CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-804

Name: Sprintec[tm] Tablets (Norgestimate and Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg)

Sponsor: Barr Laboratories, Inc.

Approval Date: September 25, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-804

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-804

APPROVAL LETTER

ANDA 75-804

SEP 25 2002

Barr Laboratories, Inc.
Attention: Nicholas C. Tantillo
2 Quaker Road
P.O. Box 2900
Pomona, NY 10970

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Sprintec™-28 Tablets (Norgestimate and Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg, respectively), packaged in a 28-day cycle regimen.

Reference is also made to your amendments dated April 10, May 2, and November 28, 2000; February 1, April 20, and October 12, 2001; and July 9, September 4, September 5, and September 10, 2002.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Sprintec™-28 Tablets to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Ortho-Cyclen®-28 Tablets, 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 abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

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

9/25/02

cc: ANDA 75-804
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205

Endorsements:
HFD-623/N.Takiar/ N. Talive 7/24/02 ; N. Talive 9/13/02
HFD-623/D.Gill/ DS Gill 7-24-02 DS Gill 9-16-02
HFD-617/S.Kim/7/24/02 S. Kim 7/25/02 S. Kim 9/16/02
HFD-613/D.Catterson/ Debra M. Catterson 7/25/02 Debra M. Catterson 9/16/02
HFD-613/J.Grace/ 7/25/2002 9/16/2002

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F/T by: gp./7/24/02

APPROVAL

PJ 7/29/02

Robert West
9/25/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-804

APPROVED LABELING

Sprintec™
(norgestimate and ethinyl estradiol tablets)

SAMPLE

Revised SEPTEMBER 2002
31090160102

APPROVED

Rx only

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

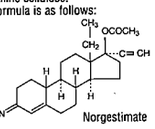
DESCRIPTION:

Sprintec™ Tablets are a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol.

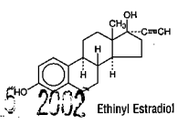
Each blue tablet contains 0.250 mg of the progestational compound norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients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

Each white tablet contains only inert ingredients as follows: anhydrous lactose, hydroxypropyl methylcellulose 2208, magnesium stearate, and microcrystalline cellulose.

The structural formula is as follows:



Norgestimate



Ethinyl Estradiol

SEP 2 9 2002

CLINICAL PHARMACOLOGY:

Oral Contraception:

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

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

Acne:

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

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

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

INDICATIONS AND USAGE:

Sprintec Tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

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

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

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

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

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

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

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

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

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

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

[7]With spermicidal cream or jelly.

[8]Without spermicides.

In clinical trials with norgestimate and ethinyl estradiol, 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.

CONTRAINDICATIONS:

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

- Thrombophlebitis or thromboembolic disorders.
- A past history of deep vein thrombophlebitis or thromboembolic disorders.
- Cerebral vascular or coronary artery disease.
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal genital bleeding.
- Cholestatic jaundice of pregnancy or jaundice with prior pill use.
- Hepatic adenomas or carcinomas.
- Known or suspected pregnancy.

WARNINGS:

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

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

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

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

Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or cohort studies. Case control studies provide a measure of the relative risk of a disease, namely, a *ratio* of the incidence of a disease among oral contraceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the *difference* in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

1. Thromboembolic Disorders and Other Vascular Problems:

a. Myocardial Infarction: An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six.[4-10] The risk is very low under the age of 30.

Smoking in combination with oral contraceptive use has been shown to contribute substantially to the incidence of myocardial infarctions in women in their mid-thirties or older with smoking accounting for the majority of excess cases.[11] Mortality rates associated with circulatory disease have been shown to increase substantially in smokers, especially in those 35 years of age and older among women who use oral contraceptives.

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

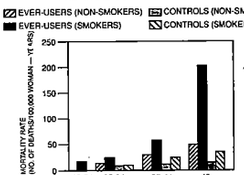


TABLE II. (Adapted from P.M. Layde and V. Beral, ref. #12.)

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.[13] In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.[14-16]

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.

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

b. Thromboembolism: An increased risk of thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. Case control studies have found the relative risk of users compared to nonusers to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease.[2,3,19-24] Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization.[25] The risk of thromboembolic disease associated with oral contraceptives is not related to length of use and disappears after pill use is stopped.[2]

A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.[9] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[26] If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast feed or four weeks after a second trimester abortion.

c. Cerebrovascular diseases: Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes), although, in general, the risk is greatest among older (>35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for both users and nonusers, for both types of strokes, and smoking interacted to increase the risk of stroke.[27-29]

In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.[30] The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension.[30] The attributable risk is also greater in older women.[3]

d. Dose-related risk of vascular disease from oral contraceptives: A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease.[31-33] A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents.[14-16] A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the activity of the progestogen used in the contraceptives. The activity and amount of both hormones should be considered in the choice of an oral contraceptive.

Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing 0.035 mg or less of estrogen.

e. Persistence of risk of vascular disease: There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives persists for at least 9 years for women 40-49 years who had used oral contraceptives for five or more years, but this increased risk was not demonstrated in other age groups.[8] In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small.[34] However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens.

2. Estimates of Mortality from Contraceptive Use:

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke, and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's.[35] Current clinical recommendation involves the use of lower estrogen dose formulations and a careful consideration of risk factors. In 1989, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

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

TABLE III: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

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

Adapted from H.W. Ory, ref. #35.

3. Carcinoma of the Reproductive Organs and Breasts:
Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. While there are conflicting reports, most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk has been reported to be related to duration of use.[36-44,79-89]
A meta-analysis of 54 studies 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.[95]
Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.[45-48] However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

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.[55,57] The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned,[55,56,58,59] when taken inadvertently during early pregnancy.
The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.
It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

7. Gallbladder Disease:
Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.[60,61] More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.[62-64] The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

8. Carbohydrate and Lipid Metabolic Effects:
Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users.[17] This effect has been shown to be directly related to estrogen dose.[65] Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[17,66] However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.[67] Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives.
A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see **WARNINGS**, 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.
In clinical studies with norgestimate and ethinyl estradiol 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.

9. Elevated Blood Pressure:
An increase in blood pressure has been reported in women taking oral contraceptives[68] and this increase is more likely in older oral contraceptive users [69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.
Women with a history of hypertension or hypertension-related diseases, or renal disease[70] should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.[68-71] It should be noted that in two separate large clinical trials (N=633 and N=911), no statistically significant changes in mean blood pressure were observed with norgestimate and ethinyl estradiol.

10. Headache:
The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evaluation of the cause.

11. Bleeding Irregularities:
Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.
Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent.

12. Ectopic Pregnancy:
Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS:

1. Physical Examination and Follow Up:
It is good medical practice for all women to have annual history and physical examinations, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undiagnosed, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

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

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

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

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

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

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

8. Interactions with Laboratory Tests:
Certain endocrine and liver function tests and blood components may be affected by oral contraceptives:
a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaltered.
c. Other binding proteins may be elevated in serum.
d. Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged.
e. High-density lipoprotein (HDL-C) and total cholesterol (Total-C) may be increased, low-density lipoprotein (LDL-C) may be increased or decreased, while LDL-C/HDL-C ratio may be decreased and triglycerides may be unchanged.
f. Glucose tolerance may be decreased.
g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. Carcinogenesis:
See **WARNINGS** section.

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

11. Nursing Mothers:
Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, 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 **Sprintec** 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.
- Change in weight (increase or decrease).
- Change in cervical erosion and secretion.
- Diminution in lactation when given immediately postpartum.
- Cholestatic jaundice.
- Migraine.
- Rash (allergic).
- Mental depression.
- Reduced tolerance to carbohydrates.
- Vaginal candidiasis.
- Change in corneal curvature (steepening).
- Intolerance to contact lenses.

The following adverse reactions have been reported in users of oral contraceptives and the association has been neither confirmed nor refuted:
- Pre-menstrual syndrome.
- Cataracts.
- Changes in appetite.
- Cystitis-like syndrome.
- Headache.
- Nervousness.
- Dizziness.
- Hirsutism.
- Loss of scalp hair.
- Erythema multiforme.
- Erythema nodosum.
- Hemorrhagic eruption.
- Vaginitis.
- Porphyria.
- Impaired renal function.
- Hemolytic uremic syndrome.
- Acne.
- Changes in libido.
- Colitis.
- Budd-Chiari Syndrome.

OVERDOSAGE:
Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

NON-CONTRACEPTIVE HEALTH BENEFITS:
The following non-contraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.[73-78]
Effects on menses:
- Increased menstrual cycle regularity.
- Decreased blood loss and decreased incidence of iron deficiency anemia.
- Decreased incidence of dysmenorrhea.

Effects related to inhibition of ovulation:
- Decreased incidence of functional ovarian cysts.
- Decreased incidence of ectopic pregnancies.

Other effects:
- Decreased incidence of fibroadenomas and fibrocystic disease of the breast.
- Decreased incidence of acute pelvic inflammatory disease.
- Decreased incidence of endometrial cancer.
- Decreased incidence of ovarian cancer.

DOSAGE AND ADMINISTRATION:

Oral Contraception:
To achieve maximum contraceptive effectiveness, **Sprintec** Tablets must be taken exactly as directed and at intervals not exceeding 24 hours. **Sprintec** Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided.

28-Day Regimen (Sunday Start):
When taking **Sprintec** 28 Tablets, 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 seven 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 **Sprintec** 28 Tablets, 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 **Sprintec** 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.

HOW SUPPLIED:
Sprintec™ 28 (norgestimate and ethinyl estradiol tablets 0.250 mg/0.035 mg) are packaged in cartons of six blister cards. Each card contains 21 blue tablets and 7 white inert ingredients. Each blue tablet contains 0.250 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol which are round, unscored tablets, debossed ♄ on one side and **987** on the other side. Each white tablet contains inert ingredients and have a debossed ♄ on one side and **143** on the other side. (**NDC** 0555-9016-58).
Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

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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.

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 and 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 leaflet given to you with your supply of pills. Notify your doctor or healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics 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 healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. Your pharmacist should have given you the detailed patient information labeling which gives you further information which you should read and discuss with your healthcare provider.

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

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.

Sprintec™ Tablets: Each blue tablet contains 0.250 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 healthcare 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 healthcare 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: 26%
Vaginal sponge: 20 to 40%
Female sterilization: <1%
Male sterilization: <1%
Cervical Cap with spermicides: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
Periodic abstinence: 25%
Withdrawal: 19%
No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES:

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

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have had 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 healthcare provider if you have ever had any of these conditions. Your healthcare provider can recommend another method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES:

Tell your healthcare provider if you have or have had:

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

Women with any of these conditions should be checked often by their healthcare provider if they choose to use oral contraceptives. Also, be sure to inform your doctor or healthcare provider if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES:

1. Risk of developing blood clots:

Blood clots and blockage of blood vessels are 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 sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for 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 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 NON-STERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

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

Adapted from H.W. Ory, ref #35.

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

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNALS:

If any of these adverse effects occur while you are taking oral contraceptives, call your doctor immediately:
- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or healthcare 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 healthcare provider.

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

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

GENERAL PRECAUTIONS:

1. Missed periods and use of oral contraceptives before or during early pregnancy:
There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your healthcare provider 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 healthcare provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

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

2. While breast-feeding:
If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, 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), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually transmitted diseases:
Sprintec Tablets (like all oral contraceptives) are intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.
On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 28 PILLS:
The 28-pill pack has 21 "active" blue pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" white pills (without hormones).
3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills
CHECK PICTURE OF THE FOLD-OVER-DOSE CARD AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE AT THE END OF THE BRIEF SUMMARY.
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 for which day to start taking your first pack of pills. **Sprintec** Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:

Take the first "active" blue pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:

1. Take the first "active" blue pill of the first pack during the *first 24 hours of your period.*
2. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

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

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** blue "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.
If you **MISS 2** blue "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as back-up for those 7 days.
If you **MISS 2** blue "active" pills in a row in **THE 3rd WEEK:**
1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.
If you **MISS 3 OR MORE** blue "active" pills in a row (during the first 3 weeks):
1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Day 1 Starter:
THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

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 one 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 healthcare provider or pharmacist.

OTHER INFORMATION:

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

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth-control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES:

In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits. They are:
- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- Pain or other symptoms during menstruation may be encountered less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

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

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised SEPTEMBER 2002
BR-9016

PROVED

Sprintec™

(norgestimate and ethinyl estradiol tablets)
28 Tablets

SAMPLE

Revised SEPTEMBER 2002
31590160102

COMBINATION BRIEF SUMMARY AND PATIENT PACKAGE INSERT

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

NOTICE: Oral contraceptives are intended to prevent pregnancy. They do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases.

DIRECTIONS FOR USE OF THIS STICKER:
The Tablet Dispenser indicates Sunday as the day you start your pills. If you are starting the pills on any other day but Sunday, peel the attached sticker by selecting the day you plan to start. Place the sticker over the pre-printed days of the week and make sure it lines up with the pills. This sticker will help to remind you to take your pill every day.

R11-01
07-0160

BARR LABORATORIES, INC.
Pomona, NY 10970

DETAILED PATIENT LABELING

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.

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

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Any woman who considers using oral contraceptives (the birth-control pill or the pill) should understand the benefits and risks of using this form of birth control. This patient labeling will give you much of the information you will need to make this decision and will also help you determine if you are at risk of developing any of the serious side effects of the pill. It will tell you how to use the pill properly so that it will be as effective as possible. However, this labeling is not a replacement for a careful discussion between you and your healthcare 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 healthcare provider's advice with regard to regular check-ups while you are on the pill.

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Implant: <1%
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Diaphragm with spermicides: 20%
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Male sterilization: <1%
Cervical Cap with spermicides: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
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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 had 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 healthcare provider if you have ever had any of these conditions. Your healthcare provider can recommend another method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES:

Tell your healthcare provider if you have or have had:

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

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

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

RISKS OF TAKING ORAL CONTRACEPTIVES:

1. Risk of developing blood clots
Blood clots and blockage of blood vessels are 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 sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your doctor about stopping oral contraceptives four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for at least four weeks after delivery if you are not breast-feeding or four weeks after a second trimester abortion. If you are breast-feeding, you should wait until you have weaned your child before using the pill. (See also the section on Breast Feeding in **GENERAL PRECAUTIONS**.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptivves 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 12,000 per year, whereas for users 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.

ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY-CONTROL METHOD ACCORDING TO AGE

Method of Control and Outcome	15-19	20-24	25-29	30-34	35-39	40-44
No fertility control methods*	7.0	7.4	9.1	14.8	25.7	28.2
Oral contraceptives non-smoker**	0.3	0.5	0.9	1.9	13.8	31.6
Oral contraceptives smoker**	2.2	3.4	6.6	13.5	51.1	117.2
IUD**	0.8	0.8	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

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

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

The suggestion that women over 40 who do not smoke should not take oral contraceptives is based on information from older, higher-dose pills. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of low-dose oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks.

WARNING SIGNALS:

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

- Sharp chest pain, coughing of blood, or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or healthcare 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 healthcare provider.

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

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

GENERAL PRECAUTIONS:

1. Missed periods and use of oral contraceptives before or during early pregnancy:
There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your healthcare provider 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 healthcare provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of contraception.

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

2. While breast-feeding:
If you are breast-feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, 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), anticonvulsants such as carbamazepine (Tegretol is one brand of this drug), phenytoin (Dilantin is one brand of this drug), phenylbutazone (Butazolidin is one brand) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. Sexually transmitted diseases:
Sprintec Tablets (like all oral contraceptives) are intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you feel sick to your stomach, 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

(Over)

Tear here at perforation.

Sprintec™
(norgestimate and ethinyl estradiol tablets)
28 Tablets

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

Sprintec™ (norgestimate and ethinyl estradiol tablets): Each blue tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

BRIEF SUMMARY
PATIENT PACKAGE INSERT

SEP 2 5 2

Rx only

Oral contraceptives, also known as "birth-control pills" or "the pill", are taken to prevent pregnancy. When taken correctly to prevent pregnancy, oral contraceptives have a failure rate of 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 and 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 healthcare provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics 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 healthcare provider. Your healthcare provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the healthcare provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient labeling gives you further information which you should read and discuss with your healthcare provider.
Sprintec Tablets (like all oral contraceptives) are intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:
1. BE SURE TO READ THESE DIRECTIONS:
Before you start taking your pills.
Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.
3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.
4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take 2 pills, to make up for missed pills, you could also feel a little sick to your stomach.
5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
7. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.

***BEFORE* YOU START TAKING YOUR PILLS**

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.
It is important to take it at about the same time every day.
2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 28 PILLS:
The 28-pill pack has 21 "active" blue pills (with hormones) to take for 3 weeks. This is followed by 1 week of "reminder" white pills (without hormones).
3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills.
CHECK PICTURE OF THE FOLD-OVER-DOSE CARD AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE AT THE END OF THE BRIEF SUMMARY.
4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up in case you miss pills.
AN EXTRA, FULL PILL PACK

WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice for which day to start taking your first pack of pills. **Sprintec** Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:
Take the first "active" blue pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:
Take the first "active" blue pill of the first pack during the first 24 hours of your period.
You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

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

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** (blue) "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.
If you **MISS 2** (blue) "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.
If you **MISS 2** (blue) "active" pills in a row in **THE 3rd WEEK:**
1. **If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.
If you **MISS 3 OR MORE** (blue) "active" pills in a row (during the first 3 weeks):
1. **If you are a Sunday Starter:**
Keep taking **1** pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up 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.

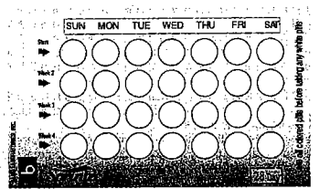
FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex. KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

INFORMATION FOR PATIENTS
PLEASE READ ME!

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

How to Use the Blister Cards for the 28 Tablets:

1. Pick the Days of the Week Sticker that starts the first day of your period. (This is the day you begin bleeding or spotting, even if it is midnight when bleeding begins.) When you have picked the right sticker, throw away the others and place the sticker on the blister card over the pre-printed days of the week and make sure it lines up with the pills.
2. Your blister package consists of three parts, the foil pouch, wallet, and a blister pack containing 28 individually sealed pills. Note that the pills are arranged in four numbered rows of 7 pills, with the pre-printed days of the week printed above them. All 21 blue pills are "active" birth control pills, and 7 white "reminder" pills. Refer to the sample of the blister card below:



3. After taking the last white pill, start a new blister card the **very next day** no matter when your period started. You will be taking a pill every day without interruption. Any time you start the pills later than directed, protect yourself by using another method of birth control until you have taken a pill a day for seven consecutive days. After taking the last white pill, start taking the first blue pill from the blister card the very next day.
4. Take the pills in each new package as before. Start with the blue pill on row #1 and take one pill each day, left to right, until the last white pill has been taken.

THREE WAYS TO REMEMBER IN WHAT ORDER TO TAKE THE PILLS.

1. Follow the sticker with the days of the week (placed above the pills).
2. Always go from left to right.
3. Always finish all your blue pills.

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

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised SEPTEMBER 2002
BS-9016

sponge) until you check with your doctor or clinic.

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

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

BEFORE YOU START TAKING YOUR PILLS

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

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

3. ALSO FIND:
1) where on the pack to start taking pills,
2) in what order to take the pills
CHECK PICTURE OF THE FOLD-OVER-DOSE CARD AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE AT THE END OF THE BRIEF SUMMARY.

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 for which day to start taking your first pack of pills. **Sprintec** Tablets are available in the Blister Pack Tablet Dispenser which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

SUNDAY START:

1.Take the first "active" blue pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2.*Use another method of birth control* as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms, foam, or the sponge are good back-up methods of birth control.

DAY 1 START:

1.Take the first "active" blue pill of the first pack during the *first 24 hours of your period.*
2.You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

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

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** (blue) "active" pill:
1.Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in one day.
2.You do not need to use a back-up birth control method if you have sex.

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

If you **MISS 2** (blue) "active" pills in a row in **THE 3rd WEEK:**
1.**If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
If you are a Day 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2.You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your doctor or clinic because you might be pregnant.
3.You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

If you **MISS 3 OR MORE** (blue) "active" pills in a row (during the first 3 weeks):
1.**If you are a Sunday Starter:**
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
If you are a DAY 1 Starter:
THROW OUT the rest of the pill pack and start a new pack that same day.
2.You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3.You MAY BECOME PREGNANT if you have sex in the *7 days* after you miss pills. You MUST use another birth control method (such as condoms, foam, or sponge) as a back-up for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS

If you forget any of the 7 "reminder" white pills in Week 4:
THROW AWAY the pills you missed.
Keep taking one 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 healthcare provider or pharmacist.

OTHER INFORMATION:

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

Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES:

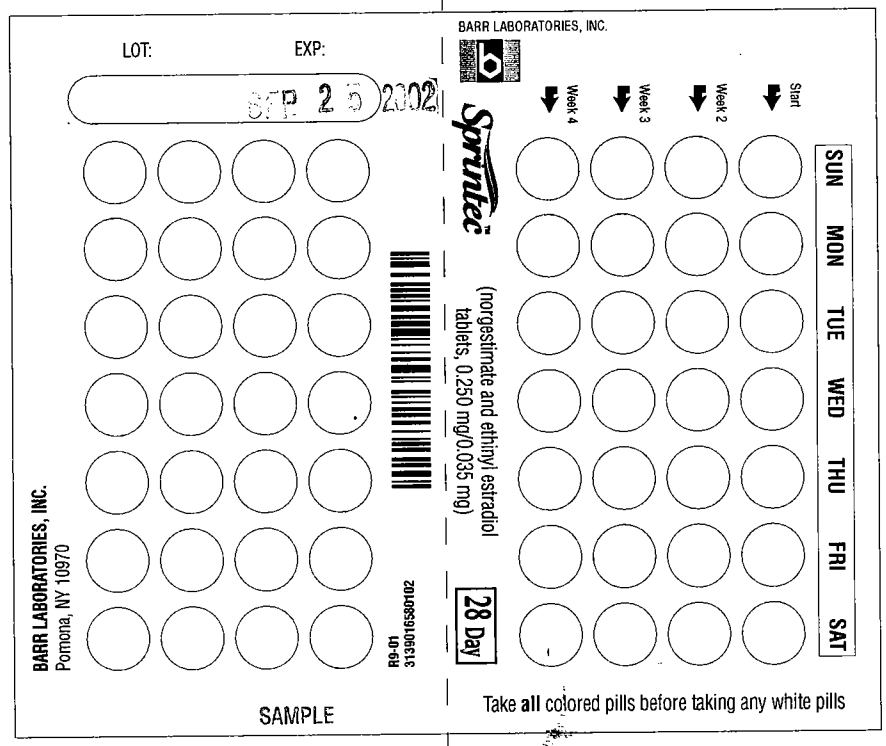
In addition to preventing pregnancy, use of combination oral contraceptives may provide certain benefits. They are:

- menstrual cycles may become more regular
- blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.
- pain or other symptoms during menstruation may be encountered less frequently
- ectopic (tubal) pregnancy may occur less frequently
- noncancerous cysts or lumps in the breast may occur less frequently
- acute pelvic inflammatory disease may occur less frequently
- oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

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

MANUFACTURED BY
BARR LABORATORIES, INC.
POMONA, NY 10970

Revised SEPTEMBER 2002
PL-9016


BARR LABORATORIES, INC.
LOT:
EXP:
SEP 25 2002
Start
Week 2
Week 3
Week 4
SUN MON TUE WED THU FRI SAT
Sprintec
(norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)
28 Day
R9-01
Take all colored pills before taking any white pills
BARR LABORATORIES, INC.
Pomona, NY 10970
SAMPLE

SEP 25 2002

APPROVED

NDC 0555-**9016**-58

Sprintec™

(norgestimate and ethinyl estradiol tablets)

0.250 mg/0.035 mg

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

28 DAY REGIMEN

℞ 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.

BARR LABORATORIES, INC.

Barr Laboratories, Inc.
Shaping Women's Health

BARR LABORATORIES, INC., Pomona, NY 10970

READ PATIENT LABELING

If this is the first time you are taking birth control pills, wait until the day your period starts, then follow the instructions in the patient labeling. Make sure to check if you are a Sunday Start or Day 1 Start.

Usual Dosage: One tablet daily as prescribed. See enclosed package information.

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

N 3 05559 01658 9

EXP:

LOT:

SAMPLE

R9-01
21690165801O2

110

APPROVED
SEP 25 2002

0.250 mg/0.035 mg

(norgestimate and ethinyl estradiol tablets)

Sprintec™

NDC 0555-9016-58

6 Blister Cards, 28 Tablets Each

28 DAY REGIMEN

SAMPLE

6 Blister Cards, 28 Tablets Each 28 DAY REGIMEN

NDC 0555-9016-58

Sprintec™

(norgestimate and ethinyl estradiol tablets)

0.250 mg/0.035 mg

℞ only

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

BARR LABORATORIES, INC.
Pomona, NY 10970

6 Blister Cards, 28 Tablets Each 28 DAY REGIMEN

NDC 0555-9016-58

Sprintec™

(norgestimate and ethinyl estradiol tablets)

0.250 mg/0.035 mg

Usual Dosage: One tablet daily for 28 consecutive days per menstrual cycle in the following order: 21 blue tablets followed by 7 white tablets as prescribed.
See enclosed package information.

To the Dispenser: This carton contains one combination labeling piece of information intended for the patient. All informational pieces are to be provided to the patient with each prescription.

BARR LABORATORIES, INC.

Barr Laboratories, Inc.
Shaping Women's Health

6 Blister Cards, 28 Tablets Each | 28 DAY REGIMEN

NDC 0555-**9016**-58

Sprintec™

(norgestimate and ethinyl estradiol tablets)

0.250 mg/0.035 mg

℞ 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.

6 Blister Cards, 28 Tablets Each | 28 DAY REGIMEN

NDC 0555-**9016**-58

Sprintec™

(norgestimate and ethinyl estradiol tablets)

0.250 mg/0.035 mg

Contains 6 blister cards, each containing 28 tablets. 21 blue tablets each contain 0.250 mg norgestimate with 0.035 mg ethinyl estradiol; and 7 white tablets each contain inert ingredients.

℞ only

BARR LABORATORIES, INC.

Barr Laboratories, Inc.
Shaping Women's Health

N 3 05559 01658 9

LOT:

EXP:

2149016580102

R9-01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-804

LABELING REVIEW(S)

FIRST GENERIC

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

ANDA Number: 75-804

Date of Submission: February 16, 2000 (Original draft labeling)

Applicant's Name: Barr Laboratories, Inc.

Established Name: Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg (——— 28 day regimens)

Labeling Deficiencies:

1. **GENERAL COMMENT:**

   We note that the draft labels and labeling you have submitted include your proposed proprietary name ——— for this drug product. Please refer to our fax dated March 22, 2001, in which we informed you that the Office of Post-Marketing Drug Risk Assessment (OPDRA) did not recommend the use of the name ———; due to the potential risk of confusion between ——— and two existing drug names, *Norinyl* and *Norethin*. Therefore, please revise your labels and labeling to remove ——— as the proprietary name.

2. **CONTAINER** (Fold-over blister dose card, ———28 Day):

   Satisfactory in draft.

3. **AUXILIARY LABEL**

   Satisfactory in draft.

4. ———28 Day):

   Satisfactory in draft.

5. **CARTON** (———6 x 28 Day):

   Revise the "21 blue tablets contain..." statement to read: "21 blue tablets each contain 0.250 mg norgestimate and 0.035 mg ethinyl estradiol; and 7 white tablets each contain inert ingredients."

6. **INSERT** (Physician Labeling, Detailed Patient Labeling, and Brief Summary Patient Labeling):

   We note that you have modeled your labeling after the reference listed drug's labeling, Ortho-Cyclen® by RW Johnson, revised May 1998. However, this labeling is not the most recently approved. 21 CFR 314.94(a)(8)(iv) requires that your labeling be the same as that approved for the reference listed drug. Please revise your physician insert labeling to be in accordance with the enclosed labeling

for the reference listed drug, revised January 2000 and approved June 5, 2000. Please also revise your Detailed Patient Labeling and Brief Summary Patient Labeling to be in accordance with the enclosed patient labeling for the reference listed drug, revised April 2000 and approved January 16, 2001.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.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
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Reference Listed Drug's Approved Labeling.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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.		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? **The proposed name ———— was not recommended by OPDRA on Feb. 22, 2001 (Consult #00-0273).**	x		
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR]		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	
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 (p. #) 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 p. # 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?[see FTR]		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. **NONE.**		X	

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Ortho-Cyclen® Tablets (28 Day Regimen) by R.W. Johnson (NDA 19-653/S-025; revised January 2000 and approved June 5, 2000; and S-027, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-653

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– NDA 19-653

Code	Reference	Expiration
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A

The firm's statements are correct. [Vol. A1.1 pg. 03-0001 and 03-00002.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Barr Laboratories, Inc.
2 Quaker Road ———
Pomona, NY 10970-0519 [Vol. A1.14 pg. 09-00002.]

4. CONTAINER/CLOSURE

Blister Film: ——————————— clear transparent plastic film.
Blister Backing: ——— push thru Aluminum Foil with ——————————— on bright side and——————————— on matte side.
[Vol. A1.14 pg. 13-00003 and 13-00004.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.14 pg. 07-00003.]

6. 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 Fold-Over Dose Card with ———

[Vol. A1.1 pg. 04-00013, 04-00016, and 04-00100.]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: None.
ANDA: Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°- 86°F)

[Vol. A1.1 pg. 04-00100.]

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: **IMPORTANT:** Each carton contains Detailed Patient Labeling and each DIALPAK® Tablet Dispenser contains the Brief Patient Labeling. Both should be included with each package dispensed to the patient.
ANDA: **To the Dispenser:** This carton contains two pieces of information intended for the patient. All informational pieces are to be provided to the patient with each prescription.

[Vol. A1.1 pg. 04-00013, and 05-00014.]

9. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

"active" tablet: "blue, round, flat-faced, beveled-edge, unscored tablet debossed with **b** on one side and **987** on the other side."
placebo tablet: "white, round, flat-faced, beveled-edge, unscored tablet debossed with **b** on one side and **143** on the other side."

[Vol. A1.14 pg. 14-00007 and 14-00014.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on December 26, 2000, that the firm's bioequivalency data were acceptable.

11. NOMENCLATURE:

The firm proposed the proprietary name ——————— for their product. OPDRA concluded on February 22, 2001, that they did not recommend the use of the name ——————— for this drug product [Consult # 00-0273]. I notified the firm of this decision in a fax dated March 22, 2001.

Date of Review: 4/4/01 Date of Submission: 2/16/00

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 4/5/01

Team Leader: John Grace Date:

4/6/2001

cc:

ANDA: 75-804
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
v:\firmsam\barr\ltrs&rev\75804NA1.L.doc
Review

APPEARS THIS WAY
ON ORIGINAL

The Labeling Approval Summary dated 7/24/2002 was not located.

(This AP Summary supersedes the AP Summary dated 7/24/02.)

APPROVAL SUMMARY

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

ANDA Number: 75-804

Date of Submission: September 10, 2002 (Amendment-FPL) and September 5, 2002 (Amendment)

Applicant's Name: Barr Laboratories, Inc.

Established Name: Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg (28 day regimen)

Proprietary Name: Sprintec™ 28 Tablets

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

Do you have 12 Final Printed Labels and Labeling? Yes.

CONTAINER Labels: (Fold-over blister dose card - 28 Day):
Satisfactory as of the October 12, 2001 submission. [Vol. 5.1, page 102]

FOIL POUCH: (Overwrap for container and wallet – 28 Day):
Satisfactory as of the October 12, 2001 submission. [Vol. 5.1, page 106]

CARTON: (6 x 28 Day):
Satisfactory as of the October 12, 2001 submission. [Vol. 5.1, page 110]

DAYS OF THE WEEK STICKER (To be affixed to the blister dose card – 28 Day):
Satisfactory as of the September 10, 2002 submission. [Vol. 6.1]

PROFESSIONAL PACKAGE INSERT:
Satisfactory as of the September 10, 2002 submission. [Vol. 6.1, Revised September 2002; Code: 31090160102]

COMBINATION DETAILED PATIENT LABELING AND BRIEF SUMMARY INSERT:
Satisfactory as of the September 10, 2002 submission. [Vol. 6.1, Revised September 2002; Code: 31590160102]

Revisions needed post-approval: **Yes**. There were several labeling revisions that were editorial in nature, and therefore could be "post-approval" revisions. I communicated these post-approval revisions to Christine Mundkur, of Barr Laboratories, Inc., by telephone and by facsimile on July 24, 2002.

Patent Data – NDA 19-653

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-653

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: ORTHO CYCLEN-28® Tablets

NDA Number: 19-653

NDA Drug Name: Norgestimate and Ethinyl Estradiol Tablets

NDA Firm: R.W. Johnson

Date of Approval of NDA Insert and supplement : NDA 19-653/S-025: Approved June 5, 2000; and S-027 (Combination Detailed Patient and Brief Summary Insert only): Approved January 16, 2001

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 innovator labels in jacket.

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

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's 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.		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? **The proposed name "Sprintec™" was found acceptable by OPDRA on August 15, 2001 (Consult #01-0159), and the final "OK" was given on Aug. 5, 2002.**	x		
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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. [see FTR]		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	
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 (p. #) 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 p. # 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?[see FTR]		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. **NONE**			

FOR THE RECORD:

1. MODEL LABELING

This review was based on the labeling for Ortho Cyclen-28® Tablets by R.W. Johnson (NDA 19-653/S-025; revised January 2000 and approved June 5, 2000; and S-027, revised April 2000 and approved January 16, 2001 (Detailed Patient and Brief Summary Patient Inserts only).

2. PATENTS/EXCLUSIVITIES

Patent Data – NDA 19-653

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 19-653

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

The firm's statements are correct. [Vol. A1.1 pg. 03-0001 and 03-00002.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

Barr Laboratories, Inc.
2 Quaker Road
Pomona, NY 10970-0519 [Vol. A1.14 pg. 09-00002.]

4. CONTAINER/CLOSURE

Blister Film: clear transparent plastic film.
Blister Backing: push thru Aluminum Foil with on bright side and on matte side.
[Vol. A1.14 pg. 13-00003 and 13-00004.]

5. INACTIVE INGREDIENTS

The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.14 pg. 07-00003.]

6. PACKAGING CONFIGURATIONS

RLD: Cartons of 6 x 28-Day Dialpak® Tablet Dispensers.
1 x 28-Day Veridate® Tablet Dispensers (unfilled) for clinic use.
ANDA: Cartons of 6 x 28-Day Fold-Over Dose Card with wallet.

[Vol. A1.1 pg. 04-00013, 04-00016, and 04-00100.]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

USP: None.
RLD: None.
ANDA: Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°- 86°F)
[Vol. A1.1 pg. 04-00100.]

8. DISPENSING STATEMENTS COMPARISON

USP: None
RLD: **IMPORTANT:** Each carton contains Detailed Patient Labeling and each DIALPAK® Tablet Dispenser contains the Brief Patient Labeling. Both should be included with each package dispensed to the patient.
ANDA:**To the Dispenser:** This carton contains one combination labeling piece of information intended for the patient. All informational pieces are to be provided to the patient with each prescription.

[Vol. A1.1 pg. 04-00013, and 05-00014.]

9. TABLET IMPRINT

The tablet imprintings have been accurately described in the HOW SUPPLIED section of the Insert according to the firm's Finished Product Specifications:

"active" tablet: "blue, round, flat-faced, beveled-edge, unscored tablet debossed with **b** on one side and **987** on the other side."
placebo tablet: "white, round, flat-faced, beveled-edge, unscored tablet debossed with **b** on one side and **143** on the other side."

[Vol. A1.14 pg. 14-00007 and 14-00014.]

10. BIOAVAILABILITY/BIOEQUIVALENCE:

The Division of Bioequivalence concluded on December 26, 2000, that the firm's bioequivalency data were acceptable.

11. NOMENCLATURE:

The firm proposed the proprietary name "Sprintec™ " for their product. OPDRA concluded on August 15, 2001, that "Sprintec" was an acceptable name for this drug product (Consult #01-0159). The final "OK" on Sprintec was given by DMETS on August 5, 2002.

Date of Review: 9/11/02 Dates of Submission: 9/10/02 and 9/5/02

Primary Reviewer: Debra Catterson Date:

Debra M. Catterson 9/12/02

Team Leader: John Grace Date:

John D. Grace 9/13/2002

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cc:

ANDA: 75-804
DUP/DIVISION FILE
HFD-613/DCatterson/JGrace (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-804

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.** **(First Generic)**
1

2. **ANDA NUMBER**
75-804

3. **NAME AND ADDRESS OF APPLICANT**
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P. O. Box 2900
Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
The listed reference drug product is **Ortho-Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19653) manufactured by Johnson RW.

The applicant certifies that in its opinion and to the best of its knowledge, there are no patents that claim ———(norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) —— 28 day regimens or the drug substances that are components of the drug product. (Section III page 03-00001 and 2)

Exclusivity: None

5. **SUPPLEMENT(s)**
None

6. **NAME OF DRUG**
———

7. **NONPROPRIETARY NAME**
Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
None

9. **AMENDMENTS AND OTHER DATES**

02-16-2000	Original submission
03-16-2000	New Correspondence – CMC and BA/BE electronic submission
04-10-2000	Telephone Amendment - Bioequivalence
05-02-2000	Telephone Amendment - Bioequivalence
03-29-2000	Letter of acceptance

10. **PHARMACOLOGICAL CATEGORY**
Oral Contraceptive

11. **HOW DISPENSED**
Prescription

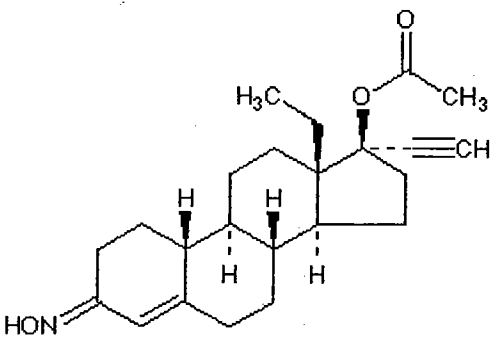
12. **RELATED IND/NDA/DMF(s)**

Product	Holder	DMF No.	LOA
			v1.2, p08-00004
			v1.2, p08-00078
			v1.3, p13-00010
			v1.3, p13-00018

13. DOSAGE FORM
Tablet

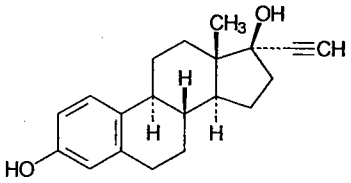
14. POTENCY
0.250 mg/0.035 mg (—— 28 day regimens)

15. CHEMICAL NAME AND STRUCTURE
Norgestimate: 18,19-Dinor- 17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17)- (+)-.



C23H31NO3, Molecular Weight: 369.51

Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS
The following sections are not satisfactory:
- 22. Synthesis
- 23. Raw Material Controls
- 26. Container
- 28. Laboratory Controls (In-Process and Finished Dosage Form)
- 29. Stability

The following sections are pending:
- 32. Labeling
- 33. Establishment Inspection

18. CONCLUSIONS AND RECOMMENDATIONS
The application is not approvable - Major.

19. REVIEWER AND DATE COMPLETED
Neeru B. Takiar/June 23, 2000; Revised on July 26, 2000

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confidential commercial

information from

CHEMISTRY REVIEW #1

3. Method validation will be requested from the District laboratory after the issues on impurities have been resolved.

4. Please provide all available room temperature stability data.

Sincerely yours,

Paul Schwartz for 8/21/00

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

CC: ANDA 75-804
Division File
Field Copy

Endorsements:

HFD-623/Neeru Takiar/6-23-00; revised on 7-26-00 8/15/00,
HFD-623/D. Gill/6-27-00 DSGill 8-16-00 for N Takiar
HFD-617/R.Yu/8-1-00 8/21/00
\\CDV008\WP51F99\FIRMSAM\BARR\LTRS&REV\75804.RV1.BARR.DOC
F/T by: bc/8-2-00

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.** **(First Generic)**
2

2. **ANDA NUMBER**
75-804

3. **NAME AND ADDRESS OF APPLICANT**
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P. O. Box 2900
Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
The listed reference drug product is **Ortho-Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19653) manufactured by Johnson RW.

The applicant certifies that in its opinion and to the best of its knowledge, there are no patents that claim ——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) ——— 28 day regimens or the drug substances that are components of the drug product. (Section III page 03-00001 and 2)

Exclusivity: None

5. **SUPPLEMENT(s)**
None

6. **NAME OF DRUG**
———

7. **NONPROPRIETARY NAME**
Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
None

9. **AMENDMENTS AND OTHER DATES**

02-16-2000	Original submission
11-28-2000	Major Amendment – Response to def. letter (CMC and BA/BE) of August 22, 2000
01-02-2001	Electronic Submission - CMC Amendment
02-01-2001	Amendment - Filing of ——— new manufacturing site for ———
02-01-2001	Amendment – Bio-equivalence
02-09-2001	Amendment - Correction to February 01, 2001 amendment regarding ——— manufacturing site for ———
03-09-2001	Amendment - Updated blend uniformity limits
04-20-2001	Amendment - Labeling

10. **PHARMACOLOGICAL CATEGORY**
Oral Contraceptive

11. HOW DISPENSED
Prescription

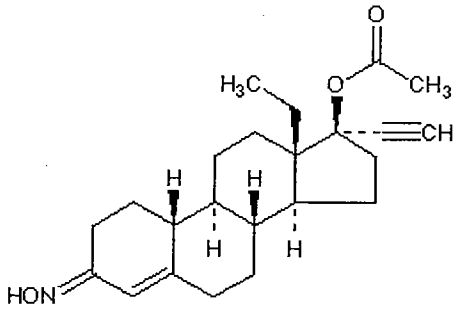
2. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
			v1.2, p08-00004
			v1.2, p08-00078
			v1.3, p13-00010
			v1.3, p13-00018

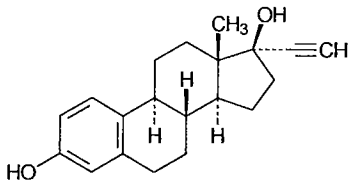
13. DOSAGE FORM
Tablet

14. POTENCY
0.250 mg/0.035 mg —— 28 day regimens)

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



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6.
USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS
The following sections are not satisfactory:

22. Synthesis
23. Raw Material Controls
28. Laboratory Controls
29. Stability
32. Labeling

18. CONCLUSIONS AND RECOMMENDATIONS
The application is *NOT* approvable - Minor.

19. REVIEWER AND DATE COMPLETED
Neeru B. Takiar/April 27, 2001; revised on May 7, 2001

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confidential commercial

information from

CHEMISTRY REVIEW #2

CC: ANDA 75-804
Division File
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Endorsements:

HFD-623/Neeru Takiar/4-27-01; 5-7-01 N. Takiar 5/7/01
HFD-623/D. Gill/ DS Gill 5-7-01
HFD-617/R.Yu/ Rosa Patel 5/9/01
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F/T by:

NA - MINOR

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ON ORIGINAL

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
3

2. **ANDA NUMBER**
75-804

3. **NAME AND ADDRESS OF APPLICANT**
Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P. O. Box 2900
Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
The listed reference drug product is **Ortho-Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19653) manufactured by Johnson RW.

The applicant certifies that in its opinion and to the best of its knowledge, there are no patents that claim ——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) ——— 28 day regimens or the drug substances that are components of the drug product. (Section III page 03-00001 and 2)

Exclusivity: None

5. **SUPPLEMENT(s)**
None

6. **NAME OF DRUG**
———

7. **NONPROPRIETARY NAME**
Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
None

9. **AMENDMENTS AND OTHER DATES**
02-16-2000 Original submission
06-11-2001 Minor Amendment – Response to CMC deficiency letter of May 14, 2001

10. **PHARMACOLOGICAL CATEGORY**
Oral Contraceptive

11. **HOW DISPENSED**
Prescription

12. **RELATED IND/NDA/DMF(s)**

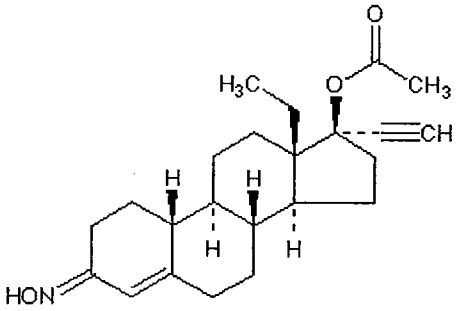
Product	Holder	DMF No.	LOA
			v1.2, p08-00004
			v1.2, p08-00078

Product	Holder	DMF No.	LOA
			v1.3, p13-00010
			v1.3, p13-00018

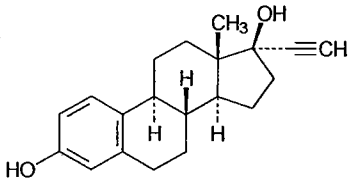
13. DOSAGE FORM
Tablets (Oral)

14. POTENCY
0.250 mg/0.035 mg (—— 28 day regimens)

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



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6. USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS
The following sections are *DEFICIENT:*
- 22. Synthesis
- 23. Raw materials
- 28. Laboratory Controls

The following section is *PENDING*:
- 32. Labeling

18. CONCLUSIONS AND RECOMMENDATIONS
Deficient – NA letter will issue.

19. REVIEWER AND DATE COMPLETED
Neeru B. Takiar/June 27, 2001

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confidential commercial

information from

CHEMISTRY REVIEW #3

cc: ANDA 75-804
Division File
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Endorsements:

HFD-623/Neeru Takiar/06-27-2001 N. Takiar 7/2/01
HFD-623/D. Gill,Ph.D./6/29/01 DSGill 7-2-01
HFD-617/R.Yu/6/29/01 RY 7-2-01

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F/T by: DJ 7/2/01

MINOR – NA Letter

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
   4

2. **ANDA NUMBER**
   75-804

3. **NAME AND ADDRESS OF APPLICANT**
   Barr Laboratories, Inc.
   Attention: Christine Mundkur
   2 Quaker Road
   P. O. Box 2900
   Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
   The listed reference drug product is **Ortho-Cyclen®-21** (Norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg Tablet; Oral-21 Day Regimen – NDA 19653) manufactured by Johnson RW.

   The applicant certifies that in its opinion and to the best of its knowledge, there are no patents that claim ——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) ——— 28 day regimens or the drug substances that are components of the drug product. (Section III page 03-00001 and 2)

   Exclusivity: None

5. **SUPPLEMENT(s)**
   None

6. **NAME OF DRUG**
   ——— (**Changed to Sprintec**)

7. **NONPROPRIETARY NAME**
   Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
   None

9. **AMENDMENTS AND OTHER DATES**

02-16-2000	Original submission
07-26-2001	Minor Amendment – Response to CMC deficiency letter of July 05, 2001
03-29-2002	Telephone Amendment - Response to CMC deficiencies per T-con of March 27, 2002
05-15-2002	Telephone Amendment - Response to CMC deficiencies per T-con of May 5, 2002
06-10-2002	Telephone Amendment - Response to T-con dated June 10, 2002

10. **PHARMACOLOGICAL CATEGORY**
    Oral Contraceptive

1. **HOW DISPENSED**
   Prescription

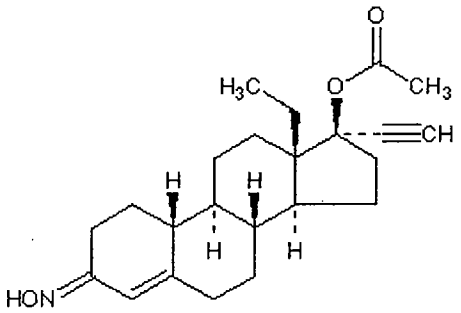
12. **RELATED IND/NDA/DMF(s)**

Product	Holder	DMF No.	LOA
			v1.2, p08-00004
			v1.2, p08-00078
			v1.3, p13-00010
			v1.3, p13-00018

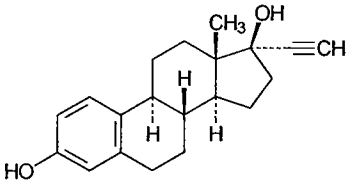
13. DOSAGE FORM
Tablets (Oral)

14. POTENCY
0.250 mg/0.035 mg —— 28 day regimens)

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



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6.
USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS See individual sections in the review

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable. NA-MINOR will issue.

19. REVIEWER AND DATE COMPLETED
Neeru B. Takiar/June 19, 2002

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confidential commercial

information from

CHEMISTRY REVIEW #4

cc: ANDA 75-804
Division File
Field Copy

Endorsements:

HFD-623/Neeru Takiar/06-19-2002; Revised 7-1-02 N. Takiar 7/1/02
HFD-623/D. Gill,Ph.D./ DS Gill 7-1-02
HFD-617/R.Wu/ RWu 7/1/02

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F/T by:

NA-MINOR

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. **Chemistry Review No.**
5

2. **ANDA NUMBER**
75-804

3. **NAME AND ADDRESS OF APPLICANT**
Barr Laboratories, Inc.
Attention: Nicholas C. Tantillo
2 Quaker Road
P. O. Box 2900
Pomona, NY 10970

4. **LEGAL BASIS for ANDA SUBMISSION**
The listed reference drug product is **Ortho-Cyclen®-21** (Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg; Oral-21 Day Regimen – NDA 19653) manufactured by Johnson RW.

The applicant certifies that in its opinion and to the best of its knowledge, there are no patents that claim ——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) ——— 28 day regimens or the drug substances that are components of the drug product. (Section III page 03-00001 and 2)

Exclusivity: None

5. **SUPPLEMENT(s)**
None

6. **NAME OF DRUG**
——— **(Changed to Sprintec)**

7. **NONPROPRIETARY NAME**
Norgestimate and Ethinyl Estradiol Tablets

8. **SUPPLEMENT(s) PROVIDE(s) FOR**
None

9. **AMENDMENTS AND OTHER DATES**
02-16-2000 Original submission
07-09-2002 Minor Amendment – Response to deficiency letter dated July 3, 2002

10. **PHARMACOLOGICAL CATEGORY**
Oral Contraceptive

11. **HOW DISPENSED**
Prescription

12. **RELATED IND/NDA/DMF(s)**

Product	Holder	DMF No.	LOA
			v1.2, p08-00004
			v1.2, p08-00078

Product	Holder	DMF No.	LOA
			v1.3, p13-00010
			v1.3, p13-00018

13. DOSAGE FORM
Tablets (Oral)

14. POTENCY
0.250 mg/0.035 mg —— 28 day regimens)

15. CHEMICAL NAME AND STRUCTURE
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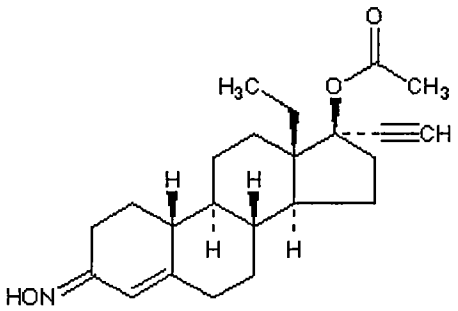
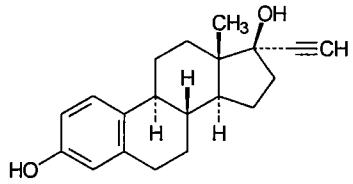
C23H31NO3, Molecular Weight: 369.51



Ethinyl Estradiol. 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17α)-. $C_{20}H_{24}O_2$. 296.41. 57-36-6.
USP 24, page 692.



16. RECORDS AND REPORTS
None

17. COMMENTS
None

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER AND DATE COMPLETED
Neeru B. Takiar/July 15, 2002

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confidential commercial

information from

CHEMISTRY REVIEW #5

cc: ANDA 75-804
Division File
Field Copy

Endorsements:

HFD-623/N.Takiar/07-15-2002 N. Takiar 7/24/02
HFD-623/D.Gill,Ph.D./07/16/02 DGill 7-24-02
HFD-617/R.Wu/07/24/02 RWu 7/25/02

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F/T by: gp/07/24/02

Approvable

APPEARS THIS WAY
ON ORIGINAL

ANDA APPROVAL SUMMARY

ANDA: 75-804	CHEMIST: Neeru B. Takiar	DATE: July 15, 2002
DRUG PRODUCT: Norgestimate and Ethinyl Estradiol Tablets		
FIRM: Barr Laboratories, Inc.		
DOSAGE FORM: Tablets	**STRENGTHs:** 0.250 mg/0.035 mg (28 day regimen)	
cGMP: EER acceptable on July 2, 2001.		
BIO: Bio study acceptable on February 12, 2001; Signed off on February 26, 2001.		
VALIDATION - *(Description of dosage form same as firm's):* The DS Norgestimate and drug product are not covered by monographs in the USP 24 (25). (Since the methods were same for both ANDAs (75-804 and 75-808), MV was sent only for 75-808). Results of method validation from the FDA District Laboratory are ***ACCEPTABLE*** December 17, 2001.		
STABILITY: The firm has provided satisfactory 3 months accelerated and 25 months room temperature stability data for active (0.250 mg/0.035 mg tablets) tablets packaged in blisters, up to 12 months room temperature in bulk, and 3 months accelerated and up to 12 months room temperature stability data for placebo tablets packaged in blister and in bulk. All stability data is satisfactory and support an expiration period of 18 months. The stability data meet the dissolution specifications recommended by DOB.		
LABELING: ***ACCEPTABLE*** on September 13, 2002.		
STERILIZATION VALIDATION *(If applicable)*: N/A		
SIZE OF BIO BATCH *(Firm's source of NDS ok?)*: Size of the bio batch for active, 0.250 mg/0.035 mg is ——— tablets and for placebo is ——— tablets. Drug substance, Norgestimate is manufactured by ——— and drug substance, Ethinyl Estradiol is manufactured by ——— Norgestimate is found adequate on March 11, 2002 and Ethinyl Estradiol on May 7, 2002.		
SIZE OF STABILITY BATCHES *(If different from bio batch, were they Manufactured via the same process?)*: Size of stability batch is same as that of the bio batch.		
PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?: Size of the proposed production batch size for active tablets, 0.250 mg/0.035 mg ———tablets) and placebo tablets (———tablets) is the same as the bio batch. The manufacturing process is identical to the exhibit batch.		
Signature of chemist: N. Takiar 9/13/02 Neeru B. Takiar 7/15/02	**Signature of supervisor:** Dave Gill, Ph.D. 7/16/02 DSGill 9-16-02	

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-804

BIOEQUIVALENCE REVIEW(S)

NORGESTIMATE-ETHINYL ESTRADIOL
0.25 mg /0.035 mg Tablets, — 28 days
ANDA 75-804
Reviewer: Moheb H. Makary
W 75804sdw.300

Barr Laboratories, Inc.
Pomona, NY

Submission Date: 03/16/00
04/10/00
05/02/00

Review of Bioequivalence Study, Dissolution Data and Waiver Request (Electronic Submission)

Introduction

Indication: Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product as a method of contraception.
Type of Submission: Original ANDA
Contents of Submission: Bioequivalence study under fasting conditions, dissolution data and a waiver request.
RLD: Ortho-Cyclen-21 Tablets (norgestimate and ethinyl estradiol, 0.25 mg/0.035 mg), Ortho Pharmaceutical Corporation is a division of RW Johnson. The composition of the Ortho-Cyclen-28 Tablets regimen is 21 Tablets each containing norgestimate and ethinyl estradiol, 0.25 mg/0.035 mg and 7 Placebo Tablets.
Recommended Dose: One pill at the same time every day until the pack is empty.

Combination oral contraceptive (OC) tablets have been determined to be a safe and effective method for preventing pregnancy when administered for a 21-day daily regimen during a woman's menstrual cycle. Two of the most common components of OCs include an estrogen (e.g., ethinyl estradiol (EE)) and a progestogen (e.g., norgestimate (NGM)). Estrogen-progestin combination has also been used for postcoital contraception and for the treatment of amenorrhea, dysmenorrhea, hypermenorrhea, polycystic ovary syndrome, hirsutism, endometriosis, acne vulgaris and dysfunctional uterine bleeding.

EE and NGM are rapidly and well absorbed from the gastrointestinal tract but are subject to some first-pass metabolism in the gut-walls and in the liver. Bioavailability is about 40-83 % for EE, and about 60% of NGM is reportedly absorbed after oral administration. The bioavailability of EE often displays great variability. The intra subject variability (CV%) for EE ranged from 20-26% for C_{max}, and 12-25% for AUC. Peak plasma concentrations (C_{max}) of 100-200 pg/mL are reached 1.0-3.0 hours after a 50-ug dose of EE, with a secondary peak at about 12 hours after dosing, due to its extensive enterohepatic circulation. Following a single oral dose of NGM 0.36 mg, the C_{max} of 0.1 and 3.6 ng/mL for NGM and 17-deacetyl NGM (an active metabolite) are reached within 1 and 1.5 hours, respectively. In addition, following an oral dose of 250 ug of NGM, significant plasma concentrations of levonorgestrel were measured: C_{max} of about 500 pg/mL was attained in 2 hours. NGM is rapidly cleared from plasma, with undetectable levels only 5 hours after dosing. This is consistent with NGM being a prodrug for levonorgestrel and the other active 17-deacetyled metabolite.

Background

On September 23, 1998, the Office of Generic Drugs provided comments regarding bioequivalence requirements for norgestimate/ethinyl estradiol tablets. The Office of Generic Drug recommended that the firm conduct a single dose fasting bioequivalence study. It was advised that the following moieties should be analyzed and quantitated: a) norgestimate (if it is possible to detect, analyze and follow for a reasonable duration), b) 17-deacetyl norgestimate, c) norgestrel and d) ethinyl estradiol.

On April 9, 1999 the firm asked whether it could measure levonorgestrel instead of norgestrel. The Office of Generic Drugs indicated that if the firm feels strongly about measuring levonorgestrel instead of norgestrel, it may do so.

Protocol No.: 98041, Randomized, open-label, 3-way crossover, bioequivalence study of Barr Laboratories, Inc. (USA) norgestimate-ethinyl estradiol, Ortho-Cyclen (USA) and Cyclen (Canada) 0.25 mg-0.035 mg tablets in healthy adult females under fasting conditions.

It should be noted that Barr's test batch 109879R01 was compared to both the USA Ortho-Cyclen and Canadian Cyclen products since Barr is interested in filing under separate cover for approval of this product in the Canadian marketplace. For the purposes of this submission, only the USA reference data is applicable.

Study Information

STUDY FACILITY INFORMATION

Clinical Facility: Medical Director: Scientific Director:	[ ]
Dosing Dates:	07/17/99, 8/14/99 and 10/05/99
Analytical Facility Principal Investigator:	[ ]
Analytical Study Dates:	09/18/99 to 01/8/99

TREATMENT INFORMATION

Treatment ID:	A	B	C
Test or Reference:	T	R	R
Product Name:	Norgestimate-ethinyl estradiol	Ortho-Cyclen	Cyclen
Manufacturer:	Barr Laboratories, Inc.	Ortho Pharmaceutical Corporation (USA)	Ortho-McNeil Inc.
Manufacture Date:	6/30/99	N/A	N/A
Expiration Date:	N/A	5/01	9/00
ANDA Batch Size:	——— Tablets		
Batch/Lot Number:	109879R01	28G075	8J138U
Potency:	101.4%	104.7%	100.4%
Content Uniformity:	101.3%	99.2%	103.0%
Strength:	0.25-0.035 mg	0.25/0.035 mg	0.25/0.035 mg
Dosage Form:	tablet	tablet	tablet
Dose Administered:	2xTablets	2xtablets	2xtablets
Study Condition:	fasting	fasting	fasting
Length of Fasting:	10 hours	10 hours	10 hours
Washout period	28 days		
No. of Subjects Enrolled:	35		
No. of Subjects Completing:	33		
No. of Subjects Plasma Analyzed:	33		
No. of Dropouts:	2		
Sex(es) Included:	Female, Age 18-35 Years		
No. of Adverse Events:	136		

Blood Sampling: Blood samples were drawn into blood collection tubes at 0, 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours.

Study Results:

Adverse Events: No serious adverse events were reported during the study. All adverse events are summarized in Table C3 and C4 Vol. 1.2 page 00296.

Analytical (Not to be Released Under FOI)

Norgestimate was not detectable for most of the samples. No statistical analysis was done for this analyte.

ANALYTE:	ETHINYL ESTRADIOL	LEVONORGESTREL	DESACETYL* NORGESTIMATE
ASSAY METHOD:	[redacted]		[redacted]
MATRIX:			
INTERNAL STANDARD:			
SENSITIVITY			
STANDARD CURVE HIGHEST CONC.:			
STANDARD CURVE LOWEST CONC.:			
R2 GREATER THAN:			
SPECIFICITY:			
ANALYTE RETENTION TIME:			
INTERNAL STANDARD RETENTION TIME:			

*Desacetylnorgestimate is also called 17-deacetyl norgestimate in this report.

Recovery: Mean recovery values were [redacted] % for desacetylnorgestimate, levonorgestrel and ethinyl estradiol, respectively.

Interday precision: Interday variability was assessed with replicate control samples analyzed on separate days. The between-day coefficients of variation ranged from [redacted] % for desacetylnorgestimate, [redacted] % for levonorgestrel and from [redacted] % for ethinyl estradiol.

Stability: Freeze-Thaw Stability: Desacetylnorgestimate, levonorgestrel and ethinyl estradiol were found stable after five freeze/thaw cycles. Long term stability: Stability was assessed by quantitation of QC samples which were frozen

at (-20°C). The results showed no significant degradation of desacetylnorgestimate, levonorgestrel and ethinyl estradiol and for 199 and 156 days, respectively.

3) Pharmacokinetics:

PARAMETER	PROGRAM USED	CALCULATION METHOD
Cmax	SAS	Observed data
Tmax	SAS	Observed data
AUC0-t	SAS	Trapezoidal
AUC0-inf	SAS	AUC0-t + fitted Ct/Kel
Kel	SAS	ln-linear regression of the terminal elimination phase
Thalf	SAS	(ln 2)/Kel

Thirty-five (35) subjects were recruited and thirty-three (33) successfully completed the three phases of the clinical portion of the study. Subject #2 elected to withdraw from study prior to Period II drug administration, due to a positive urine drug screen results at Period II check-in. Subject #29 was withdrawn from the study by the clinical manager prior to Period III drug administration due to a positive urine drug screen at Period III check-in (subject had taken a natural product "Thermo-Lift").

The mean plasma concentrations and pharmacokinetic parameters for 17-Deacetyl Norgestimate, Levonorgestrel and Ethinyl Estradiol are shown in Tables I, II and III, respectively.

Table I

Mean Plasma Concentrations (pg/mL) of 17-Deacetyl Norgestimate Following 2x Norgestimate 0.25 mg/ Ethinyl Estradiol 0.035 mg Tablets

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	REFERENCE TREATMENT C	RATIO (A/B)	RATIO (A/C)
Pre-dose	0.00 (----)	0.00 (----)	0.00 (----)	----	----
0.250	25.95 (221.80)	22.87 (217.68)	63.77 (143.39)	1.1343	0.4069
0.500	697.49 (49.39)	800.39 (47.75)	1020.30 (53.82)	0.8714	0.6836
0.750	1717.76 (36.01)	1965.50 (31.27)	2230.04 (36.11)	0.8740	0.7703
1.00	2433.01 (23.01)	2683.56 (24.77)	2804.63 (33.52)	0.9066	0.8675
1.25	2720.64 (25.20)	3065.77 (20.30)	3033.27 (28.08)	0.8874	0.8969
1.50	2900.91 (23.26)	3170.99 (18.59)	3107.19 (27.03)	0.9148	0.9336
1.75	2903.09 (21.22)	3142.79 (17.10)	2975.36 (28.62)	0.9237	0.9757
2.00	2738.59 (23.26)	3057.49 (17.06)	2879.31 (23.05)	0.8957	0.9511
2.50	2437.83 (20.81)	2703.23 (20.90)	2502.09 (23.35)	0.9018	0.9743
3.00	2110.62 (19.90)	2352.88 (21.47)	2304.32 (20.73)	0.8970	0.9159
4.00	1603.69 (22.42)	1715.87 (23.81)	1673.51 (20.25)	0.9346	0.9583
6.00	984.67 (24.77)	981.20 (25.91)	955.85 (25.35)	1.0035	1.0301

8.00	728.07 (21.02)	748.12 (22.98)	729.23 (20.36)	0.9732	0.9984
10.0	626.68 (22.46)	673.61 (17.82)	647.42 (18.20)	0.9303	0.9680
12.0	604.46 (16.78)	616.38 (18.08)	611.82 (19.31)	0.9807	0.9880
16.0	515.44 (22.14)	541.27 (20.27)	520.09 (23.79)	0.9523	0.9910
24.0	401.78 (23.16)	414.37 (25.23)	413.06 (23.28)	0.9696	0.9727
36.0	291.34 (25.43)	312.66 (28.80)	300.18 (29.21)	0.9318	0.9706
48.0	206.94 (30.75)	224.33 (27.96)	210.86 (29.75)	0.9224	0.9814
72.0	93.31 (73.12)	100.42 (71.01)	87.93 (80.64)	0.9292	1.0612

PK PARAMETER	N	TEST TREATMENT A	N	REFERENCE TREATMENT B	N	REFERENCE TREATMENT C	RATIO (A/B)	RATIO (A/C)
AUCT [pg.hr/mL]	33	29659.88 (21.90)	33	31345.01 (23.95)	33	30565.82 (22.73)	0.9462	0.9704
AUCI [pg.hr/mL]	33	36300.80 (20.10)	33	38143.11 (22.58)	33	37188.39 (22.52)	0.9517	0.9761
Cmax [pg/mL]	33	3091.96 (19.61)	33	3394.54 (14.78)	33	3362.09 (22.43)	0.9109	0.9197
Tmax [hr]	33	1.69 (23.11)	33	1.70 (26.56)	33	1.64 (37.83)	0.9911	1.0324
Kel [1/hr]	33	0.0291 (31.97)	33	0.0297 (29.88)	33	0.0293 (26.14)	0.9784	0.9937
T½ [hr]	33	25.90 (27.10)	33	25.26 (27.90)	33	25.18 (24.64)	1.0254	1.0287

	90% CI(A vs B)
LnAUC(0-t)	90-100%
LnAUCI	92-100%
LnCmax	87-95%

1. The mean 17-Deacetyl Norgestimate plasma levels peaked at 1.75 and 1.5 hours for the test and the reference products, respectively, following their administration under fasting conditions.

2. For Barr's 17-Deacetyl Norgestimate, the mean AUC(0-t), AUCinf and Cmax values were 5.4%, 4.8% and 8.9% lower, respectively, than those for the reference product (B) values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCI and Cmax.

Table II

Mean Plasma Concentrations (pg/mL) of Levonorgestrel Following 2x Norgestimate 0.25 mg/ Ethinyl Estradiol 0.035 mg Tablets

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	REFERENCE TREATMENT C	RATIO (A/B)	RATIO (A/C)
Pre-dose	35.63 (565.69)	0.00 (----)	0.00 (----)	----	----
0.250	61.82 (378.70)	52.95 (159.49)	57.00 (146.47)	1.1675	1.0846
0.500	325.43 (78.99)	425.55 (55.51)	380.93 (55.93)	0.7647	0.8543
0.750	588.18 (52.79)	721.80 (43.11)	680.85 (41.12)	0.8149	0.8639
1.00	788.24 (40.78)	880.77 (36.38)	815.01 (37.71)	0.8949	0.9672
1.25	869.19 (32.92)	989.20 (32.88)	889.07 (35.27)	0.8787	0.9776
1.50	940.47 (31.86)	1047.58 (30.10)	980.71 (33.41)	0.8978	0.9590
1.75	977.63 (28.64)	1063.56 (26.14)	992.06 (33.16)	0.9192	0.9855
2.00	988.13 (31.41)	1093.34 (29.03)	981.99 (30.22)	0.9038	1.0063
2.50	945.79 (30.45)	1048.07 (26.37)	960.11 (25.98)	0.9024	0.9851
3.00	907.99 (28.43)	991.18 (27.63)	933.56 (23.56)	0.9161	0.9726
4.00	820.54 (35.73)	881.61 (26.89)	822.45 (24.99)	0.9307	0.9977
6.00	629.10 (47.01)	644.33 (32.56)	592.44 (32.25)	0.9764	1.0619
8.00	524.30 (47.62)	547.26 (37.29)	498.53 (33.07)	0.9580	1.0517
10.0	493.86 (51.51)	515.16 (39.84)	468.52 (34.47)	0.9587	1.0541
12.0	475.37 (51.50)	494.04 (38.41)	456.94 (33.84)	0.9622	1.0403
16.0	446.52 (49.53)	460.89 (41.68)	430.98 (39.18)	0.9688	1.0361
24.0	405.03 (57.34)	420.16 (44.55)	395.12 (39.76)	0.9640	1.0251
36.0	410.57 (55.45)	412.95 (49.05)	372.52 (36.79)	0.9942	1.1021
48.0	339.94 (42.80)	362.80 (48.33)	310.31 (42.56)	0.9370	1.0955
72.0	206.33 (52.99)	237.93 (59.09)	208.42 (50.15)	0.8672	0.9900

PK PARAMETER	N	TEST TREATMENT A	N	REFERENCE TREATMENT B	N	REFERENCE TREATMENT C	RATIO (A/B)	RATIO (A/C)
AUCT [pg.hr/mL]	33	26441.17 (41.93)	33	27278.14 (46.52)	33	25039.60 (40.04)	0.9693	1.0560
AUCI [pg.hr/mL]	33	48734.58 (63.48)	33	49840.39 (68.76)	33	43124.60 (43.58)	0.9778	1.1301
Cmax [pg/mL]	33	1064.92 (29.53)	33	1159.70 (24.91)	33	1108.53 (26.24)	0.9183	0.9607
Tmax [hr]	33	2.15 (27.70)	33	2.02 (29.70)	33	2.08 (36.33)	1.0637	1.0327
Kel [1/hr]	33	0.0157 (43.78)	33	0.0164 (40.04)	33	0.0162 (40.97)	0.9581	0.9662

T½ [hr]	33	52.62 (45.78)	33	50.19 (50.07)	33	49.80 (39.47)	1.0485	1.0567

	90% CI(A vs B)
LnAUC(0-t)	89-107%
LnAUCI	88-109%
LnCmax	85-97%

1. The mean Levonorgestrel plasma levels peaked at 2 hours for both the test product and the reference product (B) following their administration under fasting conditions.

2. For Barr's Levonorgestrel, the mean AUC(0-t), AUCinf and Cmax values were 3.1%, 2.2% and 8.2% lower, respectively, than those for the reference product (B) values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCI and Cmax.

Table III

Mean Plasma Concentrations (pg/mL) of Ethinyl Estradiol Following 2x Norgestimate 0.25 mg/ Ethinyl Estradiol 0.035 mg Tablets

TIME (HR)	TEST TREATMENT A	REFERENCE TREATMENT B	REFERENCE TREATMENT C	RATIO (A/B)	RATIO (A/C)
Pre-dose	0.00 (----)	0.00 (----)	0.00 (----)	----	----
0.250	9.13 (106.82)	11.74 (97.03)	11.94 (118.78)	0.7774	0.7641
0.500	81.49 (80.98)	82.85 (60.09)	76.70 (62.13)	0.9836	1.0624
0.750	140.97 (58.13)	140.15 (47.86)	134.37 (53.73)	1.0058	1.0491
1.00	164.28 (49.20)	166.30 (46.87)	157.68 (48.07)	0.9879	1.0419
1.25	172.26 (43.81)	172.42 (41.65)	161.93 (43.23)	0.9991	1.0638
1.50	172.75 (38.26)	170.79 (37.75)	164.05 (41.84)	1.0115	1.0531
1.75	168.32 (33.91)	167.48 (38.50)	156.76 (40.76)	1.0050	1.0737
2.00	158.55 (31.34)	160.48 (34.10)	150.45 (36.34)	0.9879	1.0538
2.50	138.39 (28.65)	144.33 (33.06)	136.61 (34.83)	0.9588	1.0130
3.00	124.79 (28.73)	128.56 (32.42)	122.93 (33.67)	0.9707	1.0151
4.00	102.89 (28.81)	105.10 (31.60)	98.20 (30.13)	0.9790	1.0478
6.00	70.05 (23.36)	71.14 (26.26)	69.52 (28.88)	0.9847	1.0075
8.00	48.50 (21.36)	48.86 (26.39)	46.75 (25.97)	0.9926	1.0374
10.0	40.27 (20.52)	40.99 (27.91)	39.61 (24.76)	0.9824	1.0168
12.0	34.92 (22.01)	35.08 (26.85)	34.36 (23.05)	0.9954	1.0161
16.0	28.24 (24.94)	28.19 (29.24)	27.58 (27.79)	1.0015	1.0237
24.0	17.55 (30.85)	18.63 (33.04)	17.07 (31.28)	0.9418	1.0278
36.0	10.80 (43.41)	10.65 (47.31)	10.26 (48.98)	1.0141	1.0523
48.0	5.00 (74.93)	4.71 (94.10)	5.34 (89.17)	1.0624	0.9370
72.0	0.21 (509.90)	0.00 (----)	0.21 (500.00)	----	0.9903

PK PARAMETER	N	TEST TREATMENT A	N	REFERENCE TREATMENT B	N	REFERENCE TREATMENT C	RATIO (A/B)	RATIO (A/C)
AUCT [pg.hr/mL]	33	1503.69 (28.72)	33	1500.61 (33.17)	33	1464.38 (31.52)	1.0020	1.0268
AUCI [pg.hr/mL]	33	1677.58 (27.66)	33	1688.41 (31.18)	33	1644.84 (30.55)	0.9936	1.0199
Cmax [pg/mL]	33	185.39 (42.36)	33	182.01 (40.19)	33	173.08 (40.80)	1.0186	1.0711
Tmax [hr]	33	1.48 (19.26)	33	1.41 (27.99)	33	1.54 (57.92)	1.0538	0.9655
Kel [1/hr]	33	0.0509 (20.87)	33	0.0529 (25.27)	33	0.0507 (24.15)	0.9624	1.0031
T½ [hr]	33	14.21 (21.15)	33	13.90 (24.37)	33	14.48 (24.98)	1.0224	0.9812

	90% CI(A vs B)
LnAUC(0-t)	98-105%
LnAUCI	97-104%
LnCmax	98-107%

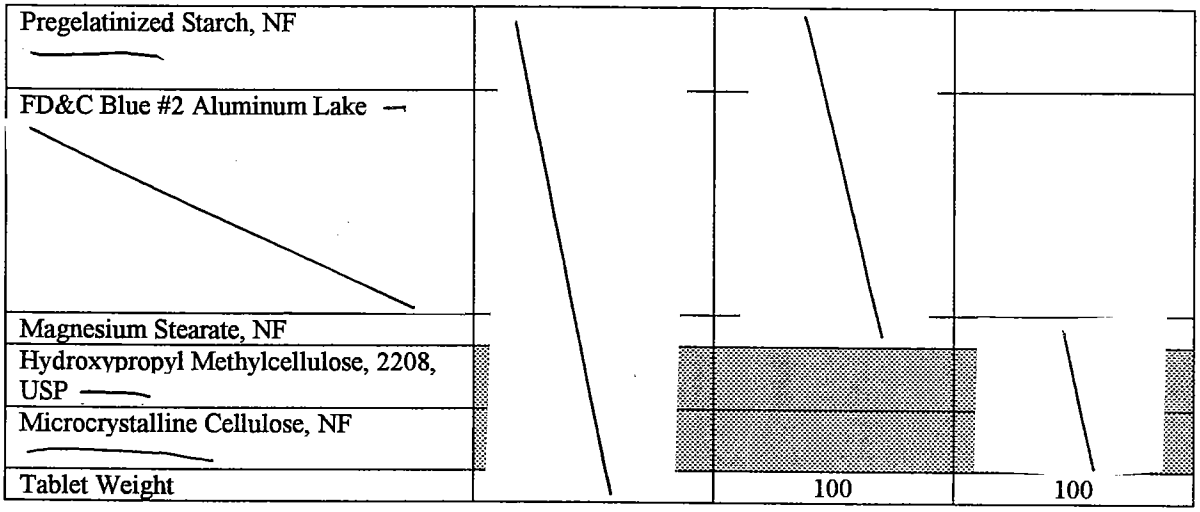
1. The mean Ethinyl Estradiol plasma levels peaked at 1.50 and 1.25 hours for the test product and the reference product (B), respectively, following their administration under fasting conditions.

2. For Barr's Levonorgestrel, the mean AUC(0-t), Cmax and AUCinf and values were 0.2%, 1.9% and 0.64% higher and lower, respectively, than those for the reference product (B) values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-t), AUCI and Cmax.

Formulations:(Not to be released under FOI)

Barr's formulations for its Norgestimate, 0.25 mg/ Ethinyl Estradiol, 0.035 mg Tablets, ——— 28 day regimens are shown below:

Ingredient		0.250 mg/0.035 mg mg/dose	
		28 Day Regimen (Active)	28 Day Regimen (Placebo)
Norgestimate		0.250	
Ethinyl Estradiol, USP		0.035	
Pregelatinized Starch, NF			
Lactose Monohydrate, NF			
Anhydrous Lactose, NF			



In Vitro Dissolution Testing:

Method:	USP 24 apparatus II at 75 rpm
Medium:	
Number of Tablets:	12
Test products:	Barr's Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablets, lot #109879R01
Reference products:	Johnson RW's Ortho Cyclen^{R}-28, 0.25 mg/0.035 mg Tablets, lot #28G075
Specifications:	NLT — % (Q) in 60 minutes (both components)

IN-VITRO COMPARATIVE DISSOLUTION STUDY

NORGESTIMATE

	Barr Laboratories' Norgestimate and Ethinyl Estradiol Tablets 0.25 mg/0.035 mg, Batch No. 109879R01					**Ortho Pharmaceutical Corporation, ORTHO-CYCLEN 28 Tablets, Exp. May 2001 Batch# 28G075 (USA)**				
Ref.:	PR1220/p1-6					**PR1222/p1-6, 26-27**				
Tablet	**% Norgestimate Dissolved**					**% Norgestimate Dissolved**				
	Time (minutes)					**Time (minutes)**				
	15	**30**	**45**	**60**	**90**	**15**	**30**	**45**	**60**	**90**
1										
2										
3										
4										
5										
6										
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10										
11										
12										
Ave	96	100	101	101	101	97	104	104	104	105
%RSD	1.1	1.2	1.3	1.3	1.3	2.9	1.2	1.1	1.2	1.4

IN-VITRO COMPARATIVE DISSOLUTION STUDY

ETHINYL ESTRADIOL

	Barr Laboratories' Norgestimate and Ethinyl Estradiol Tablets 0.25 mg/0.035 mg, Batch No. 109879R01					Ortho Pharmaceutical Corporation, ORTHO-CYCLEN 28 Tablets, Exp. May 2001 Batch# 28G075 (USA)				
Ref.:	PR1220/p1-6					PR1222/p1-6, 26-27				
Tablet	%Ethinyl Estradiol Dissolved					% Ethinyl Estradiol Dissolved				
	Time (minutes)					Time (minutes)				
	15	30	45	60	90	15	30	45	60	90
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										
12										
Ave	101	102	102	102	102	100	104	104	104	104
%RSD	1.0	1.5	1.5	1.8	1.4	2.6	1.1	0.8	1.1	1.3

The Clinical Division, HFD-580 reviewing the original NDA #19-653 for Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg, recommended the following dissolution method:

Apparatus: USP, apparatus 2 (rotating paddles), 75 rpm
Medium: 600 mL of 0.05% Tween 20, at 37^{O}C
Method: HPLC

In a telephone conversation, on April 18, 2000, the firm was advised to submit comparative dissolution testing using the above method. On May 2, 2000, the firm submitted the dissolution results according to the method mentioned above.

IN-VITRO COMPARATIVE DISSOLUTION STUDY

NORGESTIMATE

	Barr Laboratories' Norgestimate and Ethinyl Estradiol Tablets 0.25 mg/0.035 mg, Batch No. 109879R01					Ortho Pharmaceutical Corporation, ORTHO-CYCLEN 28 Tablets, Exp. May 2001 Batch# 28G075 (USA)				
Ref.:	PR1240/p104-108, DR 2003671					PR1120/p85-94, DR 2003671				
Tablet	% Norgestimate Dissolved					% Norgestimate Dissolved				
	Time (minutes)					Time (minutes)				
	15	30	45	60	90	15	30	45	60	90
1	54									
2	54									
3	51									
4	54									
5	55									
6	54									
7	56									
8	53									
9	56									
10	56									
11	55									
12	56									
Ave	55	66	72	76	81	51	72	83	86	91
%RSD	2.8	2.8	2.3	2.7	3.0	10.3	2.2	2.0	1.9	2.2
F-2 test						53.03				

IN-VITRO COMPARATIVE DISSOLUTION STUDY

ETHINYL ESTRADIOL

	Barr Laboratories' Norgestimate and Ethinyl Estradiol Tablets 0.25 mg/0.035 mg, Batch No. 109879R01					Ortho Pharmaceutical Corporation, ORTHO-CYCLEN 28 Tablets, Exp. May 2001 Batch# 28G075 (USA)				
Ref.:	PR1240/p104-108, DR 2003671					PR1120/p 85-94, DR 2003671				
Tablet	%Ethinyl Estradiol Dissolved					% Ethinyl Estradiol Dissolved				
	Time (minutes)					Time (minutes)				
	15	30	45	60	90	15	30	45	60	90
1										
2										
3										
4										
5										
6										
7										

8										
9										
10										
11										
12										
Ave	98	100	101	100	100	96	101	99	97	98
%RSD	2.3	1.5	1.8	2.2	2.1	4.6	1.9	2.3	1.6	1.5

Comments:

1. The reference listed drug for the proposed Barr's Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablets is Ortho-Cyclen^{R} 21 Tablets, 0.25 mg/0.035 mg (Ortho Pharmaceutical Corporation a division of Johnson RW). Barr Laboratories, Inc., conducted a bioequivalence study comparing its test product with that of Ortho-Cyclen^{R} 28 Tablets, 0.25 mg/0.035 mg. Barr spoke with the Division of Bioequivalence and confirmed that either the 21 or 28 Day regimens may be used for the bioequivalence study since the reference listed drug contains the same active tablet in both regimens.

2. For the single-dose bioequivalence study under fasting conditions, the confidence intervals for LnAUC(0-t), LnAUCI and LnCmax are within the acceptable range of 80-125% for 17-deacetyl norgestimate, levonorgestrel and ethinyl estradiol.

3. It should be noted that there was quantifiable plasma Levonorgestrel level (——— pg/mL) in the pre-dose sample for subject #36, Period III (test product). Additional analysis of variance was performed by the reviewer, after excluding this subject. The 90% confidence intervals for log-transformed AUC(0-t), AUCI and Cmax remained within the acceptable range of 80-125% for 17-deacetyl norgestimate, levonorgestrel and ethinyl estradiol.

4. The formulation for Barr's Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablet,

[redacted]

5. The dissolution testing conducted by the firm on its Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablets, lot #109879R01, is acceptable. ———————

[redacted]

6. The firm's financial disclosure statements submitted with the bioequivalence section in support of this application did not indicate any conflict of interests between the CRO's investigators and the firm. The reviewer agrees with that conclusion.

Recommendations:

1. The single-dose, fasting bioequivalence study conducted by Barr Laboratories, Inc., on its Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablet, lot #109879R01, comparing it to Johnson RW's Ortho-Cyclen^{R} 28 Tablet, 0.25 mg/0.035 mg, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Barr's Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablet, is bioequivalent to the reference product Ortho-Cyclen^{R} 28 Tablet, 0.25mg/0.035 mg, manufactured by Johnson RW.

2. The dissolution testing conducted by Barr Laboratories , Inc., on its Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablet, lot #109879R01, is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

> Not less than −% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes
> Not less than −% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 minutes.

The firm should be informed of the above recommendations

Moheb H. Makary

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

6/7/00

RD INITIALLED BDAVIT
FT INITIALLED BDAVIT BMDavit Date: 6/8/00

Concur: Date: 6/28/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/5-8-00, 6-8-00, 75804SDW.300
cc: ANDA #75-804, original, HFD-658 (Makary), Drug File, Division File.

DIVISION OF BIOEQUIVALENCE

ANDA # :75-804 SPONSOR : Barr Laboratories, Inc.

DRUG AND DOSAGE FORM : Norgestimate/Ethinyl Estradiol,Tablet

STRENGTH(S) : 0.25 mg/0.035 mg

TYPES OF STUDIES : One bioequivalence study under fasting conditions

CLINICAL STUDY SITE(S) : ———

ANALYTICAL SITE(S) : ———

STUDY SUMMARY : The study is acceptable

DISSOLUTION : Dissolution testing is acceptable. ———

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
~~YES~~ (NO)		
First Generic ~~Yes~~	Inspection requested: (date)	
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 6/8/00

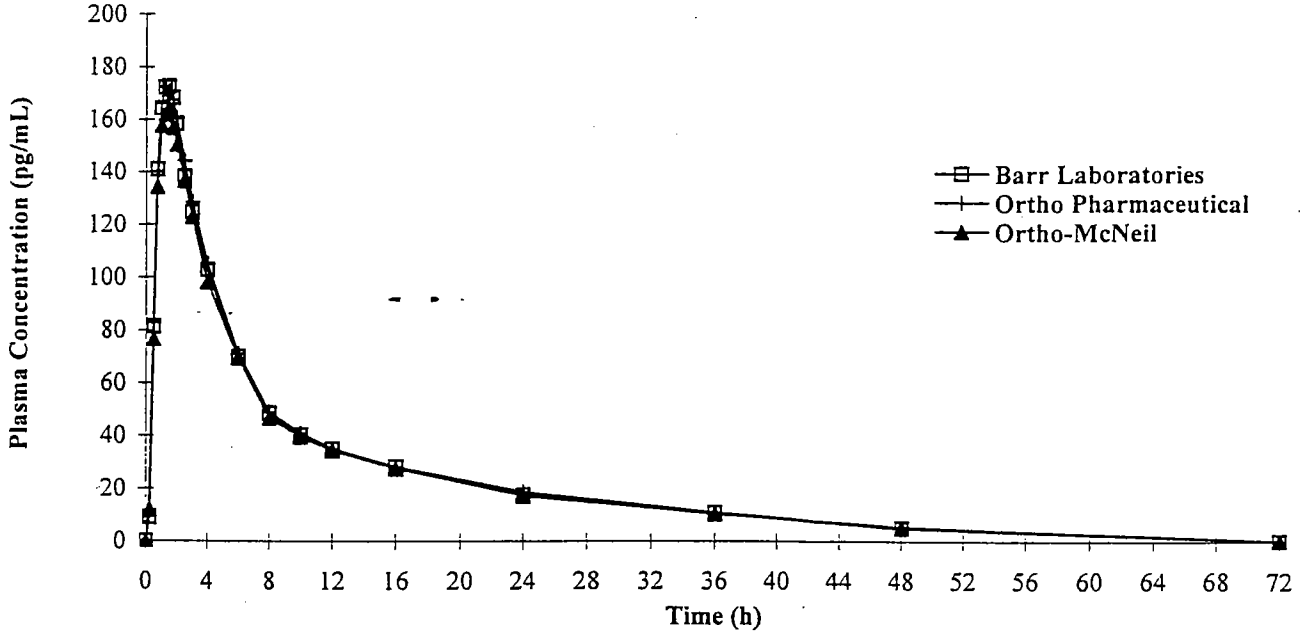
TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 6/8/00

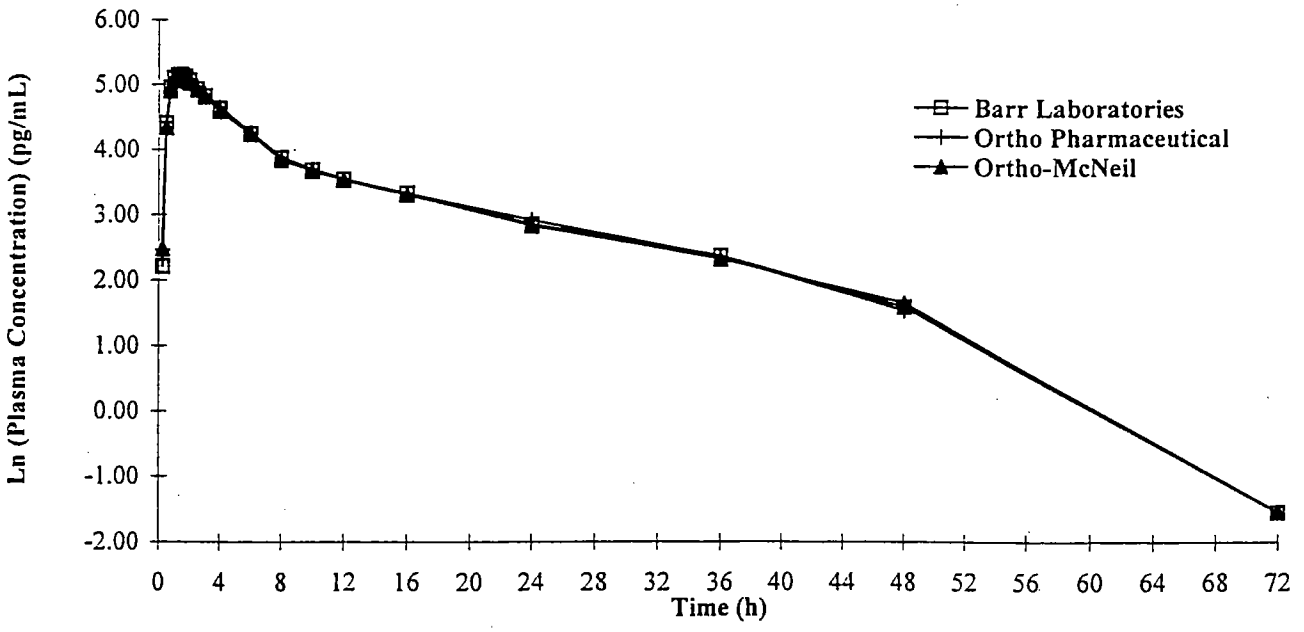
DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC **DATE :** 6/29/00

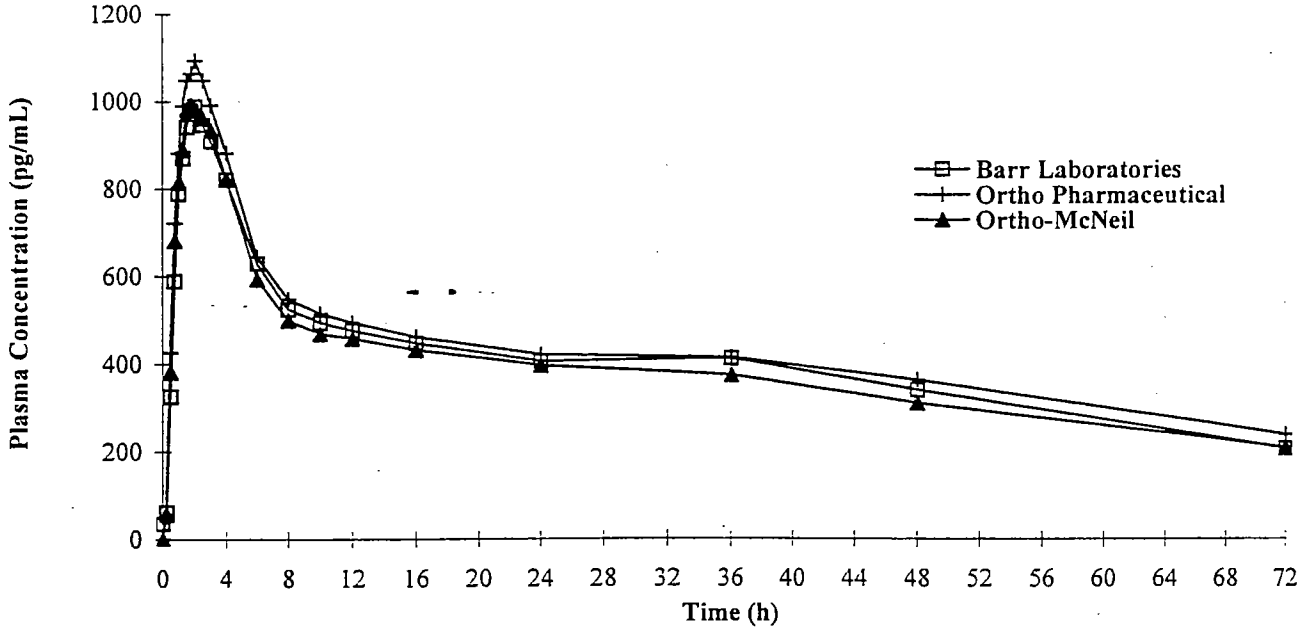
Ethinyl Estradiol Mean Concentration - Time profile
N = 33



Ethinyl Estradiol Ln (Mean Concentration) - Time profile
N = 33



Levonorgestrel Mean Concentration - Time profile
N = 33



Levonorgestrel Ln (Mean Concentration) - Time profile
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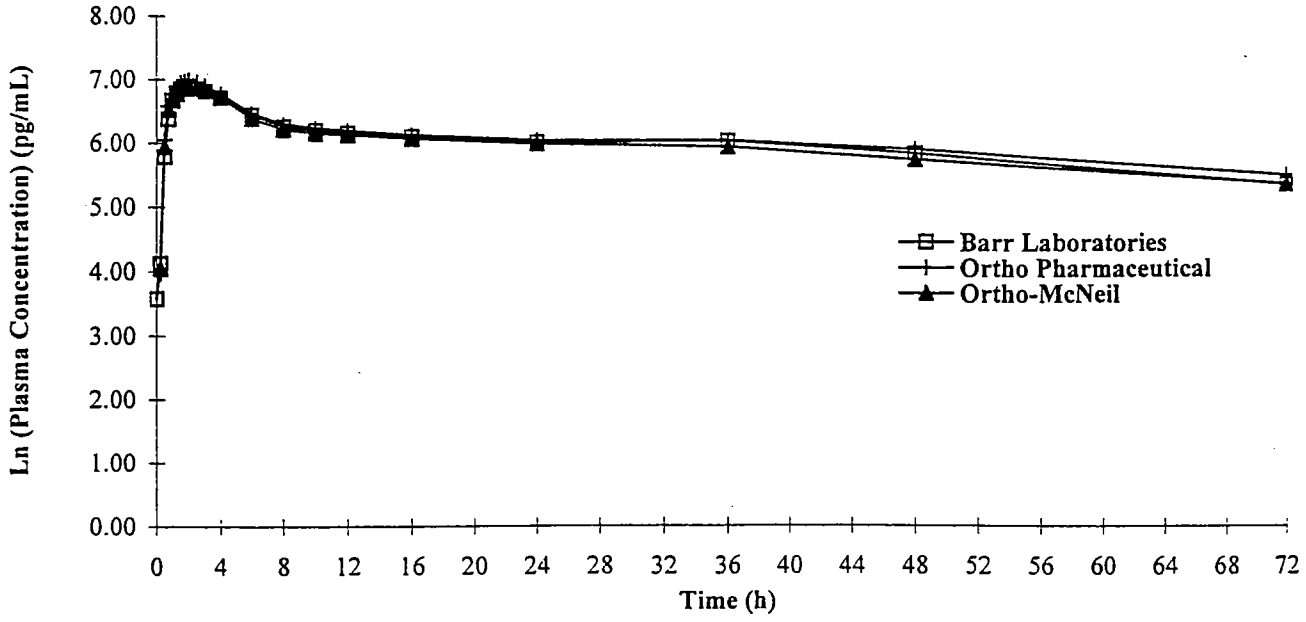
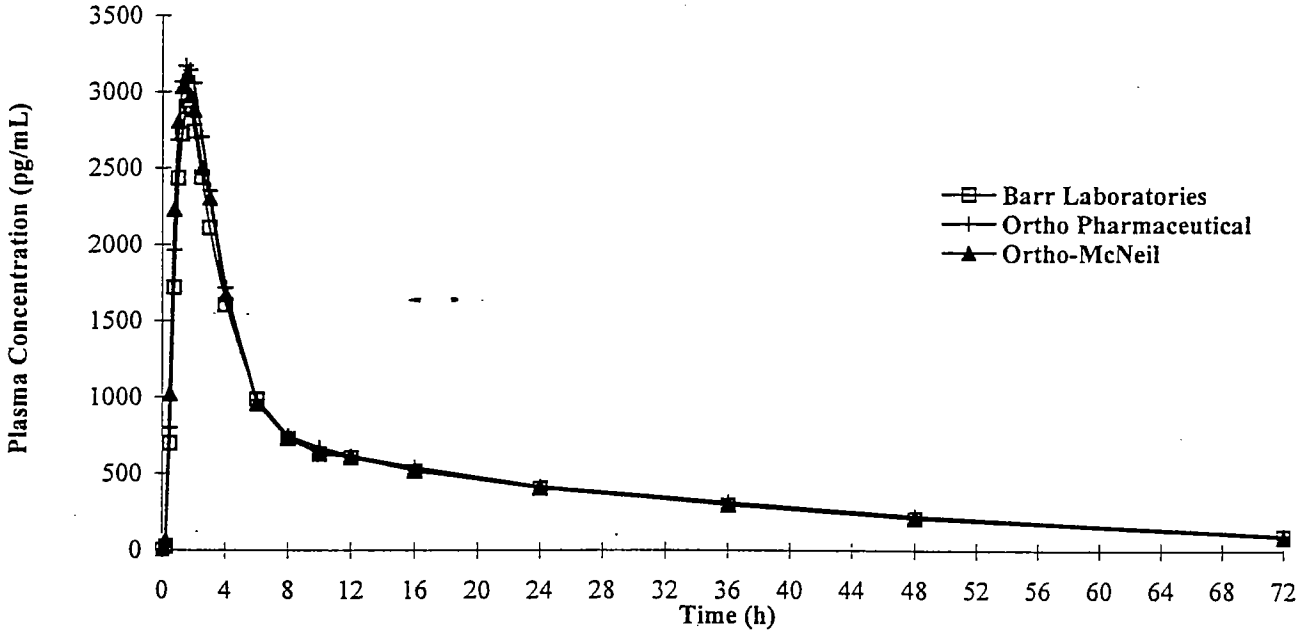
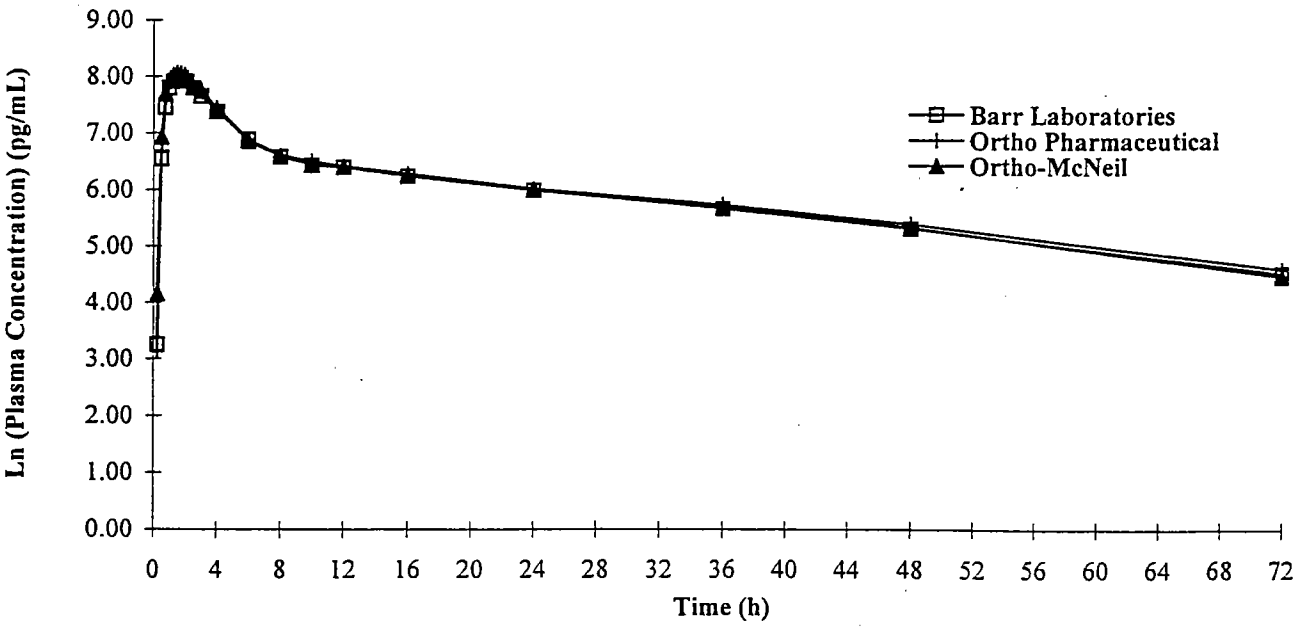


17-Deacetyl Norgestimate Mean Concentration - Time profile
N = 33



17-Deacetyl Norgestimate Ln (Mean Concentration) - Time profile
N = 33



B.1
Talcing, IV

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-804 APPLICANT: Barr laboratories, Inc.

DRUG PRODUCT: Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

> The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:
>
> > Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes
> > Not less than —% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 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,

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

CC: ANDA #75-804
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

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Printed in final on 6/8/00

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit
HFD-650/ D. Conner 6/29/00

BIOEQUIVALENCY - ACCEPTABLE submission date: 3-16-00

OK 1. **FASTING STUDY** (STF) Strengths: 0.25 mg/0.035 mg
Clinical: ———— **Outcome: AC**
Analytical: ————

OK 2. **WAIVER** (WAI) Strengths: 0.25/0.035 mg, 21 Day Regimen
Outcome: AC

OK 3. **STUDY AMENDMENT** (STA) 4/10/00 Strengths: 0.25 mg/0.035 mg
Outcome: AC

OK 4. **STUDY AMENDMENT** (STA) 5/2/00 Strengths: 0.25 mg/0.035 mg
Outcome: AC

Outcome Decisions: **AC** – Acceptable

APPEARS THIS WAY
ON ORIGINAL

Norgestimate/Ethinyl Estradiol
0.25 mg/0.035 mg Tablets
ANDA Number #75-804
Reviewer: Moheb H. Makary
W. 75804STA.N00

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
November 28, 2000

Review of an Amendment

I. Objective:

In this amendment the firm has requested that the Agency reconsider the use of the dissolution method submitted in the firm's submission dated March, 16, 2000 ([redacted], using USP 24 apparatus II at 75 rpm).

II. Background:

The firm had submitted a bioequivalence study under fasting conditions on its 0.25 mg/0.035 mg Norgestimate/Ethinyl Estradiol Tablets and dissolution data (submission dated March 16, 2000).

The Division of Bioequivalence has found the study acceptable. In the submission, the firm proposed the following dissolution method: [redacted] using USP 24 apparatus II at 75 rpm. On April 18, 2000, the firm was advised to conduct the dissolution testing using the FDA method: 600 mL of 0.05% Tween 20 (polysorbate), at 37°C, using USP, apparatus 2 (paddle) at 75 rpm. On May 2, 2000, the firm submitted the dissolution results according to the FDA method. The Division of Bioequivalence has found the results acceptable. Based on the submitted data, the following dissolution specification was recommended:

> Not less than [redacted] % (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes. Not less than [redacted]% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 minutes.

III. Barr's Arguments:

1. The firm indicated that it developed its Norgestimate/Ethinyl Estradiol tablet product using [redacted] as a dissolution medium and the

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW OF 11/28/2000 SUBMISSION

as a quality control specification for the manufacturing process.

2. The [redacted] dissolution method proposed by the firm provided — % release of norgestimate in 15 minutes from Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg. Therefore, this method is not suitable as a discriminatory tool for routine dissolution testing.

3. The 0.05% Tween-20 dissolution method recommended by the Agency and proposed by Pharmacopeial Forum (Vol. 26(5) [Sept.-Oct. 2000] provided — % and — % release of norgestimate in 15 and 90 minutes, respectively, from Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg. Therefore, the method appears to be discriminatory for routine dissolution testing.

IV. Recommendation:

The Division of Bioequivalence recommends the following interim dissolution testing method and specification for the Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg:

Apparatus: USP, apparatus 2 (paddle), 75 rpm
Medium: 600 mL of 0.05% Tween 20, at 37°C
Method: HPLC

Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes.
Not less than —% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 minutes.

The firm should be informed of the above recommendation.

Moheb H. Makary

Moheb H. Makary, Ph.D. Date: 12/18/00
Review Branch III
Division of Bioequivalence

For RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Mamata Gokhale Date: 12/18/00

Concur: Dale P. Conner Date: 12/26/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/12-12-2000, 12-18-00, 75804SD.N00
cc: ANDA #75-804, original, HFD-658 (Makary), Drug File, Division File.

CC: ANDA #75-804
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

V:\FIRMSAM\BARR\LTRS&REV\75804STA.N00
Printed in final on 12/18/00

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
For HFD-658/ Bio team Leader B. Davit MSK 12/18/00
HFD-650/ D. Conner OK 12/26/00

BIOEQUIVALENCY - ACCEPTABLE submission date: 11-28-00

1. **STUDY AMENDMENT** (STA) ok Strengths: 0.25 mg/0.035 mg
Outcome: AC

Outcome Decisions: **AC** – Acceptable

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF BIOEQUIVALENCE

ANDA # :75-804 STA SPONSOR : Barr Laboratories, Inc.

DRUG AND DOSAGE FORM : Norgestimate/Ethinyl Estradiol,Tablet

STRENGTH(S) : 0.25 mg/0.035 mg

TYPES OF STUDIES : N/A
CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY :

DISSOLUTION : Dissolution method and specifications are recommended for Norgestimate/ Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 12/11/00

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

For INITIAL : MBD DATE : 12/18/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC **DATE :** 12/26/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-804 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Your proposed ——————————— dissolution method is not acceptable for the following:

1. Your argument that by using the 0.05% Tween-20 medium the dissolution rate *in vitro* does not reflect the actual dissolution rate *in vivo*, therefore, the method is not suitable. In the absence of a suitable verified *in vivo/in vitro* correlation this argument is not relevant. Furthermore, the *in vitro* dissolution testing for Norgestimate/Ethinyl Estradiol drug products serve mainly as a quality control specification for the manufacturing process.

2. The ——————————— dissolution method you proposed provided — % release of norgestimate in 15 minutes from Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg. Therefore, this method is not suitable as a discriminatory tool for routine dissolution testing.

3. The 0.05% Tween-20 dissolution method recommended by the Agency and proposed by Pharmacopeial Forum (Vol. 26(5) [Sept.-Oct. 2000] provided — % and — % release of norgestimate in 15 and 90 minutes, respectively, from Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg. Therefore, the method appears to be discriminatory for routine dissolution testing.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes. Not less than —% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 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,

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

Norgestimate/Ethinyl Estradiol
0.25 mg/0.035 mg Tablets
ANDA Number #75-804
Reviewer: Moheb H. Makary
W. 75804STA.201

Barr Laboratories, Inc.
Pomona, NY
Submission Date:
February 1, 2001

Review of an Amendment

Objective:

In this amendment, the firm has accepted the dissolution testing method and specifications for Norgestimate/Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg, recommended by the Division of Bioequivalence (Amendment dated November 28, 2000).

Background:

In the November 28, 2000 amendment, the firm proposed the use of the dissolution method submitted in its original submission dated March, 16, 2000 (———————————————————, using USP 24 apparatus II at 75 rpm). The proposed method was denied. The Division of Bioequivalence recommended the following interim dissolution testing method and specification for the Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg:

Apparatus: USP, apparatus 2 (paddle), 75 rpm
Medium: 600 mL of 0.05% Tween 20, at 37°C
Method: HPLC

Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes.
Not less than —% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 minutes.

Recommendation:

The firm has adopted the dissolution method and specifications previously recommended by the Division of Bioequivalence in the amendment dated November 28, 2000. Consequently, no further action is needed.

Moheb H. Makary

Moheb H. Makary, Ph.D. Date: 2/12/01
Review Branch III
Division of Bioequivalence

RD INITIALLED BDAVIT BDM 2/12/01
FT INITIALLED BDAVIT Barbara M Davit Date 2/12/01

Concur: for Dale P. Conner Date: 2/26/2001
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Mmakary/2-9-200, 75804SD.201
cc: ANDA #75-804, original, HFD-658 (Makary), Drug File, Division File.

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF BIOEQUIVALENCE

ANDA # :75-804 SPONSOR : Barr Laboratories, Inc.

DRUG AND DOSAGE FORM : Norgestimate/Ethinyl Estradiol,Tablet

STRENGTH(S) : 0.25 mg/0.035 mg

TYPES OF STUDIES : STA

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : **N/A**

STUDY SUMMARY : N/A

DISSOLUTION : The firm adopted the dissolution method and specifications recommended by the Division of Bioequivalence.

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic _____ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Moheb H. Makary, Ph.D. BRANCH : III

INITIAL : MHM DATE : 2/12/01

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : Barbara M Davit DATE : 2/12/01

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : Dale Conner **DATE :** 2/26/2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-804 APPLICANT: Barr laboratories, Inc.

DRUG PRODUCT: Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:
>
> > Not less than — % (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes
> > Not less than — % (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 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 #75-804
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit

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Printed in final on 2/12/01

Endorsements: (Final with Dates)
HFD-658/ Reviewer M. Makary
HFD-658/ Bio team Leader B. Davit
HFD-650/ D. Conner for Rud 2/26/2001

BIOEQUIVALENCY - ACCEPTABLE submission date: 2-1-01

1. **STUDY AMENDMENT** (STA) Strengths: 0.25 mg/0.035 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-804

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : February 24, 2000

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

2/25/00

SUBJECT: Examination of the bioequivalence study submitted with an ANDA forNorgestimate and Ethinyl Estradiol Tabets USP to determine if the application is substantially complete for filing.

BarrLaboratories Inc. has submitted ANDA 75-804 for Norgestimate and Ethinyl Estradiol Tablets USP, 0.250 mg & 0.035 mg -——— 28 days. The ANDA contains a <u>first generic</u>. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the bioequivalence study submitted by Barr on February 16, 2000 for its Norgestimate and Ethinyl Estradiol product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

__✓__ Study meets statutory requirements

_____ Study does **NOT** meet statutory requirements

Reason: note: Bio batch size not in Bio jackets

Director, Division of Bioequivalence — 3/2/00 Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 75-804 DRUG NAME Norgestimate + ethinyl estradiol FIRM Barr Laboratories

DOSAGE FORM(s)

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				
Assay Methodology	✓				[ ]
Procedure SOP	✓				
Validation	✓				
Study Results Log Lin	✓				
Adverse Events	✓				
IRB Approve	✓				
Dissolution	✓				
Pre-screening of patients	✓				
Chromatograms	✓				
Consent form	✓				
Composition	✓				
Summary of study	✓				
Individual Data & Graphs . Linear & Semi-linear	✓				
PKPD data disk	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				[ ]
Analytical site	✓				[ ]
Study investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size		✓			[ ] In Chem Excellent Sta + X val
Assay of active content drug	✓				90–110% Nor 90 - 110% - Ethinyl Estradiol
Content uniformity		✓			stated only that it meets USP
Date of manufacture	✓				Test
Exp. Date RLD	✓				May 01 Sept 2000
Biostudy lot numbers	✓				109879R01 - T 28G075 - or the Cyclen 8J 138U - Cyclen
Statistics	✓				
Waiver request for other strengths / supporting data	✓				

Recommendation: **COMPLETE / INCOMPLETE**

ok G.H 3/1/2000

Reviewed by

Date 3/1/2000

Revised 2/19/98

RECORD OF TELEPHONE CONVERSATION

Reference is made to the firm's fax dated February 1, 2001.

Ms. Gray stated that the DMF holder has already amended the DMF file with the appropriate changes.

The firm has responded to the major deficiency letters for all 4 ANDAs. I asked Ms. Gray to send in additional amendments with the new information to these ANDAs ASAP.

Ms. Gray agreed.

APPEARS THIS WAY
ON ORIGINAL

DATE:
February 1, 2001

ANDA NUMBER:
75-803, 75-804, 75-808, 75-866

PRODUCT NAME:
Oral Contraceptives

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Elizabeth Gray

PHONE NUMBER:
845-362-1100

FDA REPRESENTATIVES:

Ruby Yu

SIGNATURES:

Ruby Yu

CC: 75-803, 75-804, 75-808, 75-866
Telecon Binder

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(1.1

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 6/26/01	**DUE DATE:** 8/20/01	**OPDRA CONSULT:** 01-0159

TO:

Peter Rickman,
Acting Director, Division of Labeling and Program Support, Office of Generic Drugs
HFD-600

THROUGH:

Harvey Greenberg, Project Manager
Office of Generic Drugs
HFD-615

PRODUCT NAME:	**MANUFACTURER:** Barr Laboratories, Inc.
Sprintec (norgestimate and ethinyl estradiol tablets) 0.25 mg/0.035 mg – ——— 28 day **ANDA #:** 75-804	

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Office of Generic Drugs, Division of Labeling and Program Support (HFD-600), OPDRA conducted a review of the proposed proprietary name "Sprintec" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA has no objection to the use of the proprietary name, "Sprintec". OPDRA considers this a final review. However, if the approval of the ANDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to ANDA approval will rule out any objections based upon approvals of other proprietary names/NDA's/ANDA's from this date forward.

Carol Holquist for 8-15-01

Carol Holquist for Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3242
Fax: 301-480-8173

Martin H Himmel 8/15/01

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Takiar, Neelu

RECORD OF TELEPHONE CONVERSATION

Barr will respond to the following cmc issues as a telephone amendment:

1. Please revise the specifications for ——— according to manufacturer's current specifications, where applicable (i.e. for melting point and ———), and please provide a copy of your and manufacturer's final specifications.
2. The firm revised the packaging and labeling of their product: replaced the ——— with a vinyl wallet and a foil pouch. The firm was asked to provide the following information about the foil pouch for CMC review: material information on the foil pouch, explain how the stability study was conducted; send samples of the final package; explain why leaching studies were not done; and revise the stability protocol to include information on the foil pouch.
3. Barr has revised the drug product release specification for the assay of norgestimate and ethinyl estradiol from ——— % to ——— %. Please revised and provide the in-process specs accordingly.
4. The current release and stability spec for ——— is NMT ———. Information about the formation of this impurity may be found in the original application, section 15; and the degradation pathway may be found on page 16. ——— ——— is produced due to degradation on stability. Therefore, the firm was asked to lower the release spec from NMT ——— based on the release data.
5. Regarding the other impurities found in the norgestimate drug substance (levonorgestrel, ———, the firm stated that the impurities may be potential degradants of the drug product. Firm was asked to set specs for these degradants.
6. Please provide data from retain samples (firm may have 12 and 18 months CRT) using the dissolution method and specs as recommended by the Division of Bioequivalency.
7. Please provided an updated stability report.

DATE:
March 27, 2002

ANDA NUMBER:
75-804 & 75-808

PRODUCT NAME:
Norgestimate and Ethinyl Estradiol Trablets

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Christine Mundkur; Liz Nobel-Gray; ———

PHONE NUMBER:
845-353-8432

FDA REPRESENTATIVES:
Dave Gill
Neeru Takiar
Ruby Wu

SIGNATURES:
Dave Gill PSGill
Neeru Takiar NT 3/28/02
Ruby Wu Ruby 4/24/02

CC: 75-808 & 75-804
Telecon Binder

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RECORD OF TELEPHONE CONVERSATION

Reference is made to the March 27, 2002 t-con.

The following requests were made:

The firm revised the packaging and labeling of their product: replaced the [redacted] with a vinyl wallet and a foil pouch. The firm was asked to provide the following information about the foil pouch for CMC review, as requested in the 3/27/02 t-con: material information on the foil pouch, explain how the stability study was conducted; send samples of the final package; explain why leaching studies were not done; and revise the stability protocol to include information on the foil pouch.

Please establish release and stability specifications for the following impurities that may be potential degradants of the drug product (as mentioned on page 37 of the March 29, 2002 telephone amendment): [redacted]

[redacted] . Please provide data, if available.

DATE:
May 8, 2002

ANDA NUMBER:
75-804 & 75-808

PRODUCT NAME:
Norgestimate and Ethinyl Estradiol Trablets

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Christine Mundkur

PHONE NUMBER:
845-353-8432

FDA REPRESENTATIVES:
Neeru Takiar
Ruby Wu

SIGNATURES:

Neeru Takiar NT 5/8/02
Ruby Wu RW 5/8/02

CC: 75-808 & 75-804
Telecon Binder

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RECORD OF TELEPHONE CONVERSATION

The following request was made:

The firm was asked to lower the acceptance limit for _____ It is high and to provide the final ___ specifications.

APPEARS THIS WAY
ON ORIGINAL

DATE:
June 10, 2002

ANDA NUMBER:
75-804 & 75-808

PRODUCT NAME:
Norgestimate and Ethinyl Estradiol Trablets

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Christine Mundkur

PHONE NUMBER:
845-353-8432

FDA REPRESENTATIVES:
Neeru Takiar

SIGNATURES:
Neeru Takiar
N. Takiar 6/10/02

CC: 75-808 & 75-804
Telecon Binder

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RECORD OF TELEPHONE CONVERSATION

Reference is made to the July 8, 2002 fax requesting a t-con.

Issue:
Firm requested redesignation of the Deficiency letter dated July 3, 2002 from a Minor to a Telephone.

Response:
The request was denied but the firm was informed that the chemist will review the amendment as soon as possible.

Issue:
Firm requested clarification on which [redacted]

Response:

[redacted]

Issue:
In the July 3, 2002 deficiency letter, the firm was asked to either [redacted] or provide

[redacted]

Response:
The firm stated that they will [redacted] and will resubmit post approval. The firm will verify that [redacted]

DATE:
July 8, 2002

ANDA NUMBER:
75-804 & 75-808

PRODUCT NAME:
Norgestimate and Ethinyl Estradiol Tablets

FIRM NAME:
Barr Laboratories, Inc

FIRM REPRESENTATIVE:
Christine Mundkur,
Nicholas Tantillo,
Linda O'Dea

PHONE NUMBER:
845-353-8432

FDA REPRESENTATIVES:
Paul Schwartz
Dave Gill
Neeru Takiar
Ruby Wu
Sarah Kim

SIGNATURES:
Paul Schwartz 7/11/02
Dave Gill DSG 7/11/02
Neeru Takiar NT 7/11/02
Ruby Wu RW 7/11/02
Sarah Kim SK 7/11/02

CC: 75-808 & 75-804
Telecon Binder

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OGD APPROVAL ROUTING SUMMARY

ANDA # 75-804 Applicant Barr Laboratories, Inc
Drug Norgestimate and Ethinyl Estradiol Tablets Strength 0.250mg/0.035mg

APPROVAL ☑ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:

1. Project Manager, Team 4 Sarah Kim
Review Support Br

DRAFT Package
Date 7/24/02
Initials SKim

FINAL Package
Date 7/26/02 9/16/02
Initials SKim SKim

Application Summary:

Original Rec'd date 2/17/00
Date Acceptable for Filing 2/17/00 J
Patent Certification (type) I
Date Patent/Exclus.expires N/A
Citizens' Petition/Legal Case Yes ☐ No ☑
(If YES, attach email from PM to CP coord)
First Generic Yes ☑ No ☐
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD = Ortho-Cyclen 21 and 28 day
Date checked 7/16/02 NDA# 19653
Nothing Submitted ☑
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status July 2, 2001
Date of Office Bio Review 2/26/01
Date of Labeling Approv. Sum 7/24/02
Date of Sterility Assur. App. NA
Methods Val. Samples Pending Yes ☑ No ☒ MV done on sister ANDA 75-805 but not accepted
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐ N/A

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

2. Gregg Davis **PPIV ANDAs Only**
Supv., Reg. Support Branch

Date 9/25/02
Initials RW

Date 9/25/02
Initials

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☐ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Has case been settled: Yes ☐ No ☐
Date settled: N/A
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Comments:

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
Date Checked N/A
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐

RLD-Ortho Cyclen-28 Tablets
RW Johnson Pharmaceutical Research Institute (003)
NDA 19-653

There are no unexpired patents or exclusivity listed in the current Orange Book for this drug product.

3. Div. Dir./Deputy Dir.
Chemistry Div. I or II
Comments:

Date 7/29
Initials PS

Specs are justified

REVIEWER:

FINAL ACTION

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)

Date 9/25/02
Initials FH

SATISFACTORY

5. Peter Rickman
Acting Director, DLPS
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 7/2/02 (Verified 9/25/02). NO OAI. Acceptable bioequivalence study (single-dose fasting) found acceptable. Dissolution data also found acceptable. Biostudy conducted by _____ (both dosing and analytical). This facility has an acceptable OSI inspectional history. Office-level bioendorsed 6/3/02, 12/26/00, 2/26/01. Methods validation commitment received from Barr 7/17/02 FPL acceptable for approval 9/13/02. Proprietary name "Sprintec" found acceptable by OPDRA. Methods validation submitted for this ~~ANDA as well as~~ ANDA 75-808. Methods found acceptable for ANDA 75-808. Methods are the same for ANDA 75-804. Thus, they were not duplicated for 75-804. CMC found acceptable 7/24/02. First generic OR MC audit completed.

Date 9/25/2002
Initials PR for

5. Robert L. West
Acting Deputy Director, OGD

Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Comments: _____

This ANDA, providing for the 28-day cycle package, is recommended for approval. The proprietary name, "Sprintec", has been found acceptable by OPDRA.

Date 9/25/2002
Initials RLW for

6. Gary Buehler
Director, OGD
Comments:

Date 9/25/02
Initials GB

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

7. Project Manager, Team Sarah Kim
Review Support Branch

Date 9/25/02
Initials SSK

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

Applicant notification:
10:10 AM Time notified of approval by phone 10:21 AM Time approval letter faxed

FDA Notification:
9/25/02 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
9/25/02 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

eports\approval\approvrou2.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-804

CORRESPONDENCE

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

February 16, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)
——————————— 28 day regimens.

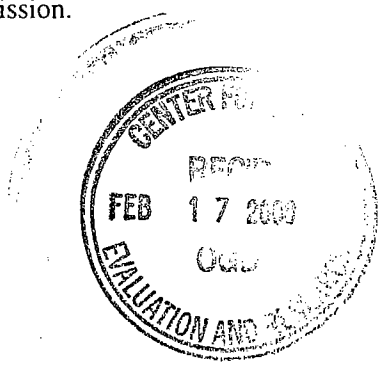
In accordance with the regulations under section 505(j) of the Federal Food and Cosmetic Act, Barr Laboratories, Inc. is submitting an Abbreviated New Drug Application for ——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) ——————————28 day regimens.

The application is provided in duplicate, as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of 15 volumes. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of 3 volumes. As stated in the February 1999 "Guidance for Industry; Organization of an ANDA", please note that two extra separately bound copies are being submitted since ——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) is not a USP product. The bioequivalence part of the review copy is contained in orange binders consisting of 13 volumes.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, are Debarment Certification Statements from Barr and its outside contractors. Field Copies of this application have been forwarded to the New York and Chicago District Offices.

Certifications of financial interests and arrangements of clinical investigators conducting the bioequivalence study are provided in Section VI.

The CMC section of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.



The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

NCE for filing
S. Middleton
505(j)(2)(A)
3/23/00

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

March 3, 2000

75-804

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW CORRESP
NC

CORRESPONDENCE TO PENDING APPLICATION

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)
——————— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) ———
——————— 28 day regimens.

Reference is also made to Barr's February 16, 2000 ANDA submission for the above referenced products.

Please be advised that at this time we are submitting additional information regarding DMF authorization for the ——————— In accordance with the April 8, 1994 Letter to Industry regarding the letter of authorization from the DMF holder, we are herewith submitting the following additional document:

- Copy of Page 5 of ——— DMF stating "we herewith authorize ——————— to represent ——————— in all matters pertaining to this file". In addition the page states DMF # —— name of ——————— and is signed and dated.

Please be advised that identical copies of this Correspondence have been provided to the New York and Chicago District Offices. Document certifications are attached.

In addition, we are also informing the Agency of Barr's intent to provide the Bioequivalence Report provided with the February 16, 2000 application in electronic format (BABE) within 30 days from that date of original filing. Barr Laboratories, Inc. will, at that time, provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 06 2000
OGD

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

NEW CORRESP
NC

March 16, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

75-804

REFERENCE: **AMENDMENT TO PENDING ANDA**
———— ,norgestimate and ethinyl estradiol tablets, 0.250 mg/ 0.035 mg)
———————— 28 day regimens.
Electronic Submission of CMC and BA/BE

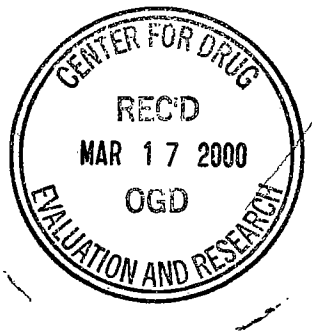
Reference is made to our Abbreviated New Drug Application submitted February 16, 2000 under 505(j) of the Food, Drug and Cosmetic Act for ———— (norgestimate and ethinyl estradiol tablets, USP 0.250 mg/ 0.035 mg).

As indicated in our original application, Barr Laboratories, Inc. is amending the above referenced application to provide the CMC and BA/BE electronic submission. The CMC and BA/BE electronic submissions are contained on separate diskettes labeled " CMC ESD & Companion Document" and BA/BE ESD" respectively. Backup diskettes containing identical information for both the CMC section and the BA/BE section are also provided.

The CMC ESD file is named "BRL0002.003" and the Microsoft Word Companion Document file is named "BRL0002.004". The BA/BE ESD is named "BRL0002.001" and the Microsoft Word Companion Document file is named "BRL0002.002".

Barr Laboratories, Inc. declares that the information provided in the electronic submission is the same as the information provided in the paper submission.

A copy of this letter has been forwarded to the New York and Chicago District Offices.



If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President of Quality and
Regulatory Counsel

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-804

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
P.O. BOX 2900
Pomona, NY 10970-0519

MAR 29

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 also made to your amendment dated March 3, 2000.

NAME OF DRUG: Ethinyl Estradiol; Norgestimate Tablets
0.035 mg; 0.25 mg

DATE OF APPLICATION: February 16, 2000

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 17, 2000

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:

Ruby Yu
Project Manager
(301) 827-5848

Sincerely yours,

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

ANDA 75-804
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/NMahmud, Chief, RSB _____ date 3/28/00
HFD-615/SMiddleton, CSO _____ date 3/27/00
Word File
V:\FIRMSAM\BARR\LTRS&REV\75804.ACK
F/T mjl/3/23/00
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

April 10, 2000

NDA ORIG AMENDMENT
N/AB

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

TELEPHONE BIOEQUIVALENCE AMENDMENT

REFERENCE: ABBREVIATED NEW DRUG APPLICATION 75-804
——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)
——————— 28 day regimens.

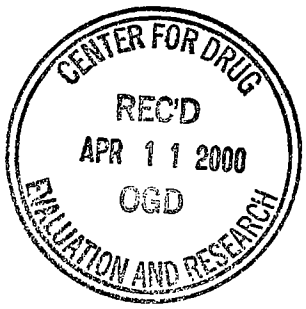
Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) · ——————— 28 day regimens.

Reference is also made to a telephone conversation on April 6, 2000 between Ms. Patricia Nguyen and Moheb Makary (FDA) and Christine Mundkur (Barr Laboratories) in which Ms. Nguyen and Mr. Makary requested that Barr provide the following:

1. Further explanation on a protocol deviation in clinical report 98-041. In particular, the last paragraph on page 06-00362 of the application stated that there was an excursion of 60.5°C in the storage of the test products.

2. Barr's submission batch size, and description (weight, thickness, hardness)

3. Reference product assay and content uniformity.



REFERENCE: ABBREVIATED NEW DRUG APPLICATION 75-804
——— (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)
————————28 day regimens.

RESPONSE 1:

The last paragraph on page 06-00362 of the application refers to a memo to file regarding drug room humidity and temperature. This memo to file was included as page 06-01555 and is being included again for ease of reference. This memo describes the events that transpired in greater detail. The 60.5 degree C temperature reading of March 26, 1999 cited was not an excursion of the actual temperature of the room, but rather was due to a malfunction of the temperature recording device, which produced erroneous readings as high as 60.5 degrees C. As stated in the memo, "Temperature levels in the medication room remained between 20 to 25 degrees C." Please also note that the date on which the 60.5 degree C reading was obtained was March 26, 1999. The faulty transformer responsible for the erroneous temperature readings was replaced on March 30, 1999. This event could not have had any impact on the test or US reference drugs used in the study, both of which were received by ———, nearly four months later, on July 15,1999 (see application pages 06-01592 and 06-01593).

RESPONSE 2:

Enclosed please find a copy of the following proposed master formula pages which specify the batch size and description of the active and placebo tablets:

- ——— (norgestimate and ethinyl estradiol tablets, USP 0.250 mg/0.035 mg) - ———28 day regimens
- ————————for Placebo Tablets for Oral Contraceptives used for ——— (norgestimate and ethinyl estradiol tablets, USP 0.250 mg/0.035 mg) - 28 day regimen
- White, Biconvex, Placebo Tablets for oral contraceptives for ——— (norgestimate and ethinyl estradiol tablets, USP 0.250 mg/0.035 mg) - 28 day regimen

REFERENCE: ABBREVIATED NEW DRUG APPLICATION 75-804
[redacted] (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)
[redacted] 28 day regimens.

RESPONSE 3:

Enclosed please find a copy of Barr's In-Vitro Comparative Analytical Study Report, RD99-168 comparing the dissolution profile, assay and content uniformity tests of Barr's test batch 109879R01 to those of Ortho Pharmaceutical Corporation's ORTHO-CYCLEN 28 Tablets USA batch 28G075. This report was inadvertently not submitted with the original application. The data obtained indicate that the assay and content uniformity of the Barr products are similar to the reference products and all products meet the required specifications. Please note that Barr's test batch 109879R01 was compared to both the USA Ortho-Cyclen and Canadian Cyclen products since Barr is interested in filing under separate cover for approval of this product in the Canadian marketplace. For the purposes of this submission, only the USA reference data is applicable.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

May 2, 2000

AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

TELEPHONE BIOEQUIVALENCE AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION 75-804**
[redacted] (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)
[redacted] 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for [redacted] (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) - [redacted] 28 day regimens.

Reference is also made to a telephone conversation on April 18, 2000 between Ms. Patricia Nguyen (FDA) and Christine Mundkur (Barr Laboratories) in which Ms. Nguyen requested Barr provide additional dissolution profiles for the submission and reference product batches using the following conditions:

Apparatus II:	Paddles
Speed:	75 rpm
Volume:	600 mL
Medium:	0.5% Tween 20

Accordingly, enclosed please find an In-Vitro Comparative Dissolution Study Report, RD00-130 comparing Barr's submission/bio batch 109879R01 to the reference product's (Ortho Pharmaceutical Corporation) batch 28G075 using the above specified conditions.

If you have any questions concerning this correspondence, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

MAJOR AMENDMENT

ANDA 75-804

AUG 22 2000

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)

TO: APPLICANT: Barr Laboratories, Inc. PHONE: 914-353-8432

ATTN: Christine Mundkur FAX: 914-353-3859

FROM: Ruby Yu PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg.

Reference is also made to your amendment(s) dated April 10 and May 2, 2000.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 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 MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR 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 this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

Chemistry and Bioequivalency comments are provided. Labeling comments will be provided when the review is completed.

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RYu
8/22/00

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confidential commercial

information from

8/22/2000 FDA FAX

3. Method validation will be requested from the District laboratory after the issues on impurities have been resolved.

4. Please provide all available room temperature stability data.

Sincerely yours,

Paul S. Howard for

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-804 APPLICANT: Barr laboratories, Inc.

DRUG PRODUCT: Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

> The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:
>
> > Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes
> > Not less than —% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 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,

Dale P. Conner

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

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 28, 2000

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NDA ORIG AMENDMENT
N/A c

MAJOR AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
[redacted] (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg)
[redacted] 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for [redacted] (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg) [redacted] 28 day regimens.

Reference is also made to the August 22, 2000 major deficiency letter. The deficiencies identified in the comment letter and Barr's responses are as follows:

COMMENT 1:

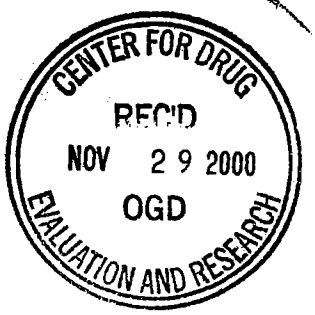
Please note that the DMF [redacted], is currently inadequate. The DMF holder, [redacted], has been notified.

Response 1:

[redacted] responded to the Agency's Deficiency Letter on October 23, 2000.

COMMENT 2:

Please add test and specification for [redacted] per supplier specifications and provide the revised specifications.



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11/28/2000 BARR LETTER

COMMENT 17:

Please modify your post approval stability protocol for both active and placebo tablets to specify the extension of expiration period requires full term room temperature stability data on at least 3 production batches.

Response 17:

As requested, Barr has updated their stability protocols for both active and placebo tablets to specify that the extension of expiration period requires full-term room temperature stability data on at least 3 production batches. **See Attachment 10.**

B.

COMMENT 1:

A satisfactory compliance evaluation of all of the facilities for drug product manufacturing and quality control in the application is necessary at the time of the approval of the application.

Response 1:

Acknowledged.

COMMENT 2:

Your labeling review is pending. Any comments found will be communicated in a separate letter.

Response 2:

Acknowledged.

COMMENT 3:

Method validation will be requested from the District laboratory after the issues on impurities have been resolved.

Response 3:

Acknowledged.

COMMENT 4:

Please provide all accumulated room temperature stability to date.

Response 4:

All of the room temperature stability data collected for Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg and placebo tablets is provided in **Attachment 10.**

Identical copies of this Amendment have been provided to the New York and Chicago District Offices. A Document certification is attached. Also enclosed is a copy of Barr's Bioequivalence Amendment.

This completes the present Amendment. If you have any questions please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Cc: New York District Field Office
Chicago District Field Office
Division of Bioequivalence

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

November 28, 2000

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/A B

BIOEQUIVALENCE AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg)
——————— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg) ——————— 28 day regimens.

Reference is also made to the August 22, 2000 bioequivalence letter that stated:

Bioequivalency Comments:

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

> The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37^{0}C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:
>
> > Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes.
> > Not less than —% (Q) of the labeled amount of Ethinyl Estradiol is dissolved in 30 minutes.

Response:

On May 2, 2000, Barr submitted additional in-vitro comparative dissolution reports using the dissolution testing described above [600 mL of water with 0.05% Tween 20 (w/v) at 37^{0}C using USP 24 apparatus II (paddle) at 75 rpm]. Barr followed Test Method, TM-461C that states the dissolution specifications as —% (Q) of the labeled amount of Norgestimate and Ethinyl Estradiol is dissolved in 60 minutes". This was done in response to an April 18, 2000 telephone call from Patty N[illegible] Div. of Bioequivalence. Barr did not and does not agree with adopting this testing nor the specifications as part of our stability and quality control programs for the following reasons:

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information from

11/28/2000 BARR LETTER
(RE: BIOEQUIVALENCE)

NS

Barr Laboratories, Inc.

2 Quaker Road P.O. Box 2900 Pomona, NY 10970-0519 • 914/362-1100

January 2, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AC

REFERENCE: **AMENDMENT TO PENDING ANDA**
ANDA 75-804
——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg)
——————— 28 day regimens.
Electronic Submission of CMC Amendment

Reference is made to our Abbreviated New Drug Application submitted November 28, 2000 under 505(j) of the Food, Drug and Cosmetic Act for ——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg).

Barr Laboratories, Inc. is amending the above referenced application to provide the CMC electronic version of our response to the Major Amendment dated November 28, 2000.

Enclosed please find the CMC ESD files "BRL0025.003" and the Microsoft Word Companion Document file "BRL0025.004". Backup diskettes containing identical information for the CMC section is also provided.

Barr Laboratories, Inc. declares that the information provided in the electronic submission is the same as the information provided in the paper submission.

A copy of this letter has been forwarded to the New York and Chicago District Offices.

If you have any questions concerning this application, please contact me by phone at (914) 353-8432 or by fax at (914) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President of Quality and
Regulatory Counsel

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 03 2001
OGD

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Generic Drugs

7500 STANDISH PLACE (HFD-600), ROCKVILLE, MD 20855

Phone: (301) 827-5763
Fax: (301) 594-0180

FAX TRANSMISSION COVER SHEET

Date:	January 4, 2001
To:	Christine Mundkur of Barr Laboratories Inc.
	(845) ~~914-~~353-8432
Fax:	(845) ~~914-~~353-3859
Re:	ANDA 75-804
Sender:	Ruby Yu, Project Manger

TOTAL NUMBER OF PAGES: ___3___

Comment(s):

Bioequivalency comments provided.

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-804 APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

Your proposed ——————————— dissolution method is not acceptable for the following:

1. Your argument that by using the 0.05% Tween-20 medium the dissolution rate *in vitro* does not reflect the actual dissolution rate *in vivo*, therefore, the method is not suitable. In the absence of a suitable verified *in vivo/in vitro* correlation this argument is not relevant. Furthermore, the *in vitro* dissolution testing for Norgestimate/Ethinyl Estradiol drug products serve mainly as a quality control specification for the manufacturing process.

2. The ——————————— dissolution method you proposed provided — % release of norgestimate in 15 minutes from Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg. Therefore, this method is not suitable as a discriminatory tool for routine dissolution testing.

3. The 0.05% Tween-20 dissolution method recommended by the Agency and proposed by Pharmacopeial Forum (Vol. 26(5) [Sept.-Oct. 2000] provided — % and — % release of norgestimate in 15 and 90 minutes, respectively, from Norgestimate/Ethinyl Estradiol Tablet, 0.25 mg/0.035 mg. Therefore, the method appears to be discriminatory for routine dissolution testing.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes. Not less than —% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 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,

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

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 1, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AC

AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg)
——————— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg) ——————— 28 day regimens.

Reference is also made to a February 1, 2001 phone conversation between Ruby Yu, CSO, OGD, FDA and Elisabeth Noble Gray, Barr Laboratories, Inc. regarding the filing of a change in the manufacturing site of the ——————— (supplied by ——————. In accordance with Ms. Yu's instructions, we are filing this change in an Amendment to the pending application.

The manufacturing site change is as follows:

Old Site:

New Site:

——————— site was inspected and approved by FDA in 1998. In July 1999, FDA set forth requirements for both ——— and their customers for the transfer of products to the new facility. ——— fulfilled all requirements and submitted an amendment to the relevant DMF's (see updated authorization letter to reference ——— DMF No. —— which includes the ——— facility).

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg)
——————— 28 day regimens.

In accordance with FDA's ——————communication to ——— (see attached), Barr hereby commits to place the first commercial batch of norgestimate and ethinyl estradiol tablets, USP using the new source of drug (new site) on stability under Barr's proposed stability protocol to support Barr's approved packaging configurations.

Please note that the processes at the ——————site do not differ materially from those of the ——————— site. Also, a GMP inspection covering the processes that are representative of process used for the four new ——————— was performed in ——————. A 483 was issued and contained minor comments. ——— believes they provided more than adequate responses in their ——————— correspondence that satisfied FDA's concerns. There have been no further communications regarding this 483 issued to ——— by FDA. Please note that FDA does not issue an acknowledgment or "approval" letter upon receipt of a satisfactory manufacturer response. It is normal practice for FDA to only respond to the manufacturer if the response is inadequate.

Enclosed please find the following documentation:

- Copy of ——— authorization letter (dated 8/21/00) to reference their DMF No. — for ——————— as last updated on 1/3/00. Please note that ——————— is owned by the parent company, ——————— Therefore, the enclosed DMF letter is on ——————— letterhead.

- Copy of the July 20, 1999 From FDA to ——— . regarding the filing requirements.

An identical copy of this Amendment has been provided to the New York and Chicago District Offices. A document certification is attached.

If you have any questions concerning this Amendment, please contact Christine Mundkur by phone at 845-353-8432 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President,
Quality and Regulatory Counsel

Cc: ———
New York and Chicago District Office

Barr Laboratories, Inc.

February 1, 2001

Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AB

BIOEQUIVALENCE AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg)
——————— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg) ——————— 28 day regimens.

Reference is also made to the January 4, 2001 bioequivalence letter that states:

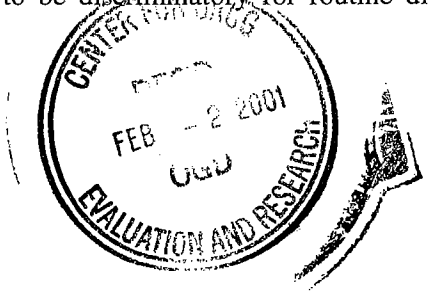
Bioequivalency Comments:

Your proposed ——————— dissolution method is not acceptable for the following:

1. Your argument that by using the 0.05% Tween-20 medium the dissolution rate *in vitro* does not reflect the actual dissolution rate *in vivo*, therefore, the method is not suitable. In the absence of a suitable verified *in vivo/in vitro* correlation this argument is not relevant. Furthermore, the *in vitro* dissolution testing for Norgestimate/Ethinyl Estradiol drug products serve mainly as a quality control specification for the manufacturing process.

2. The ——————— dissolution method you proposed provided —% release of norgestimate in 15 minutes from Norgestimate/Ethinyl Estradiol Tablet 0.25 mg/0.035 mg. Therefore, this method is not suitable as a discriminatory tool for routine dissolution testing.

3. The 0.05% Tween-20 dissolution method recommended by the Agency and proposed by Pharmacopeial Forum (Vol. 26 (5) [Sept.-Oct. 2000] provided —% and —% release of norgestimate in 15 and 90 minutes, respectively, from Norgestimate/Ethinyl Estradiol Tablet, 0.25mg/0.035mg. Therefore, the method appears to be discriminatory for routine dissolution testing.



Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37^0C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:

Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes.
Not less than —% (Q) of the labeled amount of Ethinyl Estradiol is dissolved in 30 minutes.

Response:

Barr has adopted the Agency's above recommended dissolution testing procedure and specifications into their stability and quality control programs. Enclosed please find updated method validation report RD00-124B (**Attachment I**). System Suitability, Specificity (Sample Matrix Interference), Linearity, Precision, Ruggedness, Filtration Study and Sample and Standard Solution Stability studies were performed in order to provide assurance that the dissolution test procedure for Norgestimate and Ethinyl Estradiol is appropriate for testing the Barr product. Also enclosed please find Barr's updated In-Process and Finished Product Test Method, TM-461D and corresponding Analytical Specifications and Test Record and Marketed Product Stability Specifications and Test Record (**Attachment II**) which incorporate the Agency's recommended dissolution testing procedure and specifications.

This completes the bioequivalence amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

February 9, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/A C

AMENDMENT TO 2/1/01 AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg)
——————— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for ——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg) ——————— 28 day regimens.

Reference is also made to Barr's February 1, 2001 Amendment for a change in the manufacturing site of the ——————— (supplied by ——————— from ——————— to ———————

This Amendment is to correct the February 1, 2001 Amendment that incorrectly stated ——— new manufacturing site located in ——— as a site change. The new ——— site is an ALTERNATE site to ——— existing ——— site. Therefore, the manufacturing sites for ——————— ingredient are as follows:

Site 1:

Site 2:

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 12 2001
OGD

In addition, the establishment attachment to the 356h form submitted with the February 1, 2001 Amendment has been corrected to include both manufacturing sites for ——— All documentation to support ——— new, additional ——— site was submitted with the February 1, 2001 Amendment.

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
——— (norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg)
——————— 28 day regimens.

An identical copy of this Amendment has been provided to the New York and Chicago District Offices. A document certification is attached.

If you have any questions concerning this Amendment, please contact Christine Mundkur by phone at 845-353-8432 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President,
Quality and Regulatory Counsel

Cc: ———
New York and Chicago District Office

APPEARS THIS WAY
ON ORIGINAL

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information from

3/9/2001 BARR LETTER

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

April 20, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

N/AF

ORIG AMENDMENT

Labeling Amendment

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg
—— 28 day regimens

Reference is made to submission for the pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg) —— 28 day regimens.

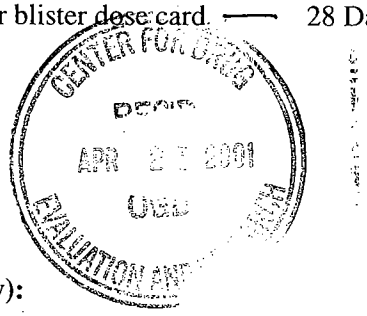
Reference is also made to your letter dated April 6, 2001 regarding Barr's February 16, 2000 submission in which the following comments were made:

1. GENERAL COMMENTS:

We note that the draft labels and labeling you have submitted include your proposed propriety name "————" for this drug product. Please refer to our fax dated March 22, 2001, in which we informed you that the Office of Post-marketing Drug Risk Assessment (OPDRA) did not recommend the use of the name ———— and ———— Therefore, please revise your labels and labeling to remove ———— as the proprietary name.

2. CONTAINER (Fold-over blister dose card —— 28 Day):

Satisfactory in draft.



3. AUXILIARY LABEL:

Satisfactory in draft.

4. ———— 28 Day):

Satisfactory in draft testing.

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg
____ 28 day regimens

5 **CARTON** (____ 6 x 28)

Revise the "21 blue tablets, contain...." Statement to read: "21 blue tablets each contain 0.250 mg norgestimate and 0.035 mg ethinyl estradiol; and 7 white tablets, each contain inert ingredients

6. **INSERT** (Physician Labeling, Detailed Patient Lableing, and Brief Summary Patient Lableing):

We note that you have modeled your labeling after the reference listed drug's labeling, Ortho-Cyclen® by RW Johnson, revised May 1998. However, this labeling is not the most recently approved. 21 CFR 314.94 (a)(8)(iv) requires that your labeling be the same as that approved for the reference listed drug. Please revise the Physician insert labeling to be in accordance with the enclosed labeling for the reference listed drug, revised January 2000 and approved June 5, 2000. Please also revise your Detailed Patient Labeling and Brief Summary Patient Labeling to be in accordance with the enclosed Patient labeling for the reference listed drug, revised April 2000 and approved January 16, 2001.

Please revise your labels and labeling, as instructed above and submit in final print.

RESPONSE:

Please note that Barr has updated it's labeling in accordance with the most recently approved labeling of RW Johnson for their Ortho Cyclen product as provided by FDA in their April 6, 20001 comment letter.

Barr acknowledges the March 22, 2001 fax amendment by the Office of Post-marketing Drug Risk Assessment ("OPDRA") in which they did not recommend the use of our proposed trade name, ____ At this time we are submitting the following newly proposed trade names for submission to OPDRA:

1 _____
2 _____
3 _____
4 SPRINTEC™
5 _____

In addition, we are changing the packaging configuration to include a foil pouch and wallet instead of _____ The foil pouch will contain the same wording as the _____ except for the Barr logo (there is no logo on the pouch). Within the foil pouch will be the following components: blister card, fold-over dose card, unprinted wallet, PPI/Brief summary combination, and days of the week sticker. This change is being done for esthetic purposes and is Annual Reportable in accordance to the Changes to an Approved NDA or ANDA Guidance, November 1999, Section IX.D.5. The new proposed package configuration (foil pouch/wallet)

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg
——— 28 day regimens

does not affect the primary packaging materials and provides the same or better protective properties as the old proposed package configuration ———.

Attached please find the following documentation in support of this Labeling Amendment:

1. Side by side comparisons
   a. New versus previous fold-over dose cards
   b. New foil pouch versus previous ———
   c. New versus previous folding carton
   d. New versus previous PPI/brief summary combination
   e. New versus previous package brochure

2. Proposed labeling (4 archival and review copies)
   a. Fold-over dose cards
   b. Folding carton
   c. PPI/brief summary combination
   d. Package brochure

   Note that the days of the week sticker is not being included since it was approved in final print. Also, Barr has further differentiated the day regimens ——— 28) by changing the percentage of PMS color used in the highlighting. This was done in response to a comment by OPDRA

3. Documentation for the foil pouch
   a. Material Specification Sheet
   b. Engineering Diagram

Upon approval of one or more of these proposed trade names, Barr will submit final printed labeling to the Agency.

This completes the Labeling Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

MINOR AMENDMENT

ANDA 75-804

MAY 1 4 2001

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)

TO: APPLICANT: Barr Laboratories, Inc.

TEL: 845-353-8432

ATTN: Christine Mundkur

FAX: 845-353-3859

FROM: Ruby Yu
for: Paras Patel

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 17, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg ——— 28 day regimens)..

Reference is also made to your amendment(s) dated: November 28, 2000, January 2, 2001, February 1, 2001, February 9, 2001 and March 9, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 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:

Your labeling review is pending. Any comments found will be communicated in a separate letter.

Cmc and Bioequivalence comments are attached.

P.M.P
5/14/01

MAY 1 4 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-804

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg (——— 28 day regimens)

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. [redacted]

2.

3.

4.

5.

Sincerely yours,

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

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-804 APPLICANT: Barr laboratories, Inc.

DRUG PRODUCT: Norgestimate, 0.25mg/Ethinyl Estradiol, 0.035 mg Tablet

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 600 mL of water with 0.05% Tween 20 (w/v) at 37°C using USP 24 apparatus II (paddle) at 75 rpm. The test product should meet the following specifications:
>
> > Not less than —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes
> > Not less than —% (Q) of the labeled amount of ethinyl estradiol is dissolved in 30 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

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

June 11, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg
—— 28 day regimens

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg —— 28 day regimens.

Reference is also made to the Agencies' letter dated May 14, 2001 regarding Barr's November 28, 2000, January 2, 2001, February 1, 2001, February 9, 2001 and March 9, 2001 amendments in which the following deficiencies are stated:

COMMENT 1:

Please note that the DMF —— remains inadequate. The DMF holder, —— has been notified of the deficiencies. Please do not respond to this MINOR amendment until you have been informed by the DMF holder stating that a satisfactory response has been submitted to Agency's DMF deficiency letter.

Response 1:

—— responded to the Agency's Deficiency Letter on June 8, 2001.

COMMENT 2:

Proposed specification for the ——
Please ——

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 12 2001
OGD

5-14-01

Redacted 1 page(s)

of trade secret and/or

confidential commercial

information from

6/11/2001 BARR LETTER

Enclosed as **Attachment III** please find the updated documentation: In-Process and Finished Product Test Method, TM-469D, corresponding Quality Control and Marketed Product Specifications and Test Records, and Marketed Product Stability Protocol.

An identical copy of this Amendment has been provided to the New York and Chicago District Field Offices. A document certification is attached.

If you have any questions concerning this Amendment, please contact Christine Mundkur by phone at 845-353-8432 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President,
Quality and Regulatory Counsel

Cc: New York and Chicago District Office

MINOR AMENDMENT

ANDA 75-804

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)

JUL - 5 2001

TO: APPLICANT: Barr Laboratories

ATTN: Christine Mundkur

TEL: 845-353-8432

FAX: 845-353-3859

FROM: Ruby Yu

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg.

Reference is also made to your amendment(s) dated: June 11, 2001.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 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, if any, will be provided when the review is completed.

RY 7/5/01

JUL - 5 2001

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-804

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg (——— 28 day regimens)

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1. Please note that the DMF ——————————— remains deficient. The DMF holder, ———————, has been notified of the deficiencies. Please do not respond to this MINOR amendment until you have been informed by the DMF holder stating that a satisfactorily response has been submitted to Agency's DMF deficiency letter.

2. Please revise the specifications for ——————————— ——————— according to manufacturer's current specifications, where applicable, and please provide a copy of your and manufacturer's updated specifications.

3. [redacted]

Sincerely yours,

Paul Schwartz for

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

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 26, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg - ——— 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg - ——— 28 day regimens.**

Reference is also made to FDA's July 5, 2001 deficiency letter in which the following is stated:

COMMENT A.1.

Please note that the DMF ——————— remains deficient. The DMF holder, ——— has been notified of the deficiencies. Please do not respond to this MINOR amendment until you have been informed by the DMF holder stating that a satisfactory response has been submitted to Agency's DMF deficiency letter.

Response A.1.

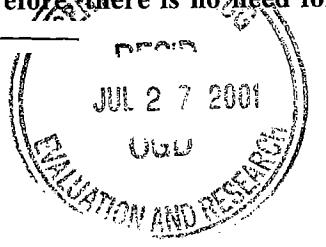
——— has informed Barr that on July 24, 2001 they submitted their response to the Agency's DMF deficiency letter.

COMMENT A.2.

Please revise the specifications for ———————, according to manufacturer's current specifications, where applicable, and please provide a copy of your and manufacturer's updated specifications.

Response A.2.

——— has not changed their specifications for the ——————— (as stated in their July 24, 2001 DMF deficiency response letter). Therefore, there is no need for Barr to revise their specifications for the———————



REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
(norgestimate and ethinyl estradiol tablets, 0.250mg/0.035 mg)
28 day regimens.

COMMENT A.3.

Response A.3.

An identical copy of this Minor Amendment has been provided to the New York and Chicago District Offices. A document certification is attached.

If you have any questions concerning this Minor Amendment, please contact Christine Mundkur by phone at 845-353-8432 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President,
Quality and Regulatory Counsel

Cc:
New York and Chicago District Offices

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

October 12, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

AT
ORIG AMENDMENT

Labeling Amendment

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg
—— 28 day regimens

Reference is made to submission for the pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg - —— 28 day regimens.

Reference is also made to Barr's Labeling Amendment dated April 20, 2001 in which five proposed trade names were submitted.

On August 17, 2001, OPDRA approved the proposed trade name, Sprintec™. In accordance with our commitment to submit final printed labeling upon approval of one or more of our proposed trade names, enclosed please find the following:

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG
OCT 15 2001
EVALUATION AND

Barr Laboratories, Inc.

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg
—— 28 day regimens

1. Side by side labeling comparisons:
   1.1 Labeling Scheme
   1.2 New versus last submitted fold-over dose cards
   1.3 New foil pouch versus last submitted foil pouch
   1.4 New versus last submitted folding carton
   1.5 New versus last submitted combination PPI/brief summary
   1.6 New versus last submitted package brochure
   1.7 New versus last submitted days of the week sticker

2. Proposed labeling (12 archival and 4 review copies)
   2.1 Fold-over dose cards
   2.2 Foil pouch
   2.3 Folding carton
   2.4 Combination PPI/brief summary
   2.5 Package brochure
   2.6 Days of the week sticker

   Note that since there is no printing on the wallet, samples are not being submitted.

This completes the Labeling Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 29, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 75-804
Sprintec™ (norgestimate and ethinyl estradiol tablets, USP 0.25/0.035 mg)
——————— **Sprintec™** 28 day regimens.
TELEPHONE AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Sprintec™** (norgestimate and ethinyl estradiol tablets, USP 0.25/0.035 mg) ———— ←— **Sprintec™** 28 day regimens.

Reference is also made to a March 27, 2002 phone conversation among Ruby Wu, Dr. David Grill, and Neeru Takiar, OGD, FDA and Christine Mundkur, ———————— ————————and Elisabeth Noble Gray, Barr Laboratories, Inc. regarding the following changes/clarifications.

———————————

Barr Laboratories, Inc. has updated the Raw Material Test Method along with the corresponding Raw Material Specification and Test Record for the ———————— ———— to incorporate the manufacturer's specifications for ———————— and Melting Point. The updated Raw Material Specification and Test Record can be found in Attachment I.

RECEIVED
APR 0 1 2002
OGD / CDER

Packaging - Secondary Pouch Material

As stated in Barr's April 20, 2001 Labeling Amendment, we are changing our packaging configuration to include an aluminum foil pouch and wallet instead of a ——— Sprintec™ will be packaged in blisters of ——— 28 tablets as follows: the blisters will be placed within a fold over card, the dose cards will be packaged in aluminum foil pouches along with a days of the week sticker, combination detailed patient labeling, brief summary, and non-printed vinyl wallet. This change is being done for esthetic reasons only.

The new proposed package configuration (foil pouch/wallet) does not affect the primary packaging materials and provides the same or better protective properties as the old proposed package configuration ———.

The following information concerning the aluminum foil pouch can be found in Attachment II.

- DMF Authorization Letter (DMF ———from ———
- ——— Material Specification
- Pouch Diagram
- ——— Material Specification
- ——— Certification of Compliance (representative Lot # 7-43614)

Finished Product Analytical Specification and Test Record and Test Method

FDA requested that Barr Laboratories, Inc. update their current In-Process and Finished Product Test Method and Analytical Specifications and Test Record to incorporate the ——— assay specification of ———% for ——— testing and to tighten the impurity specification for ——— for release purposes.

See Attachment III for our "Justification for the proposed impurities testing requirements for the Norgestimate and Ethinyl Estradiol Tablets.

A copy of the updated In-Process and Finished Product Test Method and Analytical Specifications and Test Record are provided in Attachment IV.

Stability Report/Dissolution Testing

Please find as Attachment V a copy of the updated stability report. Note that the last two time points (18 months and 25 months) were tested under the new dissolution method and specifications (NLT —% (Q) of the labeled amount of Norgestimate is dissolved in 90 minutes. NLT —% (Q) of the labeled amount of Ethinyl Estradiol is dissolved in 30 minutes). Also note that the submission batches were re-accelerated and tested with the updated dissolution method. Results of this "experimental study" are also provided in Attachment V.

A similar Telephone Amendment is being submitted under separate cover to Barr's Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035mg application, ANDA 75-808.

An identical copy of this Telephone Amendment has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this correspondence, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

May 15, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 75-804
Sprintec™ (norgestimate and ethinyl estradiol tablets, USP 0.25/0.035 mg)
———— **Sprintec™** 28 day regimens.
TELEPHONE AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Sprintec™** (norgestimate and ethinyl estradiol tablets, USP 0.25/0.035 mg) ———— ——— **Sprintec™** 28 day regimens.

Reference is also made to our March 29, 2002 Telephone Amendment and a May 5, 2002 phone conversation between Ruby Wu and Neeru Takiar, Ph.D., FDA and Christine Mundkur, Barr Laboratories, Inc. In the phone conversation Dr. Takiar requested that the following additional information be submitted in a Telephone Amendment.

Explanation on why leeching studies were not conducted

Barr Laboratories, Inc. has looked into the possibility of printing ink leeching and permeating through the pouch and dose card into the blisters. All printed materials are imprinted on the outer side of the secondary packaging component. Any leeching of ink is therefore not feasible; thus no further leeching studies will be necessary.

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

5/15/2002 BARR LETTER

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

5.1

June 10, 2002

ONG AMENDMENT
N/Am

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Via facsimile 301-594-0181

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 75-804
Sprintec™ (norgestimate and ethinyl estradiol tablets, USP 0.25/0.035 mg)
——— **Sprintec™** 28 day regimens

TELEPHONE AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Sprintec™** (norgestimate and ethinyl estradiol tablets, USP 0.25/0.035 mg) ——— **Sprintec™** 28 day regimens.

Reference is also made to a June 10, 2002 phone conversation between Neeru Takiar, Ph.D., FDA and Christine Mundkur, Barr Laboratories, Inc., in which Dr. Takiar requested we submit an updated raw material specifications & test record and test method for ——— Dr. Takiar requested that the information be submitted in a Telephone Amendment.

Accordingly, attached please find the following documents:

- Quality Control Raw Material Specifications & Test Record for ———, Revision 13
- Raw Material Test Method for ———, Version 2.0

RECEIVED
JUN 11 2002
OGD / CDER

N/A 6/18/02

A similar Telephone Amendment is being submitted under separate cover to Barr's Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035mg application, ANDA 75-808.

An identical copy of this Telephone Amendment has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this Telephone Amendment, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

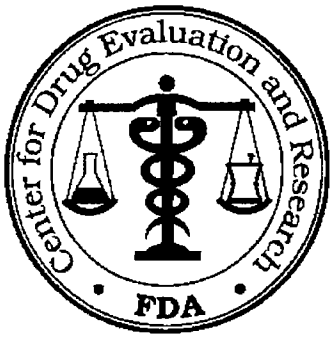
APPEARS THIS WAY
ON ORIGINAL

MINOR AMENDMENT

ANDA 75-804

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)

JUL -3 2002



TO: APPLICANT: Barr Laboratories, Inc. TEL: 845-353-8432

ATTN: Christine Mundkur FAX: 845-353-3859

FROM: Ruby Wu PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated February 16, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.25 mg/0.035 mg.

Reference is also made to your amendment(s) dated: July 26, 2001; March 29, May 15, and June 10, 2002.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (1 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, if any, will be provided under separate cover.

SN
7/03/02

JUL 3 2002

38. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-804

APPLICANT: Barr Laboratories, Inc.

DRUG PRODUCT: Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg ——— 28 day regimens)

The deficiencies presented below represent **MINOR** deficiencies.

A. Deficiencies:

1.

2.

3.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

A review of the labels and labeling 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

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

July 9, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

REFERENCE: **ABBREVIATED NEW DRUG APPLICATION**
ANDA # 75-804
Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg
—— 28 day regimens

Reference is made to our pending Abbreviated New Drug Application submitted on February 16, 2000, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Norgestimate and Ethinyl Estradiol Tablets, 0.250mg/0.035 mg - —— 28 day regimens.

Reference is also made to the Agency's letter dated July 3, 2002 and a conference call on July 8, 2002, between Linda O'Dea, Nicholas Tantillo, and Christine Mundkur from Barr Laboratories, Inc. and Ruby Wu, Paul Schwartz, Dave Gill, Neeru Takiar, and Sarah Kim from OGD in which the following deficiencies were discussed:

COMMENT 1:

[redacted]

Response 1:

As discussed in the conference call on July 8, 2002, Barr Laboratories, Inc. commits to working with the manufacturers of the [redacted] specifications based on the data that is available and submit these revised specifications post-approval in a Changes Being Effected Supplement.

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COMMENT 2:

[redacted]

Redacted 1 page(s)

of trade secret and/or

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information from

7/9/2002 BARR LETTER

A similar Minor Amendment is being submitted under separate cover to Barr's Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035mg application, ANDA 75-808.

An identical copy of this Amendment has been provided to the New York and Chicago District Field Offices. A document certification is attached.

If you have any questions concerning this Amendment, please contact Nicholas Tantillo by phone at 845-348-8051 or by fax at 845-353-3859.

Sincerely,

BARR LABORATORIES, INC.

Nicholas C. Tantillo
Sr. Director Regulatory Affairs

Cc: New York and Chicago District Office

APPEARS THIS WAY
ON ORIGINAL

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

5.1

July 17, 2002

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773

NEW IMFORMATION CORRESPONDENCE

REFERENCE: ANDA 75-804
Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)
——————— **Sprintec ™** 28 day regimens.

Reference is made to our pending Abbreviated New Drug Application under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Sprintec ™** (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) - ——————— **Sprintec™** 28 day regimens.

Reference is also made to a telephone conversation between Nicholas Tantillo, of Barr Laboratories, Inc. and Sara Kim, of FDA in which Ms. Kim requested that Barr restate our commitment to method validation post-approval. Ms. Kim requested that this information be submitted in a New Information Correspondence.

Accordingly please see method validation commitment below:

Barr commits to resolve any issues identified in the methods validation process after approval.

Please be advised that identical copies of this Correspondence have been provided to the New York and Chicago District Offices. Document certifications are attached.

A similar New Information Correspondence is being submitted under separate cover to Barr's Norgestimate and Ethinyl Estradiol Tablets, 0.180/0.035mg, 0.215mg/0.035mg, and 0.250mg/0.035mg application, ANDA 75-808.

An identical copy of this New Information Correspondence has been provided to the New York and Chicago District Offices. A document certification is attached. If you have any questions concerning this New Information Correspondence, please contact me by phone at (845) 348-8051 or by fax at (845) 353-3859.

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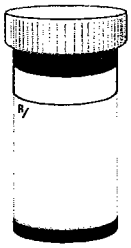
Sincerely,
BARR LABORATORIES, INC.

Nicholas C. Tantillo
Senior Director, Regulatory Affairs

Fax Cover Sheet



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Rockville, Maryland

To: Christine Mundkur
Barr Laboratories, Inc.
Fax: 845-353-3859 **Phone:** 845-353-8432

From: Debra M. Catterson
Fax: 301-443-3847 **Phone:** 301-827-5846

Number of Pages (including cover sheet): 12 **Date:** July 24, 2002
Comments:

Dear Ms. Mundkur,

Please refer to the attached mocked-up copy of your insert labeling for all of the requested labeling revisions from my review of your submission dated October 12, 2001 for ANDA 75-804 for Norgestimate and Ethinyl Estradiol Tablets, 0.250 mg/0.035 mg.

These revisions are "post-approval" revisions, which can be made at the time of next printing and submitted in an annual report provided the changes are described in full. We refer you to 21 CFR 314.81(b)(2)(iii) for guidance.

Please feel free to call me if you have any questions.

Sincerely,

Debra M. Catterson

_11_ pages of draft labeling have been removed from this portion of the document.

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 4, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

NEW CORRESP
NC

General Correspondence

REFERENCE: **ANDA 75-804**
Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)
[redacted] and **Sprintec ™** 28 day regimens.

Reference is made to Barr Laboratories, Inc.'s ("Barr") pending Abbreviated New Drug Application ("ANDA"), dated February 16, 2000 submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for **Sprintec ™** (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) - [redacted] **Sprintec™** 28 day regimens.

Reference also is made to the telephone conversation between Christine Mundkur of Barr and Peter Rickman of OGD on September 4, 2002.

As discussed with the Agency, Barr Laboratories, Inc. is hereby withdrawing information that pertains to [redacted] from this application without prejudice to future filing. As agreed upon by the Agency, Barr expects to submit [redacted] that are necessary to remove reference to [redacted] on or before September 9, 2002.

Barr has submitted an identical copy of this General Correspondence to the Chicago and New York District Office. A document certification is attached.

If you have any questions concerning this application, please contact me by telephone at (845) 348-8051 or by fax at (845) 353-3859.

Sincerely,
BARR LABORATORIES, INC.

Nicholas Tantillo
Sr. Director Regulatory Affairs

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9/5/2002 BARR LETTER

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

September 10, 2002

Labeling Amendment – Final Printed Labeling

Office of Generic Drugs
CDER/FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIG AMENDMENT
N/AF
FPL

REFERENCE: **ANDA 75-804**
Sprintec™ (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg)

Dear Sir or Madam:

Reference is made to Barr Laboratories' pending Abbreviated New Drug Application, dated February 16, 2000, submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for **Sprintec ™** (norgestimate and ethinyl estradiol tablets, 0.250 mg/0.035 mg) 28 day regimen.

Enclosed are 12 copies each of the final printed Package Brochure dated September 2002, and the Combination Detailed Patient Labeling/Brief Summary with the Days of the Week Sticker dated September 2002.

As per a conversation with Debbie Catterson at the Labeling Review Branch we are submitting this final printed labeling. The side-by-side comparisons were submitted in the September 4, 2002 correspondence along with "printer's proofs."

If you have any questions, please contact me by telephone at (845) 348-6894 or by fax at (845) 353-3859.

Sincerely,

Salvatore P. Peritore, M.S., R.Ph.
Associate Director, Regulatory Affairs

Encl.

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