 0.035 mg / 0.250 mg strength, two biowaiver requests (0.035 mg / 0.215 mg and 0.035 mg / 0.180 mg) and dissolution data on all the three strengths. The BE study is a two-way, crossover studies in healthy females (n = 35). Since norgestimate is not optimally quantifiable, the DBE accepts the measurement of its primary metabolite, 17-deacetylnorgestimate. Statistical analyses of the plasma concentration data for Ethinyl Estradiol and 17-deacetylnorgestimate demonstrate bioequivalence. Ethinyl Estradiol results are (point estimate, 90% CI): LAUCT of 0.93, 89.2 - 96.5%; LAUCI 0.92, 89.5 - 94.7%; and LCmax 0.91, 86.7 - 99.4%. Deacetylnorgestimate results are (point estimate, 90% CI): LAUCT of 0.95, 89.9 - 99.8%; LAUCI 0.95, 90.6 - 100.3%; and LCmax 1.03, 98.5 - 108.5%. The product meets the FDA dissolution specifications. The waiver requests for Ethinyl Estradiol / Norgestimate 0.035 mg / 0.215 mg and 0.035 mg / 0.180 mg strengths are granted. The application is acceptable with no deficiencies.

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II. Table of Contents

I.	Executive Summary.....	1
II.	Table of Contents.....	2
III.	Submission Summary.....	3
A.	Drug Product Information.....	3
B.	PK/PD Information.....	3
C.	Contents of Submission.....	5
D.	Pre-Study Bioanalytical Method Validation.....	5
E.	In Vivo Study.....	6
1.	Single-dose Fasting Bioequivalence Study.....	6
F.	Formulation.....	7
G.	In Vitro Dissolution.....	7
H.	Waiver Request(s).....	8
I.	Deficiency Comments.....	8
J.	Recommendations.....	8
IV.	Appendix.....	10
A.	Individual Study Reviews.....	10
1.	Single-dose Fasting Bioequivalence Study.....	10
B.	Formulation Data.....	18
D.	Consult Reviews.....	22
E.	SAS Output	23
F.	Additional Attachments.....	41

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III. Submission Summary

A. Drug Product Information

Test Product	Norgestimate and Ethinyl Estradiol Tablets
Reference Product	Ortho Tri-Cyclen®
RLD Manufacturer	Ortho McNeil Pharmaceuticals, Inc.
NDA No.	019697
RLD Approval Date	July 3, 1992
Indication	Oral Contraceptive and Treatment of Acne Vulgaris

B. PK/PD Information

Bioavailability	60% (norgestimate) and 40 - 83% (ethinyl estradiol)
Food Effect	None and no fed BE study necessary.
T_{max}	2 hours (norgestimate) and 3 hours (ethinyl estradiol)
Metabolism	GI tract and/or hepatic [ethinyl estradiol to 2-hydroxy ethinyl estradiol and norgestimate to levonorgestrel, 17-deacetyl norgestimate and 3-keto norgestimate.
Excretion	Fecal and renal
Half-life	37 hours (17-deacetyl norgestimate) and 26 hours (ethinyl estradiol).
Relevant OGD or DBE History	<p>September 23, 1998 – Barr inquired about the FDA BE requirements for Norgestimate-Ethinyl Estradiol Tablets. The OGD recommended: 1) a single dose fasting BE study and 2) norgestimate (if detectable), 17-deacetyl norgestimate, norgestrel and ethinyl estradiol should be analyzed.</p> <p>April 9, 1999 – Barr asked if it could measure levonorgestrel in lieu of norgestrel and the OGD accepted.</p> <p>In three separate control documents (_____, 00-1333, Duramed, 3/8/2000; _____) on BE requirements for Ethinyl Estradiol/norgestimate, the firms were advised to analyze only ethinyl estradiol and norgestimate and to conduct BE only under fasting conditions since no food effect is mentioned in the innovator's labeling.</p> <p>March 16, 2000 - Barr submitted an ANDA #75804 for its Ethinyl Estradiol / Norgestimate Tablets, 0.035 mg / 0.25 mg with three measured analytes (Ethinyl estradiol, levonorgestrel and desacetylnorgestimate).</p>

**Relevant OGD or DBE
History (continued)**

Two tablets of combination drug were given as the study dose (0.5 mg Norgestimate). Norgestimate was found undetectable in this BE study. Levonorgestrel was quantitated with an elimination half-life of about 50 hours. Therefore, levonorgestrel's AUC was truncated to 72 hours according to the general BA/BE guidance.

February 24, 2001 - In response to _____'s inquiry _____ on BE requirements for Ethinyl Estradiol / Norgestimate Tablets, the OGD asked the firm to measure ethinyl estradiol, and 17-deacetyl norgestimate.

December 27, 2001 - Andrx submitted a similar ANDA #76-334 for Ethinyl Estradiol / Norgestimate Tablets, 0.035 mg / 0.25 mg. Norgestimate, norgestrel and 17-deacetyl norgestimate were measured but only 17-deacetyl norgestimate data were statistically analyzed and used for BE evaluation of norgestimate component.

December 30, 2002 - Watson submitted a similar ANDA #76-626 for Ethinyl Estradiol / Norgestimate Tablets, 0.035 mg / 0.25 mg. Only 17-deacetyl norgestimate and Ethinyl Estradiol were measured and statistically analyzed for BE evaluation.

**Agency Guidance
Drug Specific Issues (if
any)**

None

Norgestimate is a pro-drug and it undergoes extensive first pass metabolism to levonorgestrel, 17-deacetyl norgestimate and 3-keto norgestimate. Only 17-deacetyl norgestimate significantly contributes to norgestimate's pharmacological activity. Norgestimate is rapidly cleared from the plasma, with undetectable levels only 5 hours after dosing. Levonorgestrel and 17-deacetyl norgestimate are quantifiable and have been measured as analytes in PK studies.

Ethinyl estradiol shows high variability in bioavailability. It has intra-subject variability (CV%) of 20 – 26% and 12 – 25% for Cmax and AUC, respectively. Peak plasma levels are attained within 3 hours but another Tmax may occur at about 12 hours since it extensively undergoes enterohepatic recycling.

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Yes	3
Waiver requests	Yes	2
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

	Parent	Parent	Metabolite
Analyte name	Ethinyl Estradiol	Norgestimate	Deacetylnorgestimate
Internal Standard	D ₄ - Ethinyl Estradiol	Norethindrone Acetate Oxime	Norethindrone Oxime
Method description			
QC range	6.00 to 375 pg/mL	60 to 1875 pg/mL	60 to 1875 pg/mL
Standard curve range	2.00 to 500.0 pg/mL	20 to 2500 pg/mL	20 to 2500 pg/mL
Limit of quantitation	2.00 pg/mL	20.0 pg/mL	20.0 pg/mL
Average recovery of Drug (%)	67%	97%	97%
Average Recovery of Int. Std (%)	61%	121%	102%
Intraday precision range (% CV)	1.6 to 8.2%	5.6 to 8.5%	1.1 to 5.9%
Intraday accuracy range (%)	97.5 to 100.4%	92.0 to 96.1%	95.2 to 101.3%
Interday precision range (% CV)	7.2 to 10.7%	8.6 to 10.2%	4.5 to 8.6%
Interday accuracy range (%)	103.3 to 104.7%	96.2 to 99.7%	99.2 to 102.0%
Bench-top stability (hrs)	48 hours	18 hours	18 hours
Stock stability (days)	N/A	N/A	N/A
Processed stability (hrs)	121 hours	51 hours	51 hours
Freeze-thaw stability (cycles)	6 cycles	6 cycles	6 cycles
Long-term storage stability (days)	357 days	84 days	84 days
Dilution integrity	2 to 10- fold	2 to 10- fold	2 to 10-fold
Specificity	Yes	Yes	Yes
SOPs submitted	Yes	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes	Yes
20% Chromatograms included (Y/N)	Yes	Yes	Yes
Random Selection of Serial Chrom	Yes	Yes	Yes

E. In Vivo Study

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	R02-123
Study Design	Randomized, single dose, two-way crossover study under fasting conditions.
No. of subjects enrolled	36
No. of subjects completing	35
No. of subjects analyzed	35
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 0 Female: 36
Test product	Ethinyl Estradiol / Norgestimate Tablets
Reference product	Ortho Tri-Cyclen® Tablets
Strength tested	0.250 mg / 0.035 mg
Dose	2 x 0.250 mg / 0.035 mg

Summary of Statistical Analysis Additional Information in Appendix, Table 7 and Table 8		
<u>Ethinyl Estradiol</u>		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	0.93	89.2 – 96.5
AUC _∞	0.92	89.5 – 94.7
C _{max}	0.91	86.7 – 99.4
<u>17-deacetylnorgestimate</u>		
Parameter	Point Estimate	90% Confidence Interval
AUC _{0-t}	0.95	89.9 – 99.8
AUC _∞	0.95	90.6 – 100.3
C _{max}	0.95	90.6 – 100.3

Reanalysis of Study Samples Additional information in Appendix, Table 6								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
N/A (no PK repeats)								
Total								

Did use of recalculated plasma concentration data change study outcome?

There were five samples reassayed (1 for ethinyl estradiol, 1 for norgestimate, 1 for deacetylnorgestimate and 2 for norgestimate/deacetylnorgestimate) as per MDSPS SOP 53.01.002 with the original values reported as the final results.

Comments on Fasting Study: The fasting study is acceptable.

F. Formulation

Location in appendix	Section B, Page 18
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored? (yes or no)	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	0.05% Polysorbate (Tween 20)
Volume (mL)	600 mL
USP Apparatus type	Paddle
Rotation (rpm)	75 rpm
Firm's proposed specifications	—% (Q) in 30 min
FDA-recommended specifications	—% (Q) in 30 min (OGD), — % (Q) in 20 min (NDA)
F2 metric calculated (yes or no)	N/A
If no, reason why F2 not calculated	Rapidly dissolving
Method is acceptable (yes or no)	Yes

F2 metric, other strengths compared to biostudy strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A (rapidly dissolving)			

F2 metric, test compared to reference	
Strength	F2 metric
N/A (rapidly dissolving)	

H. Waiver Request(s)

Strengths for which waivers requested	0.180 mg/0.035 mg and 0.215 mg /0.035
Regulation cited	21 CFR 320.22 (d)(2)
Proportional to strength tested in vivo (yes or no)	Yes
Dissolution is acceptable (yes or no)	Yes
Waiver granted (yes or no)	Yes

I. Deficiency Comments

None

J. Recommendations

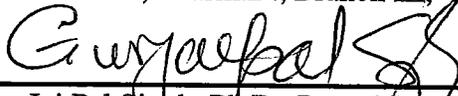
1. The in vivo bioequivalence study conducted under fasting conditions by Watson Laboratories, Inc. on its Ethinyl Estradiol / Norgestimate tablets, 0.035 mg / 0.250 mg, lot # F1122A001, comparing it to the reference product, Ortho Tri-Cyclen® tablets, 0.035 mg / 0.250 mg, lot # 21N241, manufactured by Ortho McNeil Pharmaceuticals, is acceptable to the Division of Bioequivalence. The study demonstrates that Watson's Ethinyl Estradiol / Norgestimate tablets, 0.035 mg / 0.250 mg, is bioequivalent to the reference product, Ortho Tri-Cyclen® tablets, 0.035 mg / 0.250 mg, manufactured by Ortho McNeil Pharmaceuticals.
2. The dissolution testing conducted by the firm on its Ethinyl Estradiol / Norgestimate tablets, 0.035 mg / 0.250 mg, 0.035 mg / 0.215 mg, 0.035 mg / 0.180 mg tablets are acceptable. The formulations for the .035 mg / 0.215 mg and 0.035 mg / 0.180 mg tablets are proportionally similar to the 0.035 mg / 0.250 mg tablet which underwent acceptable bioequivalency testing. The waivers of the *in vivo* bioequivalence study requirements for 0.035 mg / 0.215 mg and 0.035 mg / 0.180 mg tablets of the test product are granted. The 0.035 mg / 0.215 mg and 0.035 mg / 0.180 mg tablets are therefore deemed bioequivalent to Ortho Tri-Cyclen® 0.035 mg / 0.215 mg and 0.035 mg / 0.180 mg tablets, respectively, manufactured by Ortho McNeil Pharmaceuticals.
3. The dissolution testing (FDA "interim" method) should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 600 mL, 0.05% Tween 20 using Apparatus II (paddle) at 75 rpm. The test products should meet the following specifications: NLT — % (Q) in 20 minutes

From bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing and the application is acceptable.

 8/15/2003

Patrick Nwakama, Pharm.D., Branch III,

Date



8-15-03

RT: Gur Jai Pal Singh, Ph.D., Branch III,

Date



8/18/03

for

Dale P. Conner, Pharm. D.

Date

Director, Division of Bioequivalence
Office of Generic Drugs

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IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	PRACS R02-123
Study Title	A Relative Bioavailability Study Of Ethinyl Estradiol / Norgestimate Tablets Under Fasting Conditions
Clinical Site	_____
Principal Investigator	_____, Pharm.D.
Study/Dosing Dates	Period I: September 21 – 25, 2002; Period II: October 19 – 23, 2002
Analytical Site	_____
Analytical Director	_____, B.S.
Analysis Dates	October 30 – November 20, 2002 (Ethinyl Estradiol) and October 30 - December 2, 2002 (Norgestimate / deacetylnorgestimate).
Storage Period	60 days (Ethinyl Estradiol) and 72 days (Norgestimate / deacetylnorgestimate).

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Norgestimate and Ethinyl Estradiol Tablets	Ortho Tri-Cyclen®
Manufacturer	Watson Laboratories, Inc.	Ortho-McNeil
Batch/Lot No.	F1122A001	21N241
Manufacture Date	AL 2002	N/A
Expiration Date	05/04	12/03
Strength	0.250 mg / 0.035 mg	0.250 mg / 0.035 mg
Dosage Form	Tablet	Tablet
Batch Size	_____	N/A
Production Batch Size	N/A	N/A
Potency	97.2% (Norgestimate); 98.8% (Ethinyl Estradiol)	98.3%(Norgestimate); 99.6% (Ethinyl Estradiol)
Content Uniformity	98.5% (RSD 1.5%) – Norgestimate; 98.8% (RSD 1.1%) – Ethinyl Estradiol	N/A
Formulation	See Appendix Section B	
Dose Administered	2 x 0.250 mg / 0.035 mg	
Route of Administration	Orally	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	28 days
Randomization Scheme	AB: 2,3,5,6,8,10,11,12,13,17,19,22,25,26,28,31,34,35 BA:1,4,7,9,14,15,16,18,20,21,23,24,27,29,30,32,33,36
Blood Sampling Times	0,0.5,0.75,1,1.25,1.5,2,2.5,3,4,6,10,14,24,36,48,72, and 96 hours.
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	- 20°C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours
Length of Confinement	34 hours
Safety Monitoring	Subjects were monitored throughout the confinement portion of the study. Vital signs were taken prior to dosing and as scheduled post-dosing.

Table 1 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18				Caucasian	97.3
Mean	22.1	Mean	64.2	18-40	100	Male		Afr. Amer.	
SD	4.1	SD	8.6	41-64		Female	100	Hispanic	
Range	19 – 35	Range	49.9 – 86.7	65-75				Asian	
				>75				Others	2.7

Study Results

Table 2 Dropout Information

Subject No	11
Reason	(+) pregnancy test
Period	II (check in)
Replacement	No

Table 3 Study Adverse Events

Comments: *(on adverse events)*

Forty-two (42) adverse events were reported by 53% of the subjects with the reference outnumbering the test by 2:1 ratio. The events were mild in severity and most commonly headache, nausea, vomiting and dizziness.

Table 4 Protocol Deviations**Comments: (protocol deviations)**

Thirty (30) blood sampling delays (< 10 min) and 8 “no sample” cases were reported. Actual sampling times were used in analyses and the integrity of the study was not compromised.

Table 5 Assay Validation – Within Study

	Ethinyl Estradiol	Norgestimate	Deacetyl Norgestimate
QC Conc. (pg/mL)	6 – 375 pg/mL	60 – 1875 pg/mL	60 – 1875 pg/mL
Inter day Precision (% CV)	5.10 – 7.40%	7.24 – 8.82%	5.03 – 8.81%
Inter day Accuracy (%)	99.3 – 103.7	95.6 – 96.2%	96.4 – 98.8
Cal. Standards Conc. (pg/mL)	2 – 500 pg/mL	20 – 2500 pg/mL	20 – 2500 pg/mL
Inter day Precision (% CV)	2.48 – 7.26	2.30 – 7.39	3.4 – 9.9
Inter day Accuracy (%)	96.4 – 1.32	98.9 – 102.6	98.7 – 100.9
Linearity Range (R² values)	0.9971	0.9988	0.9982

Chromatograms: Any interfering peaks? None

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
——— SOP 53.01.002	September 23, 2002	Reporting of Data Generated from the Analysis of Biological Matrices

Comments on repeat assays:

The final values reported were as per ——— SOP 53.01.002. The reviewer agrees with the outcome of the repeat assays.

Comments on Within-Study Validation: The within-study validation is complete.

Conclusion: Analytical method is acceptable.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean Ethinyl Estradiol plasma concentrations are presented in Table 10 and Figure 1

Ethinyl Estradiol						
Parameter	Units	Test		Reference		T/R
		Mean	% CV	Mean	% CV	
AUC _{0-t}	pg*hr/mL	1847.31	26.6	1986.39	25.97	0.93
AUC _∞	pg*hr/mL	1892.82	25.04	2045.48	24.42	0.92
C _{max}	pg/mL	209.54	26.72	229.98	23.26	0.91
T _{max}	hr	1.28	32.04	1.46	41.20	0.88
T _{1/2}	hr	15.95	23.3	15.85	22.36	1.01
kel	hr ⁻¹	0.046	23.92	0.05	23.82	0.92

Mean 17-deacetylnorgestimate plasma concentrations are presented in Table 10 and Figure 1

17-deacetylnorgestimate						
Parameter	Units	Test		Reference		T/R
		Mean	% CV	Mean	% CV	
AUC _{0-t}	pg*hr/mL	29569.66	22.13	31181.69	22.45	0.95
AUC _∞	pg*hr/mL	31066.47	22.23	32527.65	21.22	0.95
C _{max}	pg/mL	3504.19	20.42	3398.32	20.29	1.03
T _{max}	hr	1.40	43.35	1.68	41.30	0.83
T _{1/2}	hr	23.87	22.95	24.60	23.95	0.97
kel	hr ⁻¹	0.03	21.81	0.03	24.71	1.00

Table 8 Least Square Geometric Ethinyl Estradiol Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
AUC _{0-t}	1786.30	1926.16	0.93	89.2 – 96.5
AUC _∞	1831.64	1988.94	0.92	89.5 – 94.7
C _{max}	203.20	223.82	0.91	86.7 – 99.4

Least Square Geometric Deacetylnorgestimate Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
AUC _{0-t}	28811.50	30412.97	0.95	89.9 – 99.8
AUC _∞	30287.79	31761.11	0.95	90.6 – 100.3
C _{max}	3432.00	3320.83	1.03	98.5 – 108.5

Table 9 Additional Ethinyl Estradiol Study Information

Root mean square error, AUC _{0-t}	0.0974	
Root mean square error, AUC _∞	0.0669	
Root mean square error, C _{max}	0.1137	
mean ratio AUC _{0-t} /AUC _∞	T = 0.98	R = 0.97

Additional Deacetylnorgestimate Study Information

Root mean square error, AUC _{0-t}	0.1286	
Root mean square error, AUC _∞	0.1234	
Root mean square error, C _{max}	0.1192	
mean ratio AUC _{0-t} /AUC _∞	T = 0.95	R = 0.96

Comments: (on pharmacokinetic analysis)

- k_{el} and AUC_∞ were determined for all subjects.
- Measurable drug concentrations at 0 hr: 1 (subj #21, ref, Ethinyl Estradiol 1.2% C_{max}). The reviewer agrees with the firm's decision to include subject in analysis.
- First measurable drug concentration as C_{max}: None.
- Were there statistically significant sequence or period effects? No
- The 90% confidence intervals are within the acceptable limits of 80-125% for AUC_T, AUC_I, C_{max}.
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer are in good agreement with firm's calculations.

Conclusion: The single-dose fasting bioequivalence study is acceptable.

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Table 10 Mean Ethinyl Estradiol Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (pg/mL)

Time	Test (n= 35)		Reference (n= 35)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0.00	0.00	-	0.08	591.61	0.00
0.50	111.31	40.33	93.63	51.56	1.19
0.75	170.36	34.83	167.79	30.76	1.01
1.00	191.99	31.54	199.72	24.95	0.96
1.25	191.92	26.36	209.78	24.13	0.91
1.50	191.78	28.66	210.79	25.58	0.91
2.00	175.44	26.41	202.66	25.71	0.87
2.50	156.49	23.33	178.91	25.10	0.87
3.00	142.69	23.25	155.11	25.08	0.92
4.00	115.38	26.12	127.67	23.63	0.90
6.00	81.40	24.81	90.58	24.63	0.90
10.00	45.30	29.32	48.45	25.27	0.93
14.00	32.16	27.33	35.43	26.61	0.91
24.00	18.27	30.96	19.75	29.57	0.92
36.00	11.60	37.19	12.19	37.57	0.95
48.00	7.09	50.19	6.83	42.38	1.04
72.00	2.46	137.77	2.63	130.62	0.93
96.00	1.24	336.35	0.73	485.19	1.70

Table 11 Mean 17-DeacetylNorgestimate Plasma Concentrations, Single-Dose Fasting BE Study

Time	Test (n= 35)		Reference (n= 35)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0.00	0.00	0.00	0.00	0.00	0.00
0.50	1349.97	56.91	976.27	71.11	1.38
0.75	2530.27	43.24	1956.20	44.43	1.29
1.00	3069.49	33.09	2516.08	38.71	1.22
1.25	3020.47	26.99	2760.44	37.79	1.09
1.50	2980.34	23.12	2969.05	28.00	1.00
2.00	2689.12	22.41	2821.29	23.62	0.95
2.50	2300.84	26.19	2459.78	23.91	0.93
3.00	1950.11	26.13	2141.46	27.82	0.91
4.00	1396.98	29.32	1584.69	29.02	0.88
6.00	862.39	30.69	984.47	25.75	0.88
10.00	554.32	32.48	573.73	23.18	0.97
14.00	442.74	25.59	485.63	23.80	0.91
24.00	329.76	26.23	350.21	26.76	0.94
36.00	232.82	32.32	248.54	30.19	0.94
48.00	162.69	34.32	166.66	35.53	0.98
72.00	84.18	55.22	91.54	60.73	0.92
96.00	45.72	111.22	53.15	109.55	0.86

Figure 1 Mean Ethinyl Estradiol Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

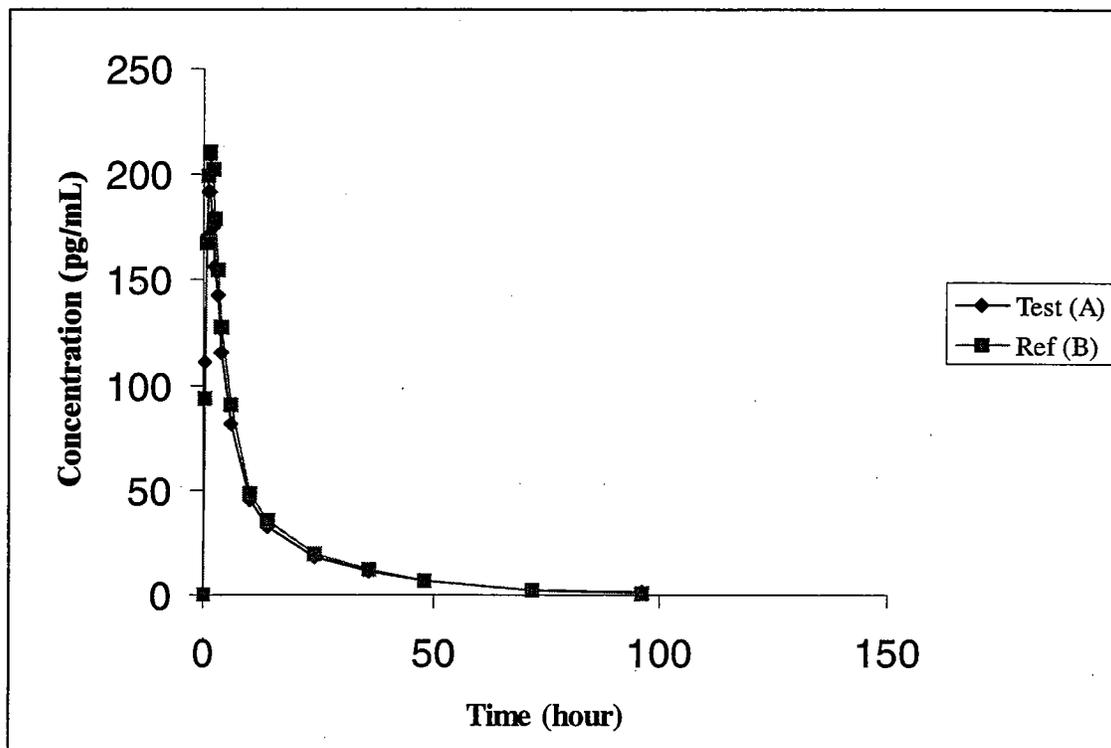
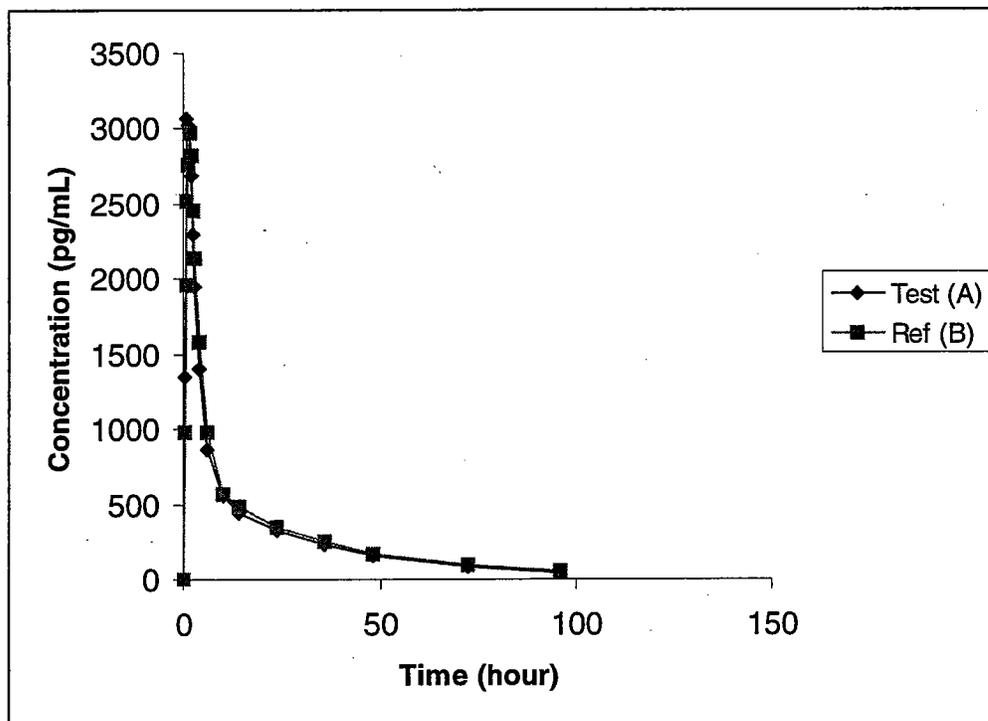


Figure 2 Mean 17-deacetylNorgestimate Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



B. Formulation Data

Dosage Strength	0.180 mg/ 0.035 mg		0.215 mg/ 0.035 mg		0.250 mg / 0.035 mg	
Ingredient	mg/tab	% w/w	mg/tab	% w/w	mg/tab	% w/w
Norgestimate	0.180	0.180	0.215	0.215	0.250	0.250
Ethinyl Estradiol, USP	0.035	0.035	0.035	0.035	0.035	0.035
Lactose Anhydrous — NF						
Providone ———, USP						
Vitamin E ———, NF						
(1)						
FD&C Yellow #6						
FD&C Yellow #10						N/A
Microcrystalline Cellulose ←, NF						
Polacrillin Potassium, NF						
Magnesium Stearate, NF						
Total Tablet Weight						100.00

(1) _____

**APPEARS THIS WAY
ON ORIGINAL**

C: Dissolution Data

Table 1

TEST				REFERENCE		
Lot No.: F1108001				Lot No.: 21N241		
Strength: 0.25 mg / 0.035 mg				Strength: 0.25 mg / 0.035 mg		
Norgestimate						
No. of Units: 12				No. of Units: 12		
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
15	97.1	↘	1.7	101.0	↘	1.4
30	97.9		1.4	102.1		1.2
45	98.1		1.1	102.3		1.4
60	98.1		1.2	102.1		1.6
Ethinyl Estradiol						
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
15	96.2	↘	1.5	100.0	↘	2.5
30	97.5		1.7	101.5		2.0
45	96.7		1.0	102.6		1.4
60	95.0		1.0	101.0		1.5
TEST				REFERENCE		
Lot No.: F1107001				Lot No.: 21N241		
Strength: 0.215 mg / 0.035 mg				Strength: 0.215 mg / 0.035 mg		
Norgestimate						
No. of Units: 12				No. of Units: 12		
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
15	95.9	↘	1.0	95.8	↘	1.0
30	97.2		1.1	96.0		1.2
45	96.5		0.9	95.9		1.1
60	97.1		1.5	95.3		1.3
Ethinyl Estradiol						
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
15	90.6	↘	1.2	89.3	↘	1.0
30	91.3		1.1	87.7		1.5
45	90.8		1.2	87.8		1.1
60	92.1		1.0	87.8		2.0

TEST				REFERENCE		
Lot No.: F1106001				Lot No.: 21N241		
Strength: 0.18 mg / 0.035 mg				Strength: 0.18 mg / 0.035 mg		
Norgestimate						
No. of Units: 12				No. of Units: 12		
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
15	97.8	\	1.0	102.3	\	1.7
30	98.6		1.0	105.3		1.8
45	98.8		1.0	105.4		1.6
60	98.4		0.9	104.9		1.7
Ethinyl Estradiol						
Time(min)	Mean	Range	%RSD	Mean	Range	%RSD
15	92.4	\	0.9	97.4	\	1.5
30	94.0		0.8	99.6		1.7
45	95.5		0.9	100.5		1.3
60	94.7		1.0	100.6		1.6

**APPEARS THIS WAY
ON ORIGINAL**

Figure 2 Dissolution Profiles (*optional*)

**APPEARS THIS WAY
ON ORIGINAL**

D. Consult Reviews

None

**APPEARS THIS WAY
ON ORIGINAL**

F. Additional Attachments

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: #76-626 APPLICANT: Watson Laboratories Inc.

DRUG PRODUCT: Ethinyl Estradiol/Norgestimate tablets,
0.035 mg/0.250 mg, 0.035 mg/0.215 mg, 0.035 mg/0.180 mg

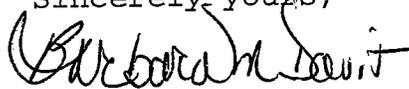
The Division of Bioequivalence has completed its review and has no further questions at this time. The dissolution testing (FDA "interim" method) should be incorporated into your manufacturing controls and stability programs. The dissolution testing should be conducted in 600 mL, 0.05% Tween 20 using Apparatus II (paddle) at 75 rpm. The test products should meet the following specifications:

Not less than —% (Q) in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for



Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA #76626
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer P. Nwakama
HFD-658/ Team leader GJP Singh

P 8/15/2003

V:\FIRMSNZ\Watson\ltrs&rev\76626SDW1202.doc

Endorsements: (Final with Dates)

HFD-658/ Reviewer P. Nwakama *P*

HFD-658/ Team Leader GJP Singh *cross 8-15-03*

HFD-650/ S. Mazzella

HFD-650/ D. Conner *brd 8/15/03*

Ar

BIOEQUIVALENCY - Acceptable

Submission date: 12/30/02

1. Fasting Study (STF) Strength: 0.035 mg/0.250 mg
Clinical: _____
Analytical: _____
2. Dissolution Waiver (DIW) Strength: 0.035 mg/0.215 mg
Outcome: AC
3. Dissolution Waiver (DIW) Strength: 0.035 mg/0.180 mg
Outcome: AC

Outcome Decisions: AC - acceptable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-626

ADMINISTRATIVE DOCUMENTS

V5.1

RECORD OF TELEPHONE CONVERSATION

On this date, I contacted Watson Laboratories, Inc. (Watson) and made reference to their ANDA 76-626 and to their submission dated July 31, 2003.

I explained to Ms. Greaves that Watson was not to respond to our deficiency letter until Watson was notified by the DMF holder that they have responded to the DMF deficiency. Watson's submission dated July 31, 2003 states that the DMF holder "is in the progress of preparing their response." Therefore, the Agency cannot accept this submission as an amendment. As a result, the July 31, 2003 submission will be converted to a "New Correspondence," and will not be reviewed.

At that time, Ms. Greaves informed me that Watson submitted an amendment to the sister application for the same drug product (ANDA 76-627) with the same information regarding the DMF. I informed Ms. Greaves that that amendment (also dated July 31, 2003) will also be converted to a "New Correspondence."

I instructed Ms. Greaves that once Watson is notified that the DMF holder has responded to the DMF deficiencies, Watson can make a submission with a copy of the DMF holder's notification and reference to the July 31, 2003 submissions. I also informed Ms. Greaves that the review clock for the two ANDA's will be restarted at that time.

Ms. Greaves acknowledged my comments.

DATE: 10-30-03
ANDA NUMBER 76-626 & 76-627
TELECON INITIATED BY AGENT
PRODUCT NAME: Norgestimate and Ethinyl Estradiol Tablets
FIRM NAME: Watson Laboratories, Inc.
FIRM REPRESENTATIVES: Theresa L. Greaves, Manager Regulatory Affairs
TELEPHONE NUMBER: 909-493-5514
FDA REPRESENTATIVES Sarah Ho, Project Manager
SIGNATURES: S.Ho

Orig: ANDA 76-626

ANDA 76-627

Cc: Division File

Chem. I Telecon Binder

V:\FIRMSNZ\WATSON\TELECONS\76626.10.30.03.doc

e

OGD APPROVAL ROUTING SUMMARY

ANDA # 16-626 Applicant Watson Laboratories, Inc.
Drug largestimate and Ethinyl Estradiol Strength(s) 0.175/0.035mg / 0.215/0.035mg / 0.250mg
Approval Tablets TENTATIVE APPROVAL SUPPLEMENTAL APPROVAL (NEW STRENGTH) OTHER

REVIEWER:

DRAFT Package

FINAL Package

1. Martin Shimer
Chief, Reg. Support Branch

Date 8 Aug 06
Initials MS

Date 8/14/06
Initials RW

Contains GDEA certification: Yes No Determ. of Involvement? Yes No
(required if sub after 6/1/92) Pediatric Exclusivity System

Patent/Exclusivity Certification: Yes No Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted

Notify patent holder/NDA holder Yes No Written request issued

Was applicant sued w/in 45 days: Yes No Study Submitted

Has case been settled: Yes No Date settled: _____

Is applicant eligible for 180 day _____

Generic Drugs Exclusivity for each strength: Yes No

Date of latest Labeling Review/Approval Summary done

Any filing status changes requiring addition Labeling Review Yes No

Type of Letter: _____
Comments: Firm with OAI and M-11 exclusivity. Once revised labeling has been submitted a review of M-11 committed will be eligible for Full AP

2. Project Manager Jeanne Kandy Team 12
Review Support Branch

Date 7/1/2006
Initials JK

Date _____
Initials _____

Original Rec'd date 1/2/2003 EER Status Pending Acceptable OAI

Date Acceptable for Filing 1/2/2003 Date of EER Status 8/17/06

Patent Certification (type) III Date of Office Bio Review 8/18/2003

Date Patent/Exclus. expired 9/26/2003 Date of Labeling Approv. Sum 9/22/2004

Citizens' Petition/Legal Case Yes No Labeling Acceptable Email Rec'd Yes No

(If YES, attach email from PM to CP coord) Labeling Acceptable Email filed Yes No

First Generic Yes No Date of Sterility Assur. App. NA

Priority Approval Yes No Methods Val. Samples Pending Yes No

(If yes, prepare Press Release) MV Commitment Rcd. from Firm Yes No

Acceptable Bio reviews tabbed Yes No Modified-release dosage form: Yes No

Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes

Pediatric Waiver Request Accepted Rejected Pending

Previously reviewed and tentatively approved Date _____

Previously reviewed and CGMP def. /NA Minor issued Date _____

Comments: _____

3. David Read (PP IVs Only) Pre-MMA Language included
OGD Regulatory Counsel, Post-MMA Language Included

Date _____
Initials _____

Comments: N/A

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III

Date 8/14/06
Initials WR

Comments: conc satisfactory.

REVIEWER:

FINAL ACTION

5. Frank Holcombe First Generics Only
Assoc. Dir. For Chemistry

Date _____
Initials _____

Comments: (First generic drug review)

N/A. Multiple ANDAs have been approved for this drug product

-28 28 Day/Remission
RCD= Ortho Tri-Cyclen Tablets ~~NDA~~ NDA 19-697

6. Vacant Deputy Dir., DLPS
R.W. Johnson Pharmaceutical Research Institute

Date 8/17/06
Initials _____

7. Peter Rickman
Director, DLPS

Date _____
Initials _____

Para. IV Patent Cert: Yes No Pending Legal Action: Yes No Petition: Yes No

Comments:

Found acceptable & 8/15/03. Dissolution, stability, and all 3 component combinations found acceptable. Waivers granted to the 0.035mg/0.215mg and 0.035mg/0.800mg strengths under 21 CFR 320.22(a)(2). Bio studies sites have acceptable ODT completion histories. Office-level bio endorsed 8/13/03. FPL found acceptable for approval 9/22/04 (as endorsed 8/10/06). CMC found acceptable for approval 7/28/06. Methods validation was not requested. Acceptable EGS dated 8/17/06. No B.A.T. alerts noted.

8. Robert L. West
Deputy Director, OGD

Date 8/17/2006
Initials _____

Para. IV Patent Cert: Yes No Pending Legal Action: Yes No Petition: Yes No

Press Release Acceptable

Comments:

There are no unexpired patents listed in the current "Orange Book" for this drug product. Watson has addressed the M-41 exclusivity (8/17/06) via "carve-out". It is not included in the FPL.

This ANDA is recommended for approval.

9. Gary Buehler
Director, OGD

Date 8/17/06
Initials _____

Comments:

First Generic Approval PD or Clinical for BE Special Scientific or Reg. Issue

Press Release Acceptable

10. Project Manager, Team JEANNE
Review Support Branch

Date 8/17/06
Initials _____

Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:

12:20 pm Time notified of approval by phone 12:22 pm Time approval letter faxed

FDA Notification:

8/17/06 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.

8/17/06 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

8/17/06 Date Press Release emailed to CDER Liaison (M.Gonitzke)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 76-626

CORRESPONDENCE



WATSON Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

December 30, 2002

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

50501(z)(A)OK
26 FEB 2003
J. L. Danz

**RE: Abbreviated New Drug Application
Norgestimate and Ethinyl Estradiol Tablets
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
and Placebo Tablets – 28 Count**

Dear Mr. Buehler:

Watson Laboratories, Inc. submits herein an original Abbreviated New Drug Application for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg and placebo tablets.

The drug product described above is the same as Ortho Tri-Cyclen® (norgestimate and ethinyl estradiol tablets) 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg and placebo tablets manufactured by ORTHO Mc-NEIL PHARMACEUTICAL, INC. We have submitted comparative information to indicate that our product is the same as the reference listed drug product. This information is presented in tabular form in Section IV, comparing active ingredient, condition of use, route of administration, dosage form, strength, bioequivalence, and labeling for the products as supplied by Watson Laboratories, Inc., (manufactured by Patheon, Inc. for Watson) and by ORTHO Mc-NEIL PHARMACEUTICAL, INC.

Watson Laboratories, Inc. commits to resolve any issues identified in the method validation process after approval.

In addition, Watson Laboratories, Inc. proposes that the above product be labeled and distributed using a proprietary tradename. Therefore, the following proposed tradename be submitted for agency evaluation and consideration:

TriNessa™

We believe the proposed proprietary name meets the requirements as set forth in 21 CFR 201.10(c)(3).

RECEIVED
JAN 02 2003

OGD / CDER



Upon acceptance by the FDA of the proprietary tradename, we will update this application with the following revised documents bearing the new tradename:

1. Compression batch records reflecting the proprietary tradename.
2. Specification and Analytical Release Forms to reflect any new information.
3. Final printed labeling to include the package insert, carton label and blister pack label reflecting the proprietary tradename.

Please note that due to the concerns over the proprietary nature of the bioassay method, the CRO has chosen to forward the bioassay method associated with this application to OGD under separate cover once the ANDA # is assigned to this application.

We have enclosed one (1) archival and one (1) review copy. As required, two (2) additional separately bound copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient and finished dosage form) are included as one of the volumes of the archival copy of this ANDA.

The number of volumes in the archival, review, and field copies of the ANDA are as follows:

Blue Archival Copy	- 8 volumes
Orange Review Copy	- 5 volumes
Red Review Copy	- 3 volumes
Burgundy Field Copy	- 3 volumes

In accordance with 21 CFR 314.94(d)(5), one (1) field copy of the application will be forwarded to Peter Rickman, Acting Director, Division of Labeling and Program Support as requested in his communication with Watson on November 6, 2002. OGD will forward the field copy to the International Group at FDA. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copy of this application.

We trust the information submitted is sufficient for this Abbreviated New Drug Application to be evaluated. Please contact me by phone at (909) 493-5475 or by fax at (909) 493-5806 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Margaret Choy, BSc., RAC
Director
Regulatory Affairs

MC/tg

ANDA 76-626

FEB 26

Watson Laboratories, Inc.
Attention: Margaret Choy
311 Bonnie Circle
Corona, CA 92880

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated February 24, 2003 and to your correspondence dated February 24, 2003.

NAME OF DRUG: Norgestimate and Ethinyl Estradiol Tablets,
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and
0.250 mg/0.035 mg (28 Day)

DATE OF APPLICATION: December 30, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 2, 2003

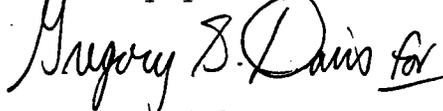
We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sarah Kim
Project Manager
(301) 827-5848

Sincerely yours



Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

A B

ANDA 76-626

cc: DUP/Jacket

Division File

Field Copy

HFD-610/R.West

HFD-610/P.Rickman

HFD-92

HFD-615/M.Bennett

HFD-600/

Endorsement:

HFD-615/GDavis, Chief, RSB *G Davis* 26-FEB-2003 date

HFD-615/CBina, CSO *M. Bina* 2-26-03 date

Word File V:\Firmsnz\Watson\Itrs&rev\76626.ACK

F/T

ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL



January 28, 2003

NEW CORRESP

NC

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Minor Amendment

**RE: ANDA 76-626
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035, 0.215 mg/0.035
mg, 0.250 mg/0.035 mg and Placebo Tablets – 28 Count**

Dear Mr. Buehler:

Watson Laboratories, Inc. submits herein a Minor Amendment to our December 30, 2002 original Abbreviated New Drug Application (ANDA 76-626) for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, 0.250 mg/0.035 mg and placebo tablets.

Documentation provided in this submission are either revised versions of documents provided in the original ANDA and will serve as replacements and/or new documents that will serve as additions to the original ANDA. These documents have been numbered accordingly for replacement and insertion into our original application, where applicable.

The attached table (**Table 1**) is a comprehensive list of all revised documents, including instructions for the replacements and additions. Please replace the documents in the original application, submitted on December 30, 2002, with the attached revised documents located in the "Blue" pressboard binder. For your convenience, we are supplying you with two (2) sets of copies (labeled "**Copy 1**" and "**Copy 2**") for replacement or insertion in the original Archival and Review copies submitted on December 30, 2002. Additionally, we have provided 2 extra copies of the replacements and/or new documents for *Section XV Analytical Methods* for inclusion in the separately bound Method Validation. Copies submitted with the original ANDA on December 30, 2002.

We have enclosed one (1) archival, and one (1) review copy of this Minor Amendment for your files, (in addition to the extra copies labeled "**Copy 1**" and "**Copy 2**"). In accordance with 21 CFR 314.94(d)(5), one (1) field copy of the application will be forwarded to the International Group at FDA. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copy of this amendment.

RECEIVED

JAN 29 2003

OGD / CDER



*Re. Norgestimate and Ethinyl Estradiol Tablets
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
ANDA 76-626
Minor Amendment
January 28, 2003
Page 2 of 8*

We trust the information submitted is sufficient for this Minor Amendment to be evaluated. Please contact me by phone at (909) 493-5514 or by fax at (909) 493-5806 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Theresa L. Greaves, RAC
Manager, Regulatory Affairs
Encl.

**APPEARS THIS WAY
ON ORIGINAL**



WATSON Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

February 24, 2003

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

Telephone Amendment

NC

NAI CMBum 2/27/03

RE: **ANDA #76-626**
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035, 0.215/0.035,
0.250 mg/0.035 and Placebo Tablets -28 Count

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting a Telephone Amendment to our December 30, 2002 original Abbreviated New Drug Application (ANDA #76-626) for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, 0.250 mg/0.035 mg and Placebo Tablets.

This Amendment is in response to a telephone request from Christine Bina, Project Manager, OGD on February 24, 2003 requesting that Watson provide a Drug Master File reference letter for _____ (DMF # _____), the makers of the _____ of the blister packaging configuration. Attached is the DMF letter from _____.

We have enclosed one (1) archival, and one (1) review copy of this Telephone Amendment for your files. In accordance with 21 CFR 314.94(d)(5), one (1) field copy of the application will be forwarded to the International Group at FDA. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copy of this amendment.

We trust the information submitted is sufficient for this Amendment to be reviewed. Please contact me by phone at (909) 493-5514 or by fax at (909) 493-5806 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Theresa L. Greaves, RAC
Manager, Regulatory Affairs

RECEIVED

FEB 25 2003

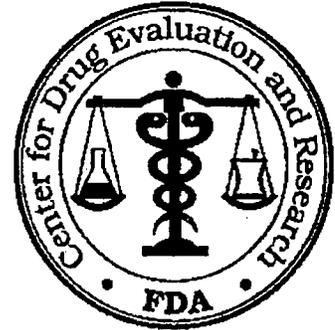
OGD / CDER

Fax sent on 02/24/03 to Christine XX, Regulatory Project Manager, OGD at 301-594-1174.

MINOR AMENDMENT

ANDA 76-626

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



JUN 25 2003

TO: APPLICANT: Watson Laboratories, Inc.

TEL: 909-493-5475

ATTN: Margaret Choy

FAX: 909-493-5806

FROM: Sarah Kim

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 31, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28-day regimen).

Reference is also made to your amendment(s) dated: January 28, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (5 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Labeling and Bioequivalency comments will be provided under separate covers.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

882
1/25/03

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of trade secret and/or

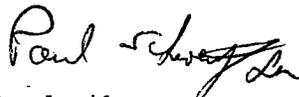
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6/25/2003 FDA FAX

4. The review of the Bioequivalency section of this application is pending. Any deficiencies found will be sent to you under separate cover.
5. The review of the Labels and Labeling of this application is pending. Any deficiencies found will be sent to you under separate cover.

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**



WATSON Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

ARCHIVAL COPY

June 30, 2003

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

Telephone Amendment

NC

RE: **ANDA #76-626**
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035, 0.215 mg
/0.035 mg, 0.250 mg/0.035 mg and Placebo Tablets -28 Count

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting a Telephone Amendment to our December 30, 2002 original Abbreviated New Drug Application (ANDA #76-626) for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, 0.250 mg/0.035 mg and Placebo Tablets.

This Amendment is in response to a telephone request on June 25, 2003 from Sarah Kim, Project Manager, OGD requesting that Watson provide confirmation that the two sites listed below are owned by Patheon, Inc.:

Patheon Inc. (YMO)
York Mills Operations – PDS Lab
865 York Mills Road
Toronto, Ontario M3B 1Y5 Canada
Foreign Establishment Inspection No.:
(FEI #) 3002807082
Central File No.: (CFN) 9690049

Patheon Inc. (Whitby)
Whitby Operations
111 Consumers Drive
Whitby, Ontario L1N 5Z5 Canada
Foreign Establishment Inspection No.:
(FEI #) 3003516812
Central File No.: (CFN) 9615377

Watson is confirming with this amendment that the above two sites are owned by Patheon, Inc. **Exhibit 1** contains a copy of the York Mills Registration of Drug Establishment (Form FDA 2656), signed on January 29, 2003, which identifies Patheon as the reporting firm. **Exhibit 2** contains a copy of the Whitby Registration of Drug Establishment (Form FDA 2656), signed on June 9, 2003, which also identifies Patheon as the reporting firm. Please note that the Central File Numbers (CFNs) included in the original ANDA on December 30, 2002 (refer to **Exhibit 3**, pages 0555-0556) have not been updated by Patheon to reflect their ownership, as FEI numbers are currently utilized for registration of foreign establishments, and therefore CFNs should not be used when referring to foreign establishments (Refer to **Exhibit 4** for Patheon letter dated June 27, 2003). Additionally, a letter from Patheon, dated June 27, 2003, is included in **Exhibit 5** confirming ownership and the dates of purchase by Patheon for the above two sites.

McW/MS/08
RECEIVED
JUL 02 2003
OGD/CDER



Mr. Gary Buehler
RE: ANDA 76-626: Telephone Amendment
June 30, 2003
Page 2 of 2

We have enclosed one (1) archival, and one (1) review copy of this Telephone Amendment for your files. In accordance with 21 CFR 314.94(d)(5), one (1) field copy of the application will be forwarded to the International Group at FDA. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copy of this amendment.

We trust the information submitted is sufficient for this Amendment to be reviewed. Please contact me by phone at (909) 493-5475 or by fax at (909) 493-5806 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Margaret Choy, BSc., RAC
Director, Regulatory Affairs

Fax sent on 06/30/03 to Sarah Kim, Regulatory Project Manager, OGD at 301-594-0180



July 31, 2003

NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Minor Amendment

**Re: ANDA #: 76-626
Norgestimate and Ethinyl Estradiol Tablets
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
and Placebo Tablets – 28 Count**

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this minor amendment to provide a complete response to the comments included in the FDA facsimile dated June 25, 2003 (copy attached) pertaining to the above product (ANDA #76-626). For convenience of review, your comments are provided in bold face type followed by our responses.

A. Deficiencies:

1.

[Empty rectangular box for response to deficiency 1]

2.

[Empty rectangular box for response to deficiency 2]

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AUG 01 2003

OGD/CDER

Handwritten notes: 8/28/03, M/W

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WATSON'S 7/31/2003 LETTER



standards. In the event of a dispute, the official USP methods will prevail.

Watson acknowledges that the USP analytical method will be regarded as the regulatory method in case of a dispute.

- 3. Please provide all available room temperature stability for the drug product accrued to date for review.**

Exhibit 8A contains the Stability Summary Reports for Norgestimate/Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg with up to 12 month dated for the on-going controlled room temperature study.

- 4. The review of the Bioequivalency section of this application is pending. Any deficiencies found will be sent to you under separate cover.**

Watson acknowledges that the bioequivalency section of this application is under review and agrees to resolve any deficiencies, if observed.

- 5. The review of the Labels and Labeling of this application is pending. Any deficiencies found will be sent to you under separate cover.**

Watson acknowledges that the Labels and Labeling of this application are under review and agrees to resolve any deficiencies, if observed.

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), a field copy of this correspondence will be forwarded to Peter Rickman, Director, Division of Labeling and Program Support. OGD will forward the field copy to the International Group at FDA. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this amendment.

We believe we have responded to all of the questions as outlined in the FDA facsimile dated June 25, 2003. If I can assist with the review of this amendment, please contact me by telephone at (909) 493-5514, or by facsimile at (909) 493-5806.

Sincerely,

Theresa L. Greaves, RAC
Manager, Regulatory Affairs

MC/tg/atc.
Enc.



August 4, 2003

RECEIVED

AUG 05 2003

OGD/CDER

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Telephone Amendment

RE: ANDA #76-626
Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035, 0.215 mg
/0.035 mg, 0.250 mg/0.035 mg and Placebo Tablets -28 Count

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting a Telephone Amendment to our December 30, 2002 original Abbreviated New Drug Application (ANDA #76-626) for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, 0.250 mg/0.035 mg and Placebo Tablets.

This Amendment is in response to a telephone request on July 29, 2003 from Steven Mazzella, Project Manager, OGD requesting that Watson provide a copy of _____ SOP (No. 53-01-002). Also, clarification was requested on an apparent lot number discrepancy between page 0144 in *Section VI.5.a. Introduction to Formulation Data* of the ANDA which references Lot No. F1122A002 and the Clinical Study Report (Protocol R02-123) included in *Section XXI* which references Lot No. F1122A001.

With this amendment, Watson is providing documentation confirming that _____ sent the requested SOP (_____ SOP 53-01-002) to Mr. Mazzella's attention on July 30, 2003. Refer to **Exhibit 1** for a copy of the letters sent by _____ with the requested SOP. Please note that it is _____ practice to send responses to FDA requests directly to the Agency.

The lot number used in the clinical study was Finished Packaged Product Lot. No. F1122A001, and is correctly noted in the Clinical Study Report. The exhibit batch bulk tablets were packaged in two separate Packaging runs as outlined below:

Bulk Tablet Lot Nos.	Finished Packaged Product Lot No.	No. of Blisters Packaged	Usage
F1108002 (0.250/0.035 mg)	F1122A001	_____	Clinical Study
F1107001 (0.215/0.035 mg)	F1122A002	_____	Stability Study and Warehouse
F1106001 (0.180/0.035 mg)			
F1105001 (Placebo)			



Mr. Gary Buehler
RE: ANDA 76-626: Telephone Amendment
August 4, 2003
Page 2 of 2

Both of the Finished Packaged Product Lots were packaged using the same bulk tablets with the same packaging materials. The packaging run had to be stopped after the first — blisters were packaged and it is Patheon's (Contract Manufacturer) practice to assign a separate lot number when a packaging run has been stopped and then resumed at a later date. Please note that both Packaging Lots (F1122A001 and F112A002) were released on the same results obtained from the testing that was performed on the bulk tablets.

We have revised the *Introduction to Formulation Data* (page 0144 of the original ANDA) to reflect the two Packaging lot numbers. Please refer to **Exhibit 2** for a revised *Section VI.5.a. Introduction to Formulation Data*, which includes both lot numbers. Additionally, we have revised *Section VI.1 Introduction to the Bioavailability/Bioequivalence Sections* (page 0113 in the original ANDA) and *Section XXI Other* (page 1926 in the original ANDA) to reflect Lot No. F1122A001 (refer to **Exhibit 3**).

We have enclosed one (1) archival, and one (1) review copy of this Telephone Amendment for your files. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the International Group at FDA. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copy of this amendment.

We trust the information submitted is sufficient for this Amendment to be reviewed. Please contact me by phone at (909) 493-5475 or by fax at (909) 493-5806 if you have any questions or if I can assist you with the review of this application.

Sincerely,

Margaret Choy, BSc., RAC
Director, Regulatory Affairs

Fax sent on 08/04/03 to Steven Mazzella, Regulatory Project Manager, OGD at 301-594-0181



November 6, 2003

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

CMC Amendment

ORIG AMENDMENT

N/A M

**Re: ANDA #: 76-626
Norgestimate and Ethinyl Estradiol Tablets
0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg
and Placebo Tablets – 28 Count**

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting a CMC Amendment in response to a telephone contact on October 30, 2003 from Ms. Sara Ho, OGD Project Manager pertaining to Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, 0.250 mg/0.035 mg and Placebo Tablets (ANDA #76-626).

Ms Ho informed Watson that our amendment dated July 31, 2003 would not be reviewed until _____ DMF Holder of _____ responds to the FDA's comments.

_____ as the US Agent for _____ has notified Watson that _____ has submitted the response to FDA's comments of July 1, 2003 for _____ DMF # _____ to the Agency on October 28, 2003 (See **Exhibit 1** for the correspondence).

In addition, we have included a copy of our cover letter for the Minor Amendment dated July 31, 2003 for your reference as requested by Ms. Ho (See **Exhibit 2**).

We have enclosed one (1) archival, and one (1) review copy of this CMC Amendment for your files. In accordance with 21 CFR 314.96(b), one (1) field copy of the application will be forwarded to the International Group at FDA. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical section contained in the archival and review copy of this amendment.

We trust the information submitted is sufficient for this Amendment to be reviewed. Please contact me by phone at (909) 493-5475 or by fax at (909) 493-5806 if you have any questions or if I can assist you with the review of this application.

Sincerely,

M. Choy

Margaret Choy, BSc., RAC
Director, Regulatory Affairs

MC/tg/atc
Enc.

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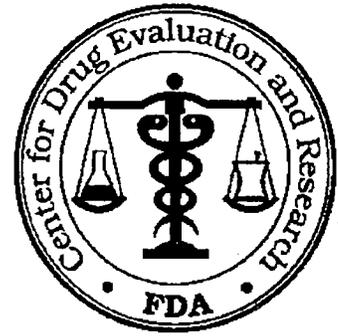
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OGD/CDER

MINOR AMENDMENT

ANDA 76-626

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)



APR 23 2004

TO: APPLICANT: Watson Laboratories, Inc.

TEL: 909-493-5475

ATTN: Margaret Choy

FAX: 909-493-~~5806~~

4581 CK

FROM: Sarah Park

PROJECT MANAGER: 301-827-5725

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated December 30, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.180 mg/0.035 mg, 0.215 mg/0.035 mg, and 0.250 mg/0.035 mg (28-day regimen).

Reference is also made to your amendment(s) dated: July 31, and November 6, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (___ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry comments provided. Labeling comments will be provided under separate cover.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

CK 4/23/04

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APRIL 24, 2003 FDA FAX

14. Please revise the dissolution testing in drug product release and stability program to incorporate as recommended by the Division of Bio-equivalence:

The dissolution testing should be conducted in 600 mL of 0.05% Tween 20 using Apparatus II (paddle) at 75 rpm. The test product should meet the following in interim specifications:

"Not less than —% (Q) in 20 minutes"

Please provide the revised specifications.

- B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:
1. Please provide all available room temperature stability data.
 2. The review of the Labels and Labeling of this application is pending. Any deficiencies found will be sent to you under separate cover.

Sincerely yours,

DS Gill

lv Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research



ORIG AMENDMENT
N/AF

August 5, 2004

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place
Rockville, MD 20855

Minor Amendment- Electronic Labeling

**Re: ANDA 76-626:
Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg
and 0.25 mg/0.035 mg and Placebo (Tri-phasic) 28 Day Regimen**

Includes Electronic Final Printed Labeling

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting this labeling amendment to provide a complete response to the comments included in the FDA original facsimile dated May 19, 2004 (copy of cover letter is attached) pertaining to the above product (ANDA #76-626). For convenience of review, your comments are provided in bold face type followed by our responses.

Labeling Deficiencies:

1. GENERAL COMMENT:

- a. Revise the storage temperature statements on all labels and labeling to read:
Store at 20-25° C (68 - 77° F) [see USP Controlled Room Temperature]**

We have revised the storage statement found on all labels and labeling (inserts and carton). Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

- b. Revise “_____” to “monophasic” and “_____” to “tri-phasic” on all affected labeling pieces.**

We have revised “_____” to “monophasic” and “_____” to “tri-phasic” on all labels and labeling (inserts, carton and blister). Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

RECEIVED
AUG 06 2004



c. Your proposed proprietary name "Trinessa™" is under review.

Watson acknowledges that the proposed proprietary name "Trinessa™" is currently under review.

2. BLISTER PACK DISPENSER

Satisfactory in final print labeling.

We have included Final Printed Labeling of the blister dispenser which incorporates the changes requested in *FDA Comment #1b*. Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

3. BLISTER PACK DISPENSER OUTER CONTAINER

We note your application does not mention an outer container for the blister pack dispenser. If you plan to use such an outer container i.e. compact, vinyl, pouch, cardboard sleeve, etc., please provide its specifications.

Watson intends place the blister pack into a plastic compact in commercialization. Refer to **Exhibit 1** for a copy of the engineering drawings.

4. START DAY STICKERS

Your application does not include day stickers for patients who choose to follow the "Day 1 Start" regimen, instead of the "Sunday Start" regimen. Please provide stickers or some other method to accommodate both regimens.

Watson intends to use "day of week" stickers in commercialization and we have included an electronic copy for your review. Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

5. CARTON

a. See GENERAL COMMENT 1a and 1b.

We have revised the carton as requested in *FDA Comments #1a and 1b*. Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

b. Please increase the prominence and readability of the tablet strength statements by increasing the font size and choosing an alternative contrasting color.

The font size in the red box has been changed to increase the prominence and readability of the tablet strength statements. Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.



- c. See the attached mocked-up copy of your carton for requested revisions.

All changes requested by FDA have been made to the carton. Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

6. PHYSICIAN INSERT

- a. See GENERAL COMMENT 1a and 1b.

We have revised the physician insert as requested in *FDA Comments #1a and 1b*. Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

- b. See the attached mocked-up copy of your insert for requested revisions.

All changes requested by FDA have been made to the insert. Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

7. DETAIL PATIENT LABELING AND BRIEF SUMMARY INSERTS

Your application did not include and patient inserts (single or combined). Please submit the DETAILED PATIENT LABELING AND BRIEF SUMMARY PATIENT inserts.

The *DETAILED PATIENT LABELING AND BRIEF SUMMARY PATIENT PACKAGE INSERT* were included as part of the complete package insert (combined). However, the single patient labeling insert was inadvertently omitted. We have included a separate file that contains the *DETAILED PATIENT LABELING AND BRIEF SUMMARY PATIENT PACKAGE INSERT* as final printed labeling (combined patient labeling). The patient labeling has been revised as requested in the full prescribing information. Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other factors (print size, prominence, etc.) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

We have included all final printed labeling in electronic format. Please refer to the enclosed computer CD.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current we suggest



that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

<http://www.fda.gov/cder/cdernew/listserv.html>

Watson acknowledges that further revisions may be necessary upon approved changes for the reference listed drug.

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

The side-by-side comparisons of Watson's proposed final printed labeling comparing with the last submitted version of proposed labeling (dated 10/02) with all differences annotated and explained are provided. Refer to the *Table of Contents* contained on the enclosed CD for file names and directory pathways.

We have enclosed one (1) archival, and one (1) review copy of this Amendment for your files.

We believe we have responded to all of the questions as outlined in the FDA facsimile dated May 19, 2004. If I can assist with the review of this amendment, please contact me by telephone at (951) 493-5514, or by facsimile at (951) 493-4581.

Sincerely,

Theresa Greaves, RAC
Associate Director, Regulatory Affairs

Desk Copy (Cover Letter only): Postelle Birch, Labeling Reviewer, OGD

TG/jl
Enc.



ORIG AMENDMENT

N/AAM

February 24, 2006

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

CMC Minor Amendment

RECEIVED

FEB 27 2006

OGD/CDER

RE: ANDA #76-626

Norgestimate and Ethinyl Estradiol Tablets

0.180 mg/0.035 mg, 0.215 mg/0.035 mg and 0.250 mg/0.035 mg – 28 Day

Dear Mr. Buehler:

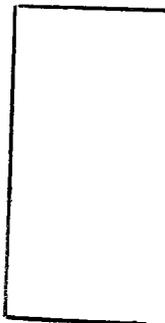
Watson Laboratories, Inc. is submitting this Minor Amendment to provide a complete response to the comments included in the FDA facsimile dated April 23, 2004 (copy attached) pertaining to the above product (ANDA #76-626). For convenience of review, your comments are provided in bold face type followed by our responses.

A. Deficiencies:

- Please note that DMF _____ for _____ is currently inadequate. The DMF holder, _____, has need notified. Please do not respond to this MINOR amendment until you have been informed by _____ stating that a satisfactory response to the DMF deficiencies has been submitted.**

The DMF holder, _____, responded and submitted their DMF amendment the agency on June 2, 2005. Please see **Exhibit 1** for correspondence.

2.



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2/24/2006 WATSON LETTER



August 7, 2006

Gary Buehler, Director
OGD, CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/MC

Telephone Amendment

RE: ANDA #76-626

Norgestimate and Ethinyl Estradiol Tablets

0.18 mg/0.035 mg, 0.215 mg/0.035 mg, 0.25 mg/0.035 mg and

Placebo Tablets- 28 Day

Dear Mr. Buehler:

Watson Laboratories, Inc. is submitting a Telephone Amendment based upon the telephone conversations with Mr. Martin Shimer, OGD, on August 3, 2006, and Ms. Jeannie Skanchy, PM, OGD, on August 4, 2006, regarding ANDA #76-626, Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, 0.25 mg/0.035 mg and Placebo Tablets – 28 Day.

Mr. Shimer had requested that Watson update their labeling and exclusivity statement for Norgestimate and Ethinyl Estradiol Tablets, 0.18 mg/0.035 mg, 0.215 mg/0.035 mg, 0.25 mg/0.035 mg and Placebo Tablets – 28 Day, as the brand had been updated in the Electronic Orange Book (copy attached). Upon further review, Watson has determined that our current labeling does not include any verbiage pertaining to the new exclusivities, and as such, does not require updating and resubmission. We will not include information related to the exclusivities in our labeling until the pediatric exclusivity expires in November 2008. At such time, Watson will revise our labeling accordingly. As requested, we have included in this Amendment a revised Exclusivity Statement.

One archival and one review copy of this amendment is included. In accordance with 21 CFR 314.96(b), a field copy of this correspondence will be forwarded Peter Rickman. Watson Laboratories, Inc. certifies that the Field Copy is a true copy of the technical sections contained in the archival and review copies of this amendment.

We trust the information submitted is sufficient for this telephone amendment to be evaluated. Please contact me by phone at (951) 493-4543 or by fax at (951) 493-4581 if you have any questions or if I can assist you with the review of this application.

Sincerely,


Jennie M. Gwinn, BSc.
Director, Regulatory Affairs

RECEIVED

AUG 08 2006

OGD / CDER