

CENTER FOR DRUG
EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

74-538

Trade Name: Trivora-21 and Trivora-28

Generic Name: Levonorgestrel and Ethinyl Estradiol
Tablets, USP

Sponsor: G.D. Searle & Co.

Approval Date: December 18, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
74-538

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**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

74-538

APPROVAL LETTER

ANDA 74-538

DEC 18 1997

G. D. Searle & Co.
Attention: Doranne Frano
4901 Searle Parkway
Skokie, IL 60077

Dear Madam:

This is in reference to your abbreviated new drug application dated August 19, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Trivora-21 and Trivora-28 (Levonorgestrel and Ethinyl Estradiol Tablets, USP), Triphasic Regimen.

Reference is also made to your amendments dated November 30, 1995; July 19, 1996; and January 27, February 20, February 25, and October 24, 1997.

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 that your Trivora[®]-21 and Trivora[®]-28 (Levonorgestrel and Ethinyl Estradiol Tablets, USP) Tablets are bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Triphasil[®]-21 and Triphasil[®]-28 of Wyeth Ayerst Laboratories, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, 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. 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 which 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-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CAR 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-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

ISI
Douglas E. Sporn
Director

Office of Generic Drugs
Center for Drug Evaluation and Research

12/18/97

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-538

Final Printed Labeling

SCS Pharmaceuticals

Trivora[®]-21 Tablets**Trivora[®]-28 Tablets**(levonorgestrel and ethinyl estradiol tablets, USP) —
triphasic regimen**Patients should be counseled that this product does not protect
against HIV infection (AIDS) and other sexually transmitted diseases.**

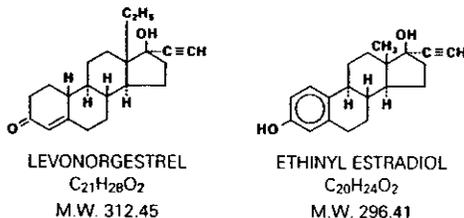
APPROVED

ORAL CONTRACEPTIVE AGENTS**DESCRIPTION**

Trivora-21 Tablets provide an oral contraceptive regimen of 6 blue tablets followed by 5 white tablets and 10 pink tablets. Each blue tablet contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg and each pink tablet contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg.

Trivora-28 Tablets provide a continuous oral contraceptive regimen of 6 blue tablets, 5 white tablets, 10 pink tablets and then 7 peach tablets. Each blue tablet contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg, each pink tablet contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg and each peach tablet contains inert ingredients.

Levonorgestrel is a totally synthetic progestogen with the chemical name (-)-13-Ethyl-17-hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one. Ethinyl estradiol is an estrogen with the chemical name 19-Nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol. Their structural formulae follow:



The inactive ingredients present in all the tablets are lactose monohydrate, magnesium stearate, povidone, starch (corn) plus the following dyes:

Blue tablet: FD&C Blue #1

Pink tablet: FD&C Red #40

Peach tablet: FD&C Yellow #6

CLINICAL PHARMACOLOGY

Combination oral contraceptives act by suppression of gonadotrophins. 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 may reduce the likelihood of implantation).

INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product 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.¹ 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 A CONTRACEPTIVE FAILURE DURING THE FIRST YEAR OF PERFECT USE AND FIRST YEAR OF TYPICAL USE

| Method | % of Women Experiencing an Accidental Pregnancy within the First Year of Use | |
|------------|--|--------------------------|
| | Typical Use ^a | Perfect Use ^b |
| Chance | 85 | 85 |
| Spermicide | 21 | 0 |

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, hypercholesterolemia, obesity and diabetes.²⁻⁵

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 both estrogen 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. Relative risk, the ratio of the incidence of a disease among oral contraceptive users to that among non-users, cannot be assessed directly from case control studies,⁶ but the odds ratio obtained is a measure of relative risk. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide not only a measure of the relative risk but a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population. (Adapted from ref. 12 and 13 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.^{2-5,13} The relative risk of heart attack for current oral contraceptive users has been estimated to be 2 to 6.^{2,14-19} The risk is very low under the age of 30. However, there is the possibility of a risk of cardiovascular disease even in very young women who take oral contraceptives.

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.²⁰

Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives (see Table II).¹⁶

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

c. Cerebrovascular diseases

An increase in both the relative and attributable risk cerebrovascular events (thrombotic and hemorrhagic strokes) has been shown in users of oral contraceptives. In general, the risk is greatest among older (>35 years) hypertensive women who also smoke. Hypertension found to be a risk factor for both users and non-users both types of strokes while smoking interacted to increase the risk for hemorrhagic strokes.³⁴

In a large study, the relative risk of thrombotic stroke has been shown to range from 3 for normotensive users to 14 for users with severe hypertension.³⁵ The relative of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who not use oral contraceptives, 7.6 for smokers who used contraceptives, 1.8 for normotensive users and 25.7 for users with severe hypertension.³⁵ The attributable risk is greater in women in their mid-thirties or older and among smokers.¹³

d. Dose-related risk of vascular disease from oral contraceptives

A positive association has been observed between amount of estrogen and progestogen in oral contraceptive and the risk of vascular disease.³⁶⁻³⁸ A decline in serum high-density lipoproteins (HDL) has been reported in many progestational agents.²²⁻²⁴ A decline in serum HDL density lipoproteins has been associated with an increased incidence of ischemic heart disease.³⁹ Because estrogen increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between dose of estrogen and progestogen and the nature and also amount of progestogens used in the contraceptives. Amount of both hormones should be considered in choice of an oral contraceptive.³⁷

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

e. Persistence of risk of vascular disease

There are three studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives.^{17,34,40} 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 5 or more years, but this increased risk was not demonstrated in other age groups.¹⁷ In another study in Great Britain, the risk of developing cerebrovascular disease persisted for at least 15 years after discontinuation of oral contraceptives, although excess risk was very small.⁴⁰ There is a significant increased relative risk of subarachnoid hemorrhage after discontinuation of use of oral contraceptives.³⁴ However, these studies were performed with oral contraceptive formulations containing 50 μ g or higher of estrogen.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages (see Table III).⁴¹ 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 methods of birth control is low and below that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users based on data gathered in the 1970s—but not reported in the U.S. until 1983.^{16,41} However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed,^{78,79} the Federal and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may increase with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are greater potential health risks associated with

The inactive ingredients present in all the tablets are lactose monohydrate, magnesium stearate, povidone, starch (corn) plus the following dyes:

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INDICATIONS AND USAGE

Oral contraceptives are indicated for the prevention of pregnancy in women who elect to use this product 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.¹ 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 A CONTRACEPTIVE FAILURE DURING THE FIRST YEAR OF PERFECT USE AND FIRST YEAR OF TYPICAL USE

| Method | % of Women Experiencing an Accidental Pregnancy within the First Year of Use | |
|--------------------------|--|--------------------------|
| | Typical Use ^a | Perfect Use ^b |
| Chance | 85 | 85 |
| Spermicides | 21 | 6 |
| Periodic abstinence | 20 | 1-9 |
| Withdrawal | 19 | 4 |
| Cap | | |
| Parous | 36 | 26 |
| Nulliparous | 18 | 9 |
| Sponge | | |
| Parous | 36 | 20 |
| Nulliparous | 18 | 9 |
| Diaphragm | 18 | 6 |
| Condom | | |
| Female | 21 | 5 |
| Male | 12 | 3 |
| Pill | 3 | |
| Progestin only | | 0.5 |
| Combined | | 0.1 |
| IUD | | |
| Progesterone | 2 | 1.5 |
| Copper T 380A | 0.8 | 0.6 |
| Injection (Depo-Provera) | 0.3 | 0.3 |
| Implants (Norplant) | 0.09 | 0.09 |
| Female sterilization | 0.4 | 0.4 |
| Male sterilization | 0.15 | 0.10 |

Adapted with permission¹.

^a 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.

^b 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.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who 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, carcinomas or benign liver tumors
- Known or suspected pregnancy

a measure of the relative risk of a disease. Relative risk, the ratio of the incidence of a disease among oral contraceptive users to that among non-users, cannot be assessed directly from case control studies,² but the odds ratio obtained is a measure of relative risk. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide not only a measure of the relative risk but a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and non-users. The attributable risk does provide information about the actual occurrence of a disease in the population. (Adapted from ref. 12 and 13 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

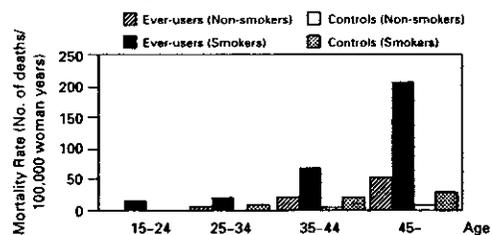
a. Myocardial Infarction

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.^{2-5,13} The relative risk of heart attack for current oral contraceptive users has been estimated to be 2 to 6.^{2,14-19} The risk is very low under the age of 30. However, there is the possibility of a risk of cardiovascular disease even in very young women who take oral contraceptives.

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.²⁰

Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and non-smokers over the age of 40 among women who use oral contraceptives (see Table II).¹⁶

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



Adapted from P.M. Layde and V. Beral, Table VI¹⁶

Oral contraceptives may compound the effects of well-known risk factors such as hypertension, diabetes, hyperlipidemias, hypercholesterolemia, age and obesity.^{3,13,21} In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.²¹⁻²⁵ Oral contraceptives have been shown to increase blood pressure among users (see **WARNINGS**, section 9). 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.

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 non-users 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.^{12,13,26-31} 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.³² The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped.¹²

A 2- to 6-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.⁸³ If feasible, oral contraceptives should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery and during and following prolonged immobilization. Since the immediate postpartum period also is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than 4 to 6 weeks after delivery in women who elect not to breast feed.³³

years after discontinuation of oral contraceptives, although excess risk was very small.⁴⁰ There is a significant increased relative risk of subarachnoid hemorrhage after initiation of use of oral contraceptives.³⁴ However, if studies were performed with oral contraceptive formulations containing 50 µg or higher of estrogen.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources we have estimated the mortality rates associated with different methods of contraception at different ages (Table III).⁴¹ These estimates include the combined risk death associated with contraceptive methods plus the attributable to pregnancy in the event of method fail. Each method of contraception has its specific benefits risks. The study concluded that with the exception of contraceptive users 35 and older who smoke and 40 older who do not smoke, mortality associated with methods of birth control is low and below that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users based on data gathered in the 1970s—but not reported the U.S. until 1983.^{16,41} However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed,^{78,79} the Family and Maternal Health Drugs Advisory Committee asked to review the topic in 1989. The Committee concluded that although cardiovascular disease risks may increase with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are 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.

Therefore, the Committee recommended that the benefits of 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 the lowest possible dose formulation that is effective.⁸⁰

TABLE III: ESTIMATED ANNUAL NUMBER OF BIRTH RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERIL 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 | 47.0 |
| Oral contraceptives non-smoker** | 0.3 | 0.5 | 0.9 | 1.9 | 13.8 | 20.8 |
| Oral contraceptives smoker** | 2.2 | 3.4 | 6.6 | 13.5 | 51.1 | 108.1 |
| IUD** | 0.8 | 0.8 | 1.0 | 1.0 | 1.4 | 1.4 |
| Condom* | 1.1 | 1.6 | 0.7 | 0.2 | 0.3 | 0.3 |
| Diaphragm/Spermicide* | 1.9 | 1.2 | 1.2 | 1.3 | 2.2 | 2.2 |
| Periodic abstinence* | 2.5 | 1.6 | 1.6 | 1.7 | 2.9 | 2.9 |

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

Estimates adapted from H.W. Ory, Table 3⁴¹

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed to determine the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. The overwhelming evidence in the literature suggests that use of oral contraceptives is not associated with an increase in risk of developing breast cancer, regardless of the age at parity of first use or with most of the marketed brands and doses.⁴²⁻⁴⁴ The Cancer and Steroid Hormone (CASH) study also showed no latent effect on the risk of breast cancer for at least a decade following long-term use.⁴³ A few studies have shown a slightly increased relative risk of developing breast cancer,⁴⁴⁻⁴⁷ although the methodology of these studies, which included differences in examining users and non-users and differences in age at start of use, has been questioned.⁴⁷⁻⁴⁹ Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use.^{81,82}

c. Cerebrovascular diseases

An increase in both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes) has been shown in users of oral contraceptives. 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 non-users for both types of strokes while smoking interacted to increase the risk for hemorrhagic strokes.³⁴

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.³⁵ 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.³⁵ The attributable risk also is greater in women in their mid-thirties or older and among smokers.¹³

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.³⁶⁻³⁸ A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents.²²⁻²⁴ A decline in serum high-density lipoproteins has been associated with an increased incidence of ischemic heart disease.³⁹ 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 nature and absolute amount of progestogens used in the contraceptives. The amount of both hormones should be considered in the choice of an oral contraceptive.³⁷

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

e. Persistence of risk of vascular disease

There are three studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives.^{17,34,40} 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 5 or more years, but this increased risk was not demonstrated in other age groups.¹⁷ 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.⁴⁰ There is a significantly increased relative risk of subarachnoid hemorrhage after termination of use of oral contraceptives.³⁴ However, these studies were performed with oral contraceptive formulations containing 50 µg or higher of estrogen.

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One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages (see Table III).⁴¹ 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 a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s—but not reported in the U.S. until 1983.^{16,41} However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed,^{78,79} the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. 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 greater potential health risks associated with pregnancy in older women and with the alternative

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intra-epithelial neoplasia in some populations of women.⁵⁰⁻⁵³ However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast or cervical cancers, a cause and effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use.⁵⁴ Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.⁵⁵⁻⁵⁶

Studies in the United States and Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users.⁵⁷⁻⁵⁹ However, these cancers are extremely rare in the United States and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than 1 per 1,000,000 users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.⁶⁰⁻⁶² Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.^{60,61,63,64}

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 2 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 first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.⁶⁵⁻⁶⁶ More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.⁶⁷ The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.⁶⁸

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users.²⁵ Oral contraceptives containing greater than 75 µg of estrogen cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance.⁷⁰ Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.^{25,71} However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.⁶⁹ Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

Some women may develop persistent hypertriglyceridemia while on the pill.⁷² As discussed earlier (see **WARNINGS**, sections 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.²³

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use.^{73,84} Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease 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,

4. FLUID RETENTION

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

5. EMOTIONAL DISORDERS

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

6. CONTACT LENSES

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

7. DRUG INTERACTIONS

Reduced efficacy and increased incidence of bleeding and menstrual irregularities have been reported with concomitant use of rifampin. A similar interaction, though less marked, has been suggested with phenylbutazone, phenytoin sodium, and possibly efavir, ampicillin and tetracyclines.⁷⁶

8. INTERACTIONS WITH LABORATORY TESTS

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

- Increased prothrombin and factors VII, V, VIII, IX, and X; decreased antithrombin III; increased risk of thrombotic and thrombolytic events.
- Increased thyroid binding globulin (TBG) levels; increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T₄ by radioimmunoassay (RIA), or free T₄ by equilibrium dialysis; free T₄ concentration is unaltered.
- Other binding proteins may be elevated.
- Sex steroid binding globulins are increased; levels of total circulating sex steroids are increased; however, free or biologically active sex steroids remain unchanged.
- Triglycerides may be increased.
- Glucose tolerance may be decreased.
- Serum folate levels may be depressed; oral contraceptive therapy may be indicated 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 steroid have been identified in the milk of nursing mothers and effects on the child have been reported, including breast enlargement. In addition, oral contraceptive use during the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. The nursing mother should be advised to discontinue oral contraceptives while breast feeding. She should use another method of contraception since breast feeding provides partial protection from becoming pregnant and protection decreases significantly as she breast feeds longer periods of time. The nursing mother should start oral contraceptives only after she has weaned her child completely.

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
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas, carcinomas or benign neoplasms

There is evidence of an association between the following conditions and the use of oral contraceptives; additional confirmatory studies are needed:

- Mesenteric thrombosis
- Retinal thrombosis

The following adverse reactions have been reported:

Serious adverse effects of oral contraceptive use. Women should be strongly advised to stop taking the pill if they experience any of the following symptoms:

• Sudden onset of chest pain, shortness of breath, or coughing up blood.

• Sudden onset of severe headache, dizziness, or fainting.

• Sudden onset of severe abdominal pain, especially in the upper right quadrant.

• Sudden onset of severe leg pain, especially in the calf.

• Sudden onset of severe vision changes, such as blurring or double vision.

OTHER

• Sudden onset of severe nausea, vomiting, or diarrhea.

• Sudden onset of severe depression or anxiety.

MORTALITY RATES AND MORTALITY STATUS

developing cerebrovascular disease persisted for at least 6 years after discontinuation of oral contraceptives, although excess risk was very small.⁴⁰ There is a significantly increased relative risk of subarachnoid hemorrhage after termination of use of oral contraceptives.³⁴ However, these studies were performed with oral contraceptive formulations containing 50 µg or higher of estrogen.

2. ESTIMATES OF MORTALITY FROM CONTRACEPTIVE USE

One study gathered data from a variety of sources which have estimated the mortality rates associated with different methods of contraception at different ages (see Table III).⁴¹ 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 a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970s—but not reported in the U.S. until 1983.^{16,41} However, current clinical practice involves the use of lower estrogen dose formulations combined with careful restriction of oral contraceptive use to women who do not have the various risk factors listed in this labeling.

Because of these changes in practice and, also, because of some limited new data which suggest that the risk of cardiovascular disease with the use of oral contraceptives may now be less than previously observed,^{78,79} the Fertility and Maternal Health Drugs Advisory Committee was asked to review the topic in 1989. 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 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.

Therefore, the Committee recommended that the benefits of 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 the lowest possible dose formulation that is effective.⁸⁰

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

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

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

Estimates adapted from H.V. Ory, Table 3⁴¹

3. CARCINOMA OF THE REPRODUCTIVE ORGANS AND BREASTS

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian and cervical cancer in women using oral contraceptives. The overwhelming evidence in the literature suggests that use of oral contraceptives is not associated with an increase in the risk of developing breast cancer, regardless of the age and parity of first use or with most of the marketed brands and doses.⁴²⁻⁴⁴ The Cancer and Steroid Hormone (CASH) study also showed no latent effect on the risk of breast cancer for at least a decade following long-term use.⁴³ A few studies have shown a slightly increased relative risk of developing breast cancer,⁴⁴⁻⁴⁷ although the methodology of these studies, which included differences in examination of users and non-users and differences in age at start of use, has been questioned.⁴⁷⁻⁴⁹ Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk appears to be related to duration of use.^{81,82}

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.⁶⁵⁻⁶⁶ More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.⁶⁷ The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.⁶⁸

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users.²⁵ Oral contraceptives containing greater than 75 µg of estrogen cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance.⁷⁰ Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.^{25,71} However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.⁶⁹ Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

Some women may develop persistent hypertriglyceridemia while on the pill.⁷² As discussed earlier (see **WARNINGS**, sections 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.²³

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use.^{73,84} Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease 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 among ever- and never-users.⁷³⁻⁷⁵

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 3 months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

PRECAUTIONS

GENERAL

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

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 oral contraceptives the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

11. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptive given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If sible, the nursing mother should be advised not to use contraceptives while breast feeding. She should use any method of contraception since breast feeding provides partial protection from becoming pregnant and this protection decreases significantly as she breast feeds longer periods of time. The nursing mother should start oral contraceptives only after she has weaned her child completely.

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
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas, carcinomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

- Mesenteric thrombosis
- Retinal thrombosis

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

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- 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 neither been 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
- Budd-Chiari syndrome
- Acne
- Changes in libido
- Colitis

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intra-epithelial neoplasia in some populations of women.⁵⁰⁻⁵³ However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

In spite of many studies of the relationship between oral contraceptive use and breast or cervical cancers, a cause and effect relationship has not been established.

4. HEPATIC NEOPLASIA

Benign hepatic adenomas are associated with oral contraceptive use although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases per 100,000 for users, a risk that increases after 4 or more years of use.⁵⁴ Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.⁵⁵⁻⁵⁶

Studies in the United States and Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) oral contraceptive users.⁵⁷⁻⁵⁹ However, these cancers are extremely rare in the United States and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than 1 per 1,000,000 users.

5. OCULAR LESIONS

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. ORAL CONTRACEPTIVE USE BEFORE OR DURING EARLY PREGNANCY

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.⁶⁰⁻⁶² Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned, when taken inadvertently during early pregnancy.^{60,61,63,64}

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 2 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 first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

7. GALLBLADDER DISEASE

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens.⁶⁵⁻⁶⁶ More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal.⁶⁷ The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.⁶⁸

8. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users.²⁵ Oral contraceptives containing greater than 75 µg of estrogen cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance.⁷⁰ Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.^{25,71} However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.⁶⁹ Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed while taking oral contraceptives.

Some women may develop persistent hypertriglyceridemia while on the pill.⁷² As discussed earlier (see **WARNINGS**, sections 1a. and 1d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.²³

9. ELEVATED BLOOD PRESSURE

An increase in blood pressure has been reported in women taking oral contraceptives and this increase is more likely in older oral contraceptive users and with continued use.^{73,84} Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases or renal disease 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,

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, and possibly with griseofulvin, ampicillin and tetracyclines.⁷⁶

8. INTERACTIONS WITH LABORATORY TESTS

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

- Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
- Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 concentration is unaltered.
- Other binding proteins may be elevated in serum.
- Sex steroid binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
- Triglycerides may be increased.
- Glucose tolerance may be decreased.
- Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral contraceptives.

9. CARCINOGENESIS

See **WARNINGS** section.

10. PREGNANCY

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

11. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives while breast feeding. She should use another method of contraception since breast feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as she breast feeds for longer periods of time. The nursing mother should consider starting oral contraceptives only after she has weaned her child completely.

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
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There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

- Mesenteric thrombosis
- Retinal thrombosis

The following adverse reactions have been reported in

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.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

The following health benefits related to the use of 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 of mestranol.⁶⁻¹¹

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

Effects from long-term use:

- 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

To achieve maximum contraceptive effectiveness, oral contraceptives must be taken exactly as directed and at intervals not exceeding 24 hours.

21-Day Schedule: For a DAY 1 START, count the first day of menstrual flow as Day 1 and the first blue tablet is then taken on Day 1. For a SUNDAY START, when menstrual flow begins on or before Sunday, the first blue tablet is taken on that day. With either a DAY 1 START or SUNDAY START, 1 blue tablet is taken for 6 days, then 1 white tablet for 5 days, then 1 pink tablet for 10 days. With either a DAY 1 START or SUNDAY START, 1 tablet is taken each day at the same time for 21 days. No tablets are taken for 7 days, then, whether bleeding has stopped or not, a new course is started of 1 tablet a day for 21 days. This institution a 3 weeks on, 1 week off dosage regimen.

28-Day Schedule: For a DAY 1 START, count the first day of menstrual flow as Day 1 and the first blue tablet is then taken on Day 1. For a SUNDAY START when menstrual flow begins on or before Sunday, the first blue tablet is taken on that day. With either a DAY 1 START or SUNDAY START, 1 blue tablet is taken for 6 days, then 1 white tablet for 5 days, then 1 pink tablet for 10 days, then 1 peach (inert) tablet for 7 days. With either a DAY 1 START or SUNDAY START, 1 tablet is taken each day at the same time for 28 days. After all 28 tablets are taken, whether bleeding has stopped or not, the same dosage schedule is repeated beginning on the following day.

INSTRUCTIONS TO PATIENTS

- To achieve maximum contraceptive effectiveness, the oral contraceptive pill must be taken exactly as directed and at intervals not exceeding 24 hours.
- Important: Women should be instructed to use an additional method of protection until after the first 7 days of administration in the initial cycle.
- Due to the normally increased risk of thromboembolism occurring postpartum, women should be instructed not to initiate treatment with oral contraceptives earlier than 4 weeks after a full-term delivery. If pregnancy is terminated in the first 12 weeks, the patient should be instructed to start oral contraceptives immediately or within 7 days. If pregnancy is terminated after 12 weeks, the patient should be instructed to start oral contraceptives after 2 weeks.^{33,77}
- If spotting or breakthrough bleeding should occur, the patient should continue the medication according to the schedule. Should spotting or breakthrough bleeding persist, the patient should notify her physician.
- If the patient misses 1 pill, she should be instructed to take it as soon as she remembers and then take the next pill at the regular time. The patient should be advised that missing a pill can cause spotting or light bleeding and that she may be a little sick to her stomach on the days she takes the missed pill with her regularly scheduled pill. If the patient has missed more than one pill, see **DETAILED PATIENT LABELING: HOW TO TAKE THE PILL, WHAT TO DO IF YOU MISS PILLS.**
- Use of oral contraceptives in the event of a missed menstrual period:
 - If the patient has not adhered to the prescribed dosage regimen, the possibility of pregnancy should be considered after the first missed period and oral contra-

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HEADACHE

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

BLEEDING IRREGULARITIES

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first 3 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. 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 present.

PRECAUTIONS

GENERAL

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

PHYSICAL EXAMINATION AND FOLLOW-UP

As 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 requested by the woman and judged appropriate by the physician. The physical examination should include special attention 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 considered to rule out malignancy. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care.

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 control of hyperlipidemias more difficult.

LIVER FUNCTION

Jaundice develops in any woman receiving oral contraceptives the medication should be discontinued. Steroid hormones may be poorly metabolized in patients with impaired liver function.

11. NURSING MOTHERS

Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use oral contraceptives while breast feeding. She should use another method of contraception since breast feeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as she breast feeds for longer periods of time. The nursing mother should consider starting oral contraceptives only after she has weaned her child completely.

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
- Arterial thromboembolism
- Pulmonary embolism
- Myocardial infarction
- Cerebral hemorrhage
- Cerebral thrombosis
- Hypertension
- Gallbladder disease
- Hepatic adenomas, carcinomas or benign liver tumors

There is evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:

- Mesenteric thrombosis
- Retinal thrombosis

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

- Nausea
- Vomiting
- Gastrointestinal symptoms (such as abdominal cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow
- Amenorrhea
- Temporary infertility after discontinuation of treatment
- Edema
- Melasma which may persist
- Breast changes: tenderness, enlargement, secretion
- Change in weight (increase or decrease)
- Change in cervical erosion and secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Migraine
- 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
- Budd-Chiari syndrome
- Acne
- Changes in libido
- Colitis

... days, then 1 pink tablet for 10 days, then 1 peach inert tablet for 7 days. With either a DAY 1 START or SUNDAY START, 1 tablet is taken each day at the same time for 28 days. After all 28 tablets are taken, whether bleeding has stopped or not, the same dosage schedule is repeated beginning on the following day.

INSTRUCTIONS TO PATIENTS

- To achieve maximum contraceptive effectiveness, the oral contraceptive pill must be taken exactly as directed and at intervals not exceeding 24 hours.
- Important: Women should be instructed to use an additional method of protection until after the first 7 days of administration in the initial cycle.
- Due to the normally increased risk of thromboembolism occurring postpartum, women should be instructed not to initiate treatment with oral contraceptives earlier than 4 weeks after a full-term delivery. If pregnancy is terminated in the first 12 weeks, the patient should be instructed to start oral contraceptives immediately or within 7 days. If pregnancy is terminated after 12 weeks, the patient should be instructed to start oral contraceptives after 2 weeks.^{33,77}
- If spotting or breakthrough bleeding should occur, the patient should continue the medication according to the schedule. Should spotting or breakthrough bleeding persist, the patient should notify her physician.
- If the patient misses 1 pill, she should be instructed to take it as soon as she remembers and then take the next pill at the regular time. The patient should be advised that missing a pill can cause spotting or light bleeding and that she may be a little sick to her stomach on the days she takes the missed pill with her regularly scheduled pill. If the patient has missed more than one pill, see **DETAILED PATIENT LABELING: HOW TO TAKE THE PILL, WHAT TO DO IF YOU MISS PILLS**.
- Use of oral contraceptives in the event of a missed menstrual period:
 1. If the patient has not adhered to the prescribed dosage regimen, the possibility of pregnancy should be considered after the first missed period and oral contraceptives should be withheld until pregnancy has been ruled out.
 2. If the patient has adhered to the prescribed regimen and misses 2 consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

HOW SUPPLIED

Trivora®-21 Tablets are available in 21-tablet blister cards. Six blister cards are packaged in a carton. All the tablets are unscored, round in shape. The blue tablets are debossed with "SCS" on one side and "50/30" on the other side. The white tablets are debossed with "SCS" on one side and "75/40" on the other side. The pink tablets are debossed with "SCS" on one side and "125/30" on the other side.

Trivora®-28 Tablets are available in 28-tablet blister cards. Six blister cards are packaged in a carton. Trivora®-28 Tablets contain the same 21 active tablets as Trivora®-21 Tablets with 7 additional inert tablets. The peach inert tablets are unscored, round in shape with "SCS" debossed on one side and "P" on the other side.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15°-30°C (59°-86°F).

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DETAILED PATIENT LABELING

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

INTRODUCTION

Any woman who considers using oral contraceptives ("birth control pills" or "the pill") should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make his decision and also will 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 leaflet is not

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 also should not use the pill if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), brain (stroke), lungs (pulmonary embolism) or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

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

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health care provider if you have or have had:

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

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

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

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of developing blood clots

Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

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

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 temporary or permanent 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 may have a greater risk than non-users of having gallbladder disease, although this risk may be related to pills containing high doses of estrogen.

4. Liver tumors

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in 2 studies in which a few women who developed these very rare cancers were found to have used oral

be seen from 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 is always lower than that associated with pregnancy for any age group, although over the age of 40 the risk increases to 32 deaths per 100,000 women compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35 the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is 4 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 don't smoke should not take oral contraceptives is based on information from older high-dose pills and on less selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks. However, all women, especially older women, are cautioned to use the lowest dose pill that is effective.

WARNING SIGNALS

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

- Sharp chest pain, coughing of blood or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast; ask your doctor or health care provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possible 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 pill. 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 1 cycle or lasts for more than a few days, talk to your doctor or health care provider.

2. Contact lenses

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

3. Fluid retention

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

4. Melasma

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

5. Other side effects

Other side effects may include change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash and vaginal infections.

If any of these side effects occurs, contact your doctor or health care provider.

GENERAL PRECAUTIONS

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

At times you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss 1 menstrual period, continue taking your pills for the next cycle but be sure to inform your health care provider before doing so. If you have not taken the pills daily as instructed and miss 1 menstrual period,

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EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, without missing any pills, the chance of becoming pregnant is less than 1% (pregnancy per 100 women per year of use). 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 nonsurgical methods of birth control during the first year are as follows:

Comparison of reversible contraceptive methods: percentage of women experiencing a contraceptive failure (pregnancy) during the first year of use.

| Method | % of Women Experiencing an Accidental Pregnancy within the First Year of Use | |
|----------------------|--|-------------|
| | Average Use | Correct Use |
| Oral contraception | 85 | 85 |
| Chemical spermicides | 21 | 6 |
| Periodic abstinence | 20 | 1-9* |
| Withdrawal | 19 | 4 |
| Diaphragm | 36 | 26 |
| Ever given birth | 18 | 9 |
| Diaphragm | 36 | 20 |
| Ever given birth | 18 | 9 |
| Diaphragm | 18 | 6 |
| Female condom | 21 | 5 |
| Female condom | 12 | 3 |
| Progestin only | | 0.5 |
| Combined | | 0.1 |
| Progesterone | 2 | 1.5 |
| Oppor T 380A | 0.8 | 0.6 |
| Diaphragms | 0.3 | 0.3 |
| Latex | 0.09 | 0.09 |

* Data with permission¹.

* Depending on method (calendar, ovulation, symptom-thermal)

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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 three to four weeks before surgery and not taking oral contraceptives for two weeks after surgery or during bed rest. You should also not take oral contraceptives soon after delivery of a baby. It is advisable to wait for at least four weeks after delivery if you are not breast feeding. If you are breast feeding, you should wait until you have weaned your child before using the pill (see **GENERAL PRECAUTIONS, While Breast Feeding**).

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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 temporary or permanent 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 may have a greater risk than non-users of having gallbladder disease, although this risk may be related to pills containing high doses of estrogen.

4. Liver tumors

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in 2 studies in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

5. Cancer of the reproductive organs and breasts

There is, at present, no confirmed evidence that oral contraceptives increase the risk of cancer of the reproductive organs in human studies. Several studies have found no overall increase in the risk of developing breast cancer. However, women who use oral contraceptives and have a strong family history of breast cancer or who have breast nodules or abnormal mammograms should be closely followed by their doctors. 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.

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.

ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY

All methods of birth control and pregnancy are associated with a risk of developing certain diseases which may lead to disability or death. An estimate of the number of deaths associated with different methods of birth control and pregnancy has been calculated and is shown in the following table:

| Method of control and outcome | ESTIMATED ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NON-STERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE | | | | | |
|----------------------------------|--|-------|-------|-------|-------|-------|
| | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 |
| No fertility control methods* | 7.0 | 7.4 | 9.1 | 14.8 | 25.7 | 28.2 |
| Oral contraceptives non-smoker** | 0.3 | 0.5 | 0.9 | 1.9 | 13.8 | 31.6 |
| Oral contraceptives smoker** | 2.2 | 3.4 | 6.6 | 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

... are taking the pill. 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 1 cycle or lasts for more than a few days, talk to your doctor or health care provider.

2. Contact lenses

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

3. Fluid retention

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

4. Melasma

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

5. Other side effects

Other side effects may include change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash and vaginal infections.

If any of these side effects occurs, contact your doctor or health care provider.

GENERAL PRECAUTIONS

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

At times you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss 1 menstrual period, continue taking your pills for the next cycle but be sure to inform your health care provider before doing so. If you have not taken the pills daily as instructed and miss 1 menstrual period, or if you miss 2 consecutive menstrual periods, you may be pregnant. Check with your health care provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of birth control.

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 studies have not been confirmed. 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 from any medication taken during pregnancy.

2. While breast feeding

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

3. Laboratory tests

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

4. Drug interactions

Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin; drugs used for epilepsy such as barbiturates (for example, phenobarbital) and phenytoin (Dilantin is one brand of this drug); phenylbutazone (Butazolidin is one brand of this drug) 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

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DO NOT STOP OR TAKE ORAL CONTRACEPTIVES

smoking increases the risk of serious car- ar side effects from oral contraceptive use. increases with age and with heavy smok- r more cigarettes per day) and is quite r women over 35 years of age. Women oral contraceptives are strongly advised orke.

en should not use the pill. For example, you ke the pill if you are pregnant or think you may . You also should not use the pill if you have llowing conditions:

- of heart attack or stroke
- s in the legs (thrombophlebitis), brain (stroke), onary embolism) or eyes
- of blood clots in the deep veins of your legs (angina pectoris)
- suspected breast cancer or cancer of the lining us, cervix or vagina
- ed vaginal bleeding (until a diagnosis is reached actor)
- of the whites of the eyes or of the skin (aun- g pregnancy or during previous use of the pill r (benign or cancerous)
- suspected pregnancy
- ith care provider if you have ever had any of ons. Your health care provider can recommend od of birth control.

CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

ith care provider if you have or have had: dules, fibrocystic disease of the breast, an breast x-ray or mammogram

- holesterol or triglycerides
- l pressure
- r other headaches or epilepsy
- ression
- ; heart or kidney disease
- scanty or irregular menstrual periods
- any of these conditions should be checked ir health care provider if they choose to use ptives.
- ire to inform your doctor or health care provider : or are on any medications.

F TAKING ORAL CONTRACEPTIVES

Developing blood clots
and blockage of blood vessels are the most effects of taking oral contraceptives. In par- in the legs can cause thrombophlebitis and a els to the lungs can cause a sudden blocking rrying blood to the lungs. Rarely, clots occur vessels of the eye and may cause blindness, , or impaired vision.

oral contraceptives and need elective surgery, in bed for a prolonged illness or have recently aby, you may be at risk of developing blood ould consult your doctor about stopping oral s three to four weeks before surgery and not ntraceptives for two weeks after surgery or est. You should also not take oral contracep- ter delivery of a baby. It is advisable to wait ur weeks after delivery if you are not breast u are breast feeding, you should wait until you your child before using the pill (see **GENERAL VS. While Breast Feeding**).

icks and strokes
ptives may increase the tendency to develop age or rupture of blood vessels in the brain) ectoris and heart attacks (blockage of blood a heart). Any of these conditions can cause porary or permanent disability. reatly increases the possibility of suffering and strokes. Furthermore, smoking and the ntraceptives greatly increase the chances of id dying of heart disease.

r disease
ptive users may have a greater risk than non- g gallbladder disease, although this risk may pills containing high doses of estrogen.

rs
oral contraceptives can cause benign but dan- rmors. These benign liver tumors can rupture al internal bleeding. In addition, a possible but ssociation has been found with the pill and r 2 studies in which a few women who devel- ry rare cancers were found to have used oral s for long periods. However, liver cancer is

be seen in the table 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 is always lower than that associated with pregnancy for any age group, although over the age of 40 the risk increases to 32 deaths per 100,000 women compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35 the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is 4 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 don't smoke should not take oral contraceptives is based on information from older high-dose pills and on less selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks. However, all women, especially older women, are cautioned to use the lowest dose pill that is effective.

WARNING SIGNALS

If any of these adverse effects occurs 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 fibro- cystic disease of the breast: ask your doctor or health care provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possible 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, accom- panied 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 pill. Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleed- ing 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 prob- lems. It is important to continue taking your pills on sched- ule. If the bleeding occurs in more than 1 cycle or lasts for more than a few days, talk to your doctor or health care provider.

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

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

4. Melasma
A spotty darkening of the skin is possible, particularly of the face.

5. Other side effects
Other side effects may include change in appetite, head- ache, nervousness, depression, dizziness, loss of scalp hair, rash and vaginal infections.
If any of these side effects occurs, contact your doctor or health care provider.

GENERAL PRECAUTIONS

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

At times you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss 1 menstrual period, continue taking your pills for the next cycle but be sure to inform your health care provider before doing so. If you have not taken the pills daily as instructed and miss 1 menstrual period, or if you miss 2 consecutive menstrual periods, you may

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

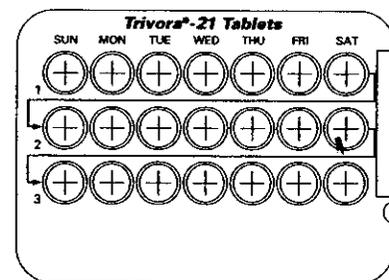
BEFORE YOU START TAKING YOUR PILLS:

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. **ALL 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 anti- biotics, your pills may not work as well.**
Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.
6. **IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your doctor or clinic about how to make pill- taking easier or about using another method of birth control.**
7. **IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your doctor or clinic.**

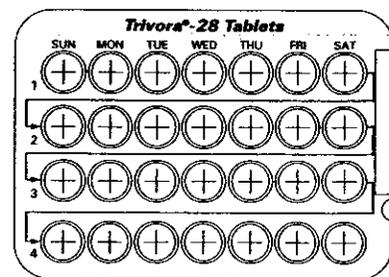
BEFORE YOU START TAKING YOUR PILLS

1. **DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.**
It is important to take it at about the same time every day.
2. **LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:**
The **21-pill pack** has 21 "active" blue, white and pink pills (with hormones) to take for 3 weeks, followed by 1 week without pills.
The **28-pill pack** has 21 "active" blue, white and pink pills (with hormones) to take for 3 weeks, followed by 1 week of reminder peach pills (without hormones).
3. **ALSO FIND:**
 - 1) where on the pack to start taking pills,
 - 2) in what order to take the pills and
 - 3) the week numbers as shown in the picture below.

Active Pill Colors: Blue, White and Pink



**Active Pill Colors: Blue, White and Pink
Reminder Pill Color: Peach**



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

HOW TO TAKE THE PILL

1. **If you an THROW (pack that If you ar Keep taki On Sunda a new pa**
2. You may expected. a row, ca pregnant.
3. You MAY 7 days aft control m, a back-up
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1. **If you are THROW (pack of pi If you ar Keep takir On Sunda a new pac**
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A REMINDE
If you forget THROW AW Keep taking You do not r

FINALLY, IF ABOUT THE
Use a BACK KEEP TAKIN can reach yc

6. Missed p
At times, y pleted a pac taken the pil as usual into correctly, and and you sho determines v talk to your d control meth should stop are not pregn

Even if spr taking the pi or light bleec clinic.

7. Stopping bed rest
If you are scf for a long pe you are on 1 weeks before blood clots. 1 taking the pil

8. Starting t
After you ha before startir when you m:

9. Pregnancy
When the pil rate is approx per year). If p little risk to th bers of pill us: missed pills should discus

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11. Overdos

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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 studies have not been confirmed. 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 from any medication taken during pregnancy.

2. While breast feeding

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

3. Laboratory tests

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

4. Drug interactions

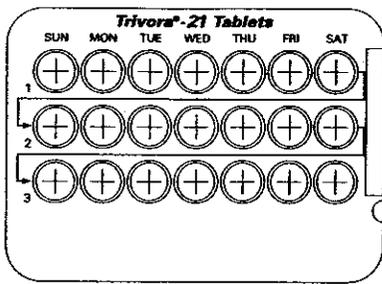
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5. Sexually transmitted diseases

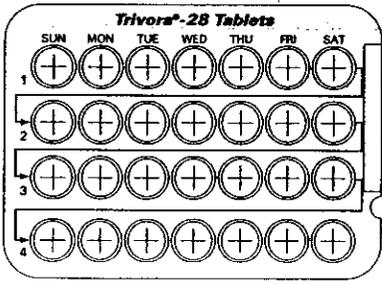
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3) the week numbers as shown in the picture below.

Active Pill Colors: Blue, White and Pink



**Active Pill Colors: Blue, White and Pink
Reminder Pill Color: Peach**



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

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

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.

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.

WHAT TO DO DURING THE MONTH

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

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

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

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

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

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

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** blue, white or pink "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 or white "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.

determines whether or not you are pregnant. You talk to your doctor or clinic, use an appropriate backup control method. If you miss 2 consecutive pills you should stop taking the pill until it is determined you are not pregnant.

Even if spotting or light bleeding should occur taking the pill according to the schedule. Should or light bleeding persist, you should notify your clinic.

7. Stopping the pill before surgery or prolonged rest

If you are scheduled for surgery or you need to be in bed for a long period of time you should tell your doctor you are on the pill. You should stop taking the pill a few weeks before your operation to avoid an increase in blood clots. Talk to your doctor about when you should stop taking the pill again.

8. Starting the pill after pregnancy

After you have a baby it is advisable to wait 4 weeks before starting to take the pill. Talk to your doctor when you may start taking the pill after pregnancy.

9. Pregnancy due to pill failure

When the pill is taken correctly, the expected pregnancy rate is approximately 1% (i.e., 1 pregnancy per 100 women per year). If pregnancy occurs while taking the pill, the risk to the fetus. The typical failure rate of pill users is less than 3% when women miss pills are included. If you become pregnant, you should discuss your pregnancy with your doctor.

10. Pregnancy after stopping the pill

There may be some delay in becoming pregnant after you stop taking the pill, especially if you had irregular periods before you started using the pill. Your doctor may recommend that you delay becoming pregnant until you have had one or more regular periods.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

11. Overdosage

Serious side effects have not been reported following the use of large doses of oral contraceptives by young women. Overdosage may cause nausea and withdrawal bleeding. In case of overdosage, contact your doctor or pharmacist.

12. Other information

Your doctor or clinic will take a medical and family history and will examine you before prescribing the pill. A physical examination may be delayed to another time if you request it and the health care provider believes that a good medical practice to postpone it. You should be examined at least once a year. Be sure to inform your doctor or clinic if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep appointments with your doctor or clinic because this is important to determine if there are early signs of side effects from the pill.

Do not use the pill for any condition other than that for which it was prescribed. The pill has been prescribed specifically for you, do not give it to others who do not use birth control pills.

HEALTH BENEFITS

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

- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur
- Pain or other symptoms during menstruation are encountered less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Non-cancerous 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, contact your doctor or clinic. They have a more technical leaflet called **PHYSICIAN LABELING** which you might read.

Store at controlled room temperature 15°-30°C (59°-86°F)

BRIEF SUMMARY

PATIENT PACKAGE INSERT

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

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

BE SURE TO READ THESE DIRECTIONS:

Before you start taking your pills. Anytime you are not sure what to do. 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. 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.

MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.

In the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some anti-infectives, 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.

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.

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

DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.

It is important to take it at about the same time every day.

LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS.

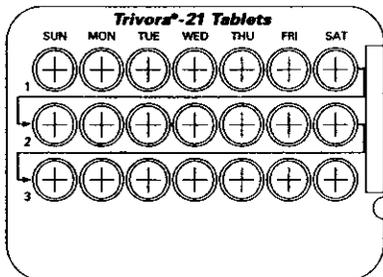
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The 28-pill pack has 21 "active" blue, white and pink pills with hormones) to take for 3 weeks, followed by 1 week of reminder peach pills (without hormones).

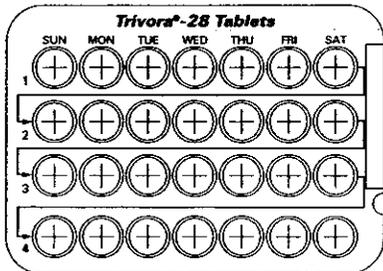
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Active Pill Colors: Blue, White and Pink



**Active Pill Colors: Blue, White and Pink
Reminder Pill Color: Peach**



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

If you have a choice of which day to start taking your first

if you miss 2 or more active pills in a row in the first week:

1. **If you are a Day 1 Starter:**
THROW OUT the rest of the pill pack and start a new pack that same day.
- 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.
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, white or pink "active" pills in a row (during the first 3 weeks):

1. **If you are a Day 1 Starter:**
THROW OUT the rest of the pill pack and start a new pack of pills that same day.
- 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.
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 peach "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.

6. Missed periods, spotting or light bleeding

At times, you may not have a period after you have completed a pack of pills. If you miss 1 period but you have taken the pills exactly as you were supposed to, continue as usual into the next cycle. If you have not taken the pills correctly, and have missed a period, you may be pregnant and you should stop taking the pill until your doctor or clinic determines whether or not you are pregnant. Until you can talk to your doctor or clinic, use an appropriate back-up birth control method. If you miss 2 consecutive periods, you should stop taking the pill until it is determined that you are not pregnant.

Even if spotting or light bleeding should occur, continue taking the pill according to the schedule. Should spotting or light bleeding persist, you should notify your doctor or clinic.

7. Stopping the pill before surgery or prolonged bed rest

If you are scheduled for surgery or you need to stay in bed for a long period of time you should tell your doctor that you are on the pill. You should stop taking the pill four weeks before your operation to avoid an increased risk of blood clots. Talk to your doctor about when you may start taking the pill again.

8. Starting the pill after pregnancy

After you have a baby it is advisable to wait 4-6 weeks before starting to take the pill. Talk to your doctor about when you may start taking the pill after pregnancy.

9. Pregnancy due to pill failure

When the pill is taken correctly, the expected pregnancy rate is approximately 1% (i.e., 1 pregnancy per 100 women per year). If pregnancy occurs while taking the pill, there is little risk to the fetus. The typical failure rate of large numbers of pill users is less than 3% when women who have missed pills are included. If you become pregnant, you should discuss your pregnancy with your doctor.

10. Pregnancy after stopping the pill

There may be some delay in becoming pregnant after you stop taking the pill, especially if you had irregular periods before you started using the pill. Your doctor may recommend that you delay becoming pregnant until you have had one or more regular periods.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

11. Overdosage

Serious ill effects have not been reported following inces-

oral contraceptives, also known as birth control pills or "the pill," are taken to prevent pregnancy and, when taken correctly, have a failure rate of about 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 oral contraceptives 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 life-threatening or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- Smoke
- Have high blood pressure, diabetes or 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

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 3 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) or lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris), eye or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or health care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anti-convulsants and some antibiotics, may decrease oral contraceptive effectiveness.

Studies to date of women taking the pill have not shown an increase in the incidence of cancer of the breast or cervix. There is, however, insufficient evidence to rule out the possibility that the pill may cause such cancers. 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.

Taking the pill provides some important non-contraceptive health benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections and fewer cancers of the ovary and the lining of the uterus.

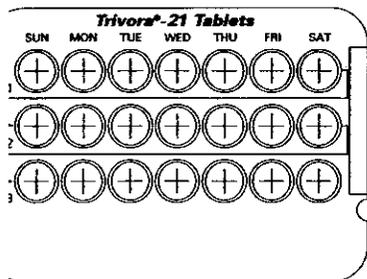
Be sure to discuss any medical condition you may have with your health care provider. Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your health care provider.

HOW TO TAKE THE PILL

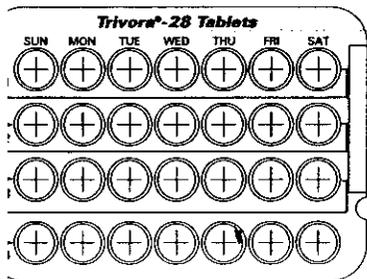
See full text of HOW TO TAKE THE PILL which is printed in full in the Detailed Patient Labeling.

that should be taken the first 7 days of each week numbers as shown in the picture below.

Five Pill Colors: Blue, White and Pink



**Five Pill Colors: Blue, White and Pink
Minder Pill Color: Peach**



ARE YOU READY AT ALL TIMES:
EVERY KIND OF BIRTH CONTROL (such as condoms,
or sponge) to use as a back-up in case you miss

TRA, FULL PILL PACK.

HOW TO START THE FIRST PACK OF PILLS

...a choice of which day to start taking your first pills. Decide with your doctor or clinic which is the best for you. Pick a time of day which will be easy to remember.

Start:
...the first "active" blue pill of the first pack during the first 24 hours of your period.

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

Start:
...the first "active" blue pill of the first pack on the first day after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that day.

...use another method of birth control as a back-up method to have sex anytime from the Sunday you start your pill pack until the next Sunday (7 days). Condoms, foam, or sponge are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH

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.

YOU FINISH A PACK OR SWITCH YOUR METHOD OF PILLS:

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

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

WHAT TO DO IF YOU MISS PILLS

MISS 1 blue, white or pink "active" pill:
...take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.

...do not need to use a back-up birth control method to have sex.

MISS 2 blue or white "active" pills in a row in **WEEK 1** or **WEEK 2** of your pack:
...take 2 pills on the day you remember and 2 pills the next day.

...take 1 pill a day until you finish the pack.
DO NOT 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 are not pregnant. If you can talk to your doctor or clinic, use an appropriate back-up birth control method. If you miss 2 consecutive periods, you should stop taking the pill until it is determined that you are not pregnant.

Even if spotting or light bleeding should occur, continue taking the pill according to the schedule. Should spotting or light bleeding persist, you should notify your doctor or clinic.

7. Stopping the pill before surgery or prolonged bed rest

If you are scheduled for surgery or you need to stay in bed for a long period of time you should tell your doctor that you are on the pill. You should stop taking the pill four weeks before your operation to avoid an increased risk of blood clots. Talk to your doctor about when you may start taking the pill again.

8. Starting the pill after pregnancy

After you have a baby it is advisable to wait 4-6 weeks before starting to take the pill. Talk to your doctor about when you may start taking the pill after pregnancy.

9. Pregnancy due to pill failure

When the pill is taken correctly, the expected pregnancy rate is approximately 1% (i.e., 1 pregnancy per 100 women per year). If pregnancy occurs while taking the pill, there is little risk to the fetus. The typical failure rate of large numbers of pill users is less than 3% when women who have missed pills are included. If you become pregnant, you should discuss your pregnancy with your doctor.

10. Pregnancy after stopping the pill

There may be some delay in becoming pregnant after you stop taking the pill, especially if you had irregular periods before you started using the pill. Your doctor may recommend that you delay becoming pregnant until you have had one or more regular periods.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

11. Overdosage

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health care provider or pharmacist.

12. Other information

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

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

HEALTH BENEFITS

In addition to preventing pregnancy, use of oral contraceptives may provide certain health 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
- Non-cancerous 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 or clinic. They have a more technical leaflet called **PHYSICIAN LABELING** which you might want to read.

Store at controlled room temperature 15°-30°C (59°-86°F).

BRIEF SUMMARY

PATIENT PACKAGE INSERT

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

...liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or health care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anti-convulsants and some antibiotics, may decrease oral contraceptive effectiveness.

Studies to date of women taking the pill have not shown an increase in the incidence of cancer of the breast or cervix. There is, however, insufficient evidence to rule out the possibility that the pill may cause such cancers. 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.

Taking the pill provides some important non-contraceptive health benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your health care provider. Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your health care provider.

HOW TO TAKE THE PILL

See full text of **HOW TO TAKE THE PILL** which is printed in full in the Detailed Patient Labeling.

Revised: Nov. 20, 1996

Manufactured for
SCS Pharmaceuticals
Chicago IL 60680 USA
By Syntex (F.P.) Inc.
Humacao, PR 00791

Address medical inquiries to:
G.D. Searle & Co.
Healthcare Information Services
5200 Old Orchard Road
Skokie IL 60077

SCS Pharmaceuticals

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Printed in USA

**Trivora®-21 Tablets
Trivora®-28 Tablets**

(levonorgestrel and ethinyl estradiol tablets, USP)—triphasic regimen



168 Tablets
NDC 0905-0291-28

Trivora[®]-28

(levonorgestrel and ethinyl
estradiol tablets, USP) -
Triphasic Regimen

Each blue tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet (5) contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg, each pink tablet (10) contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg and each peach tablet (7) contains inert ingredients.

Tablet Dispenser

6 units of 28 tablets

Caution: Federal law prohibits dispensing without prescription.

Usual Dosage: One tablet daily as recommended in enclosed detailed product information.

Store at controlled room temperature 5°-30°C (59°-86°F).

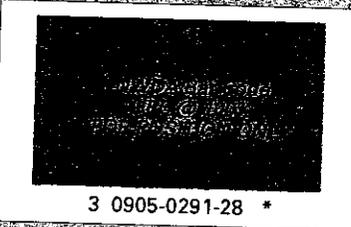
Manufactured for
CS Pharmaceuticals, Chicago IL 60680 USA
by Syntex (F.P.) Inc., Húmacao PR 00791

Trivora[®]-28

(levonorgestrel and ethinyl
estradiol tablets, USP)
Triphasic Regimen

Tablet Dispenser

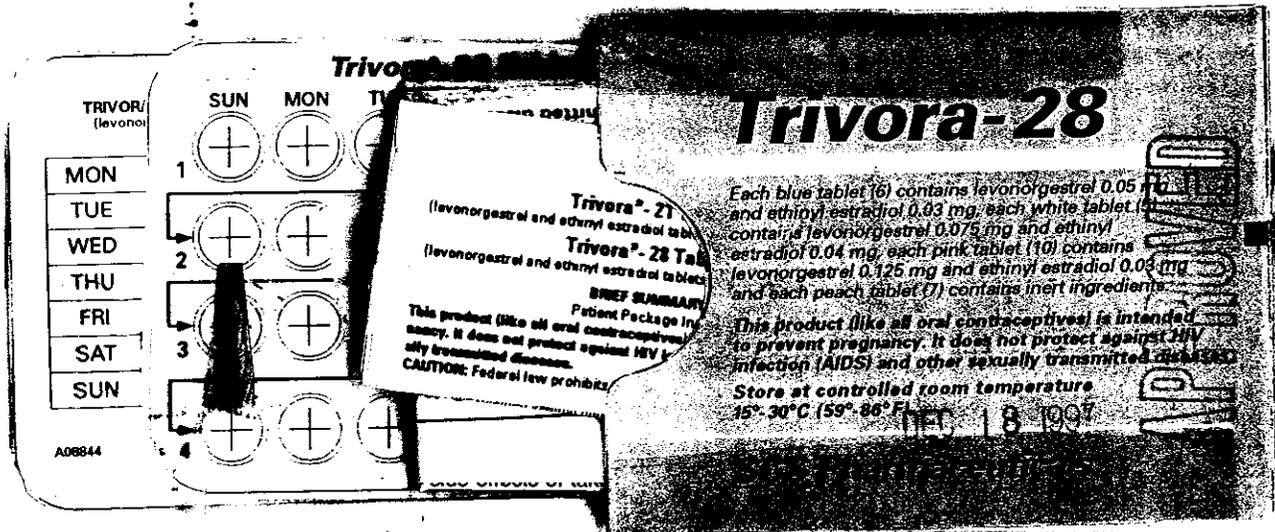
6 units of 28 tablets



SCS Pharmaceuticals

**EXAMPLE OF
TRIVORA
PACKAGING CONFIGURATION**

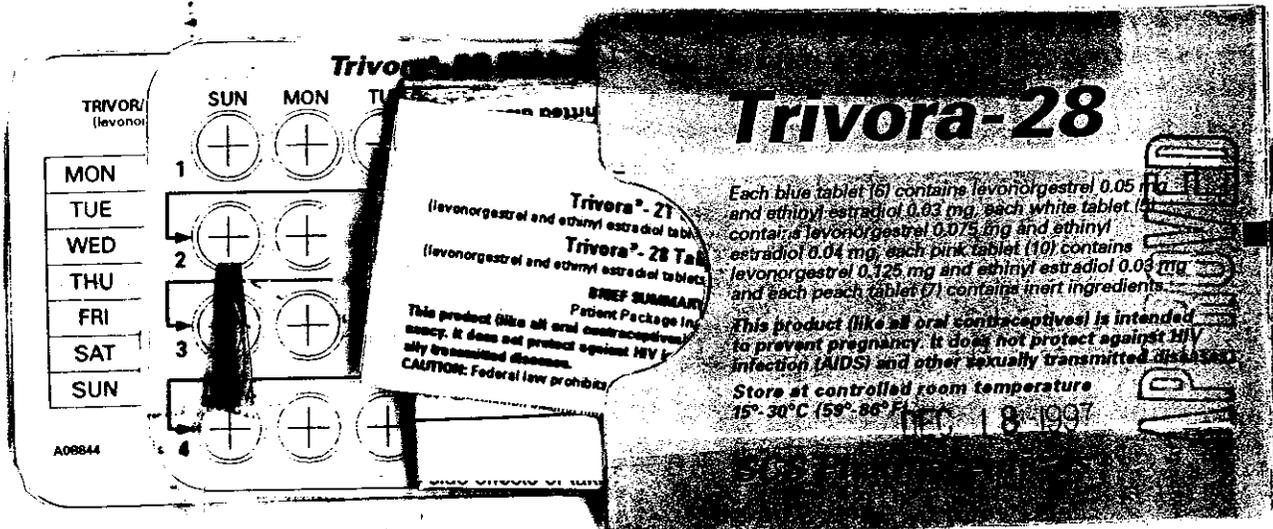
**Pill Blister, StickerCard,
Detailed Patient Labeling and Brief Summary
are inserted into the pocket**



**Physician Insert with assembled
pockets are placed in the Carton**

**EXAMPLE OF
TRIVORA
PACKAGING CONFIGURATION**

**Pill Blister, StickerCard,
Detailed Patient Labeling and Brief Summary
are inserted into the pocket**



**Physician Insert with assembled
pockets are placed in the Carton**

Trivora[®]- 21 Tablets
(levonorgestrel and ethinyl estradiol tablets, USP) – triphasic regimen

Trivora[®]- 28 Tablets
(levonorgestrel and ethinyl estradiol tablets, USP) – triphasic regimen

BRIEF SUMMARY
Patient/Package Insert

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

CAUTION: Federal law prohibits dispensing without prescription.

A08832

DETAILED PATIENT LABELING

Trivora[®]- 21 Tablets
(levonorgestrel and ethinyl estradiol tablets, USP) – triphasic regimen

Trivora[®]- 28 Tablets
(levonorgestrel and ethinyl estradiol tablets, USP) – triphasic regimen

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

Date

Trivora[®]- 21 Tablets: Each blue tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet (5) contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg, each pink tablet (10) contains levonorgestrel 0.125 mg and ethinyl estradiol 0.02 mg.

Trivora[®]- 28 Tablets: Each blue tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet (5) contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg, each pink tablet (10) contains levonorgestrel 0.125 mg and ethinyl estradiol 0.02 mg and each peach tablet (7) contains inert ingredients.

SCS Pharmaceuticals
Manufactured for SCS Pharmaceuticals
Chicago, IL 60680 USA
By ~~Sumitomo Co., Sumitomo~~

SHINYA HUNACCO R200791

BRIEF SUMMARY
Patient Package Insert

AUGUST 1995

Trivora™ - 21 Tablets

(levonorgestrel and ethinyl estradiol tablets, USP) - triphasic regimen
Each blue tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet (5) contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg and each pink tablet (10) contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg.

Trivora™ - 28 Tablets

(levonorgestrel and ethinyl estradiol tablets, USP) - triphasic regimen
Each blue tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet (5) contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg, each pink tablet (10) contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg and each peach tablet (7) contains inert ingredients.

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

Oral contraceptives, also known as "birth control pills" or "the pill," are taken to prevent pregnancy and, when taken correctly, have a failure rate of about 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 life-threatening or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- Smoke
- Have high blood pressure, diabetes or 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

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 3 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) or lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris), eye or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. Liver tumors, which may rupture and cause severe bleeding. A possible but not definite association has been found with the pill and liver cancer. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed leaflet given to you with your supply of pills. Notify your doctor or health care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anti-convulsants and some antibiotics, may decrease oral contraceptive effectiveness.

Studies to date of women taking the pill have not shown an increase in the incidence of cancer of the breast or cervix. There is, however, insufficient evidence to rule out the possibility that the pill may cause developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use.

Taking the pill provides some important non-contraceptive health benefits. These include less painful menstruation, less menstrual blood loss and anemia, fewer pelvic infections and fewer cancers of the ovary and the lining of the uterus.

Be sure to discuss any medical condition you may have with your health care provider. Your health care provider will take a medical and family history before prescribing oral contraceptives and will examine you. The physical examination may be delayed to another time if you request it and the health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year while taking oral contraceptives. The detailed patient information leaflet gives you further information which you should read and discuss with your health care provider.

This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

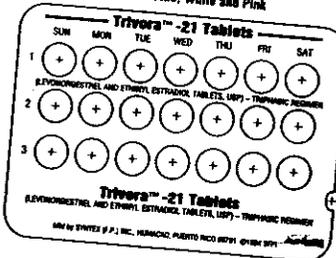
BEFORE YOU START TAKING YOUR PILLS:

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

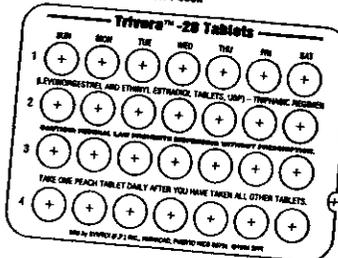
BEFORE YOU START TAKING YOUR PILLS

1. **DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.**
It is important to take it at about the same time every day.
2. **LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS.**
The 21-pill pack has 21 "active" blue, white and pink pills (with hormones) to take for 3 weeks, followed by 1 week without pills (without hormones).
The 28-pill pack has 21 "active" blue, white and pink pills (with hormones) to take for 3 weeks, followed by 1 week of reminder peach pills (without hormones).
3. **ALSO FIND:**
 - 1) where on the pack to start taking pills,
 - 2) in what order to take the pills and
 - 3) the week numbers as shown in the picture below.

Active Pill Colors: Blue, White and Pink



Active Pill Colors: Blue, White and Pink
Reminder Pill Color: Peach



Trivora™ - 21 Tablets (levonorgestrel and ethinyl estradiol tablets, USP) - triphasic regimen

Trivora™ - 28 Tablets (levonorgestrel and ethinyl estradiol tablets, USP) - triphasic regimen

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

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

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.

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.

WHAT TO DO DURING THE MONTH

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

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

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

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

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

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** blue, white or pink "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 or white "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** pink "active" pills in a row in **THE 3rd WEEK:**

1. **If you are a Day 1 Starter:**
THROW OUT the rest of the pill pack and start a new pack that same day.

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.

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, white or pink "active" pills in a row (during the first 3 weeks):

1. **If you are a Day 1 Starter:**
THROW OUT the rest of the pill pack and start a new pack of pills that same day.

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.

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 peach "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 OF BIRTH CONTROL** anytime you have sex.

KEEP TAKING ONE "ACTIVE" PILL EACH DAY until you can talk to your doctor or clinic.

6. Missed periods, spotting or light bleeding

At times, you may not have a period after you have completed a pack of pills. If you miss 1 period but you have taken the pills exactly as you were supposed to, continue as usual into the next cycle. If you have not taken the pills correctly, and have missed a period, you may be pregnant and you should stop taking the pill until your doctor or clinic determines whether or not you are pregnant. Until you can talk to your doctor or clinic, use an appropriate back-up birth control method. If you miss 2 consecutive periods, you should stop taking the pill until it is determined that you are not pregnant.

Even if spotting or light bleeding should occur, continue taking the pill according to the schedule. Should spotting or light bleeding persist, you should notify your doctor or clinic.

7. Stopping the pill before surgery or prolonged bed rest

If you are scheduled for surgery or you need to stay in bed for a long period of time you should tell your doctor that you are on the pill. You should stop taking the pill 4 weeks before your operation to avoid an increased risk of blood clots. Talk to your doctor about when you may start taking the pill again.

8. Starting the pill after pregnancy

After you have a baby it is advisable to wait 4-6 weeks before starting to take the pill. Talk to your doctor about when you may start taking the pill after pregnancy.

9. Pregnancy due to pill failure

When the pill is taken correctly, the expected pregnancy rate is approximately 1% (i.e., 1 pregnancy per 100 women per year). If pregnancy occurs while taking the pill, there is little risk to the fetus. The typical failure rate of large numbers of pill users is less than 3% when women who have missed pills are included. If you become pregnant, you should discuss your pregnancy with your doctor.

10. Pregnancy after stopping the pill

There may be some delay in becoming pregnant after you stop taking the pill, especially if you had irregular periods before you started using the pill. Your doctor may recommend that you delay becoming pregnant until you have had one or more regular periods.

There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

11. Overdosage

There are no reports of serious illness or side effects in young children who have swallowed a large number of pills. In adults, overdosage may cause nausea and/or bleeding in females. In case of overdosage, contact your doctor, clinic or pharmacist.

12. Other information

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

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

If you have more information about birth control pills, ask your doctor or clinic. They have a more technical leaflet called **PHYSICIAN LABELING** which you might want to read.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15°-30°C (59°-86°F).

MANUFACTURED BY
SYNTEX (F.P.) INC.
HUMACAO, PUERTO RICO 00791

18-0151-00-02

REVISED AUGUST 1995
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DETAILED PATIENT LABELING

Trivora™- 21 Tablets

(levonorgestrel and ethinyl estradiol tablets, USP)
- triphasic regimen

Each blue tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet (5) contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg and each pink tablet (10) contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg.

Trivora™- 28 Tablets

(levonorgestrel and ethinyl estradiol tablets, USP)
- triphasic regimen

Each blue tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet (5) contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg, each pink tablet (10) contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg and each peach tablet (7) contains inert ingredients.

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

INTRODUCTION

Any woman who considers using oral contraceptives ("birth control pills" or "the pill") should understand the benefits and risks of using this form of birth control. This leaflet will give you much of the information you will need to make this decision and also will 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 leaflet is not a replacement for a careful discussion between you and your health care provider. You should discuss the information provided in this leaflet with him or her, both when you first start taking the pill and during your regular visits. You also should follow the advice of your health care provider with regard to regular checkups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives are used to prevent pregnancy and are more effective than other non-surgical methods of birth control. When they are taken correctly, without missing any pills, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use). 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 nonsurgical methods of birth control during the first year are as follows:

Comparison of reversible contraceptive methods: Percentage of women experiencing a contraceptive failure (pregnancy) during the first year of use.

| Method | % of Women Experiencing a Pregnancy within the First Year of Use | |
|---------------------|--|------------------|
| | Average Use | Correct Use |
| No contraception | 85 | 85 |
| Spermicides | 21 | 6 |
| Periodic abstinence | 20 | 1-9 ^a |
| Withdrawal | 19 | 4 |
| Cap | | |
| Given birth | 36 | 26 |
| Never given birth | 18 | 9 |
| Sponge | | |
| Given birth | 36 | 20 |
| Never given birth | 18 | 9 |
| Diaphragm | 18 | 6 |
| Condom | | |
| Female | 21 | 5 |
| Male | 12 | 3 |
| Pill | 3 | |
| Progestin only | | 0.5 |
| Combined | | 0.1 |
| IUD | | |
| Progesterone | 2 | 1.5 |
| Copper T 380A | 0.8 | 0.6 |
| Injectables | 0.3 | 0.3 |
| Implant | 0.09 | 0.09 |

Adapted with permission.

^a Depending on method (calendar, ovulation, symptom-thermal)

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 also should not use the pill if you have any of the following conditions:

- A history of heart attack or stroke
- Blood clots in the legs (thrombophlebitis), brain (stroke), lungs (pulmonary embolism) or eyes
- A history of blood clots in the deep veins of your legs
- Chest pain (angina pectoris)
- Known or suspected breast cancer or cancer of the lining of the uterus, cervix or vagina
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor)

- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill
- Liver tumor (benign or cancerous)
- Known or suspected pregnancy

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

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health care provider if you have or have had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast x-ray or mammogram
 - Diabetes
 - Elevated cholesterol or triglycerides
 - High blood pressure
 - Migraine or other headaches or epilepsy
 - Mental depression
 - Gallbladder, heart or kidney disease
 - History of scanty or irregular menstrual periods
- Women with any of these conditions should be checked often by their health care provider if they choose to use oral contraceptives.

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

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of developing blood clots

Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blocking of the vessel carrying blood to the lungs. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

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

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 temporary or permanent 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 may have a greater risk than non-users of having gallbladder disease although this risk may be related to pills containing high doses of estrogen.

4. Liver tumors

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, a possible but not definite association has been found with the pill and liver cancers in 2 studies in which a few women who developed these very rare cancers were found to have used oral contraceptives for long periods. However, liver cancers are extremely rare. The chance of developing liver cancer from using the pill is thus even rarer.

5. Cancer of the breast and reproductive organs

There is, at present, no confirmed evidence that oral contraceptives increase the risk of cancer of the reproductive organs in human studies. Several studies have found no overall increase in the risk of developing breast cancer. However, women who use oral contraceptives and have a strong family history of breast cancer or who have breast nodules or abnormal mammograms should be followed closely by their doctors. 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.

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.

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:

| ESTIMATED ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH CONTROL OF FERTILITY PER 100,000 NONSTERILE WOMEN, BY FERTILITY CONTROL METHOD ACCORDING TO AGE | | | | | | |
|---|-------|-------|-------|-------|-------|-------|
| Method of control and outcome | 15-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 |
| No fertility control methods* | 7.0 | 7.4 | 9.1 | 14.8 | 25.7 | 28.2 |
| Oral contraceptives non-smoker** | 0.3 | 0.5 | 0.9 | 1.9 | 13.8 | 31.6 |
| Oral contraceptives smoker** | 2.2 | 3.4 | 6.6 | 13.5 | 51.1 | 117.2 |
| IUD** | 0.8 | 0.8 | 1.0 | 1.0 | 1.4 | 1.4 |
| Condom* | 1.1 | 1.8 | 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 from the table that for women aged 15 to 39 the risk of death is highest with pregnancy (7-26 deaths per 100,000 women, depending on age). Among pill users who do not smoke the risk of death is always lower than that associated with pregnancy for any age group, although over the age of 40 the risk increases to 32 deaths per 100,000 women compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35 the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes her estimated risk of death is 4 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 don't smoke should not take oral contraceptives is based on information from older high-dose pills and on less selective use of pills than is practiced today. An Advisory Committee of the FDA discussed this issue in 1989 and recommended that the benefits of oral contraceptive use by healthy, non-smoking women over 40 years of age may outweigh the possible risks. However, all women, especially older women, are cautioned to use the lowest dose pill that is effective.

WARNING SIGNALS

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

- Sharp chest pain, coughing of blood or sudden shortness of breath (indicating a possible clot in the lung)
- Pain in the calf (indicating a possible clot in the leg)
- Crushing chest pain or heaviness in the chest (indicating a possible heart attack)
- Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness or numbness in an arm or leg (indicating a possible stroke)
- Sudden partial or complete loss of vision (indicating a possible clot in the eye)
- Breast lumps (indicating possible breast cancer or fibrocystic disease of the breast: ask your doctor or health care provider to show you how to examine your breasts)
- Severe pain or tenderness in the stomach area (indicating a possible 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 pill. 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 problem...It is important to continue taking your pills on schedule. If the bleeding occurs in more than 1 cycle or lasts for more than a few days, talk to your doctor or health care provider.

2. Contact lenses

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

3. Fluid retention

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

4. Melasma (Mask of Pregnancy)

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

5. Other side effects

Other side effects may include change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash and vaginal infections.

If any of these side effects occurs, contact your doctor or health care provider.

GENERAL PRECAUTIONS

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

At times you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss 1 menstrual period, continue taking your pills for the next cycle but be sure to inform your health care provider before doing so. If you have not taken the pills daily as instructed and miss 1 menstrual period, or if you miss 2 consecutive menstrual periods, you may be pregnant. Check with your health care provider immediately to determine whether you are pregnant. Do not continue to take oral contraceptives until you are sure you are not pregnant, but continue to use another method of birth control.

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 studies have not been confirmed. 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 from any medication taken during pregnancy.

2. While breast feeding

If you are breast feeding, consult your doctor before starting oral contraceptives. Some of the drug will be passed on to the child in the milk. A few adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. In addition, oral contraceptives may decrease the amount and quality of your milk. If possible, do not use oral contraceptives and use another method of contraception while breast feeding. You should consider starting oral contraceptives only after you have weaned your child completely.

3. Laboratory tests

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

4. Drug interactions

Certain drugs may interact with birth control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin; drugs used for epilepsy such as barbiturates (for example, phenobarbital) and phenytoin (Dilantin is one brand of this drug); phenylbutazone (Butazolidin is one brand of this drug) and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.

5. This product (like all oral contraceptives) is intended to prevent pregnancy. It does not protect against transmission of HIV infection (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING YOUR PILLS:

1. BE SURE TO READ THESE DIRECTIONS:

Before you start taking your pills.

Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.

If you miss pills you could get pregnant. This includes starting the pack late.

The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST 1-3 PACKS OF PILLS.

If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

4. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills.

On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

5. IF YOU HAVE VOMITING OR DIARRHEA, for any reason, or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well.

Use a back-up method (such as condoms, foam, or sponge) until you check with your doctor or clinic.

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

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

BEFORE YOU START TAKING YOUR PILLS

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL.

It is important to take it at about the same time every day.

2. LOOK AT YOUR PILL PACK TO SEE IF IT HAS 21 OR 28 PILLS:

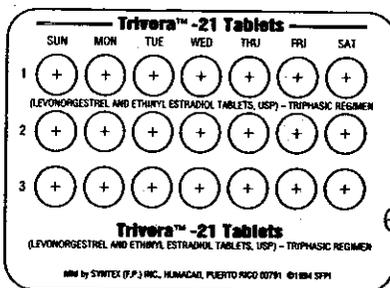
The 21-pill pack has 21 "active" blue, white and pink pills (with hormones) to take for 3 weeks, followed by 1 week without pills.

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

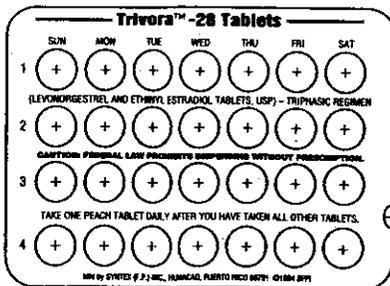
3. ALSO FIND:

- 1) where on the pack to start taking pills,
- 2) in what order to take the pills and
- 3) the week numbers as shown in the picture below.

Active Pill Colors: Blue, White and Pink



Active Pill Colors: Blue, White and Pink
Reminder Pill Color: Peach



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

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

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.

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.

WHAT TO DO DURING THE MONTH

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

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

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

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

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

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

WHAT TO DO IF YOU MISS PILLS

If you MISS 1 blue, white or pink "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 or white "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.

orig

PS

21 Tablets • NDC 0905-0289

Trivora-21

Each blue tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet (5) contains levonorgestrel 0.015 mg and ethinyl estradiol 0.04 mg, and each pink tablet (10) contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg.

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

Store at controlled room temperature
15°-30°C (59°-86°F)

SCS Pharmaceuticals

Pharmacist
Place Rx
Label Here

Caution: Federal law prohibits dispensing
without prescription

BE SURE TO READ THE PATIENT LABELING

Manufactured for
SCS Pharmaceuticals - Chicago, IL 60680 USA
By Syntex, U.S.A., Inc. - Humaçao, PR 00791

7A08790

1-inch Bar Code

PS

28 Tablets • NDC 4505-0291

Trivora-28

Each white tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg; each white tablet (6) contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg; each pink tablet (10) contains levonorgestrel 0.025 mg and ethinyl estradiol 0.03 mg; and each peach tablet (6) contains iron. *See package insert for complete list of ingredients.*

This product is a hormonal contraceptive. It is intended to prevent pregnancy. It does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Store at controlled room temperature.
20° to 25°C (68° to 77°F)

SCS Pharmaceuticals

Pharmacist
Place Rx
Label Here

Caution: Federal law prohibits dispensing without a prescription.

BE SURE TO READ THE PATIENT LABELING

Manufactured by
SCS Pharmaceuticals, Inc., 11111 E. 15th Ave.,
Denver, CO 80231, USA

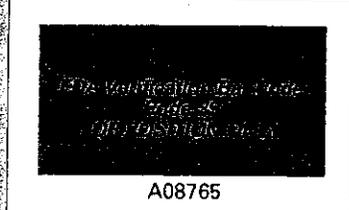
408791

1/2 - inch bar code

A08765

Note to Dispensing Pharmacist:
The "Patient Package Insert" including directions for use and the "Detailed Patient Labeling" are both enclosed inside each tablet dispenser. These are for the patient and are part of the official labeling for the product. FEDERAL REGULATIONS REQUIRE that they be GIVEN TO THE PATIENT when dispensing

Important



A08765

126 Tablets
NDC 0905-0289-21

Trivora®-21

(levonorgestrel and ethinyl estradiol tablets, USP) - Triphasic Regimen

Each blue tablet (6) contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg, each white tablet (5) contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg and each pink tablet (10) contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg.

Tablet Dispenser

6 units of 21 tablets

Caution: Federal law prohibits dispensing without prescription.

Usual Dosage: One tablet daily as recommended in enclosed detailed product information.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured for
SCS Pharmaceuticals, Chicago IL 60680 USA
By Syntex (F.P.) Inc., Humaçao, PR 00791

NO VARNISH-CODE DATE AREA

Trivora®-21

(levonorgestrel and ethinyl estradiol tablets, USP) - Triphasic Regimen

Tablet Dispenser

6 units of 21 tablets

APPROVED

SCS Pharmaceuticals

PS

126 Tablets
NDC 0905-0289-21

Trivora-21

(levonorgestrel and ethinyl
estradiol tablets, USP)
Triphasic Regimen

Each blue tablet (6) contains levonorgestrel 0.05 mg
and ethinyl estradiol 0.03 mg, each white tablet (5)
contains levonorgestrel 0.075 mg and ethinyl
estradiol 0.04 mg, and each pink tablet (10) contains
levonorgestrel 0.125 mg and ethinyl estradiol 0.06 mg.

Tablet Dispenser

6 units of 21 tablets

Caution: Federal law prohibits
dispensing without a prescription.

Usage: Do not use orally until you
are informed in writing by a doctor
of the proper use.

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

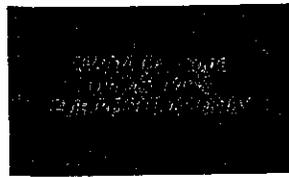
Manufacturer:
SCS Pharmaceuticals, Glendale, IL 60130 USA
By: SCS Pharmaceuticals, Glendale, IL 60130 USA

Trivora-21

(levonorgestrel and ethinyl
estradiol tablets, USP)
Triphasic Regimen

Tablet Dispenser

6 units of 21 tablets



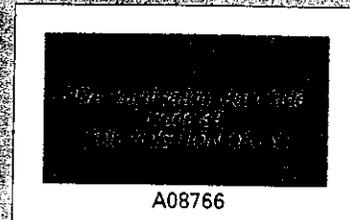
3 0905-0289-21 *

SCS Pharmaceuticals

A08766

Note to Dispensing Pharmacist:
The "Patient Package Insert" including
directions for use and the "Detailed
Patient Labeling" are both enclosed
inside each tablet dispenser. These
are for the patient and are part of
the official labeling for the product.
FEDERAL REGULATIONS
REQUIRE that they be GIVEN
TO THE PATIENT when dispensing.

Important



A08766

168 Tablets
NDC 0905-0291-28

Trivora® -28

(levonorgestrel and ethinyl
estradiol tablets, USP) -
Triphasic Regimen

Each blue tablet (6) contains levonorgestrel 0.05 mg
and ethinyl estradiol 0.03 mg, each white tablet (5)
contains levonorgestrel 0.075 mg and ethinyl
estradiol 0.04 mg, each pink tablet (10) contains
levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg
and each peach tablet (7) contains inert ingredients.

Tablet Dispenser

6 units of 28 tablets

Caution: Federal law prohibits
dispensing without prescription.

Usual Dosage: One tablet daily as
recommended in enclosed detailed
product information.

Store at controlled room temperature
15°-30°C (59°-86°F)

Manufactured for
SCS Pharmaceuticals, Chicago IL 60680 USA
By Syntex (F.P.) Inc., Humacao PR 00791

NO VARNISH-CODE DATE AREA

Trivora® -28

(levonorgestrel and ethinyl
estradiol tablets, USP)
Triphasic Regimen

Tablet Dispenser
6 units of 28 tablets



SCS Pharmaceuticals

PS

**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

74-538

CHEMISTRY REVIEW(S)

CHEMISTRY REVIEW NO. 1

2. ANDA # 74-538

3. NAME AND ADDRESS OF APPLICANT

Syntex (F.P.), Inc.
HCO1 Box 16625, Bo. Mariana Road. 909, KM. 111
Humacao, Puerto Rico 00791

Mailing Address:
3401 Hillview Avenue
Palo Alto, CA 94304

4. BASIS OF SUBMISSION

Listed drug product is Triphasil^R by Wyeth Ayerst Labs. approved in NDA # 19-192 and 19-190. A patent certification is submitted on page 12. Syntex certified that the three US patents; 3,666,858, 3,850,911, 3,959,322, and 3,957,982 which claim the listed drug have expired. No exclusivity exists for the drug product. The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

TrivoraTM 21 and 28 Tablets

7. NONPROPRIETARY NAME

Levonorgestrel and Ethinyl Estradiol Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 8-19-94

Amendment: 9-27-94 & 10-7-94 (To submit response to OGD's letter dated 9-12-94)

FDA:

Incomplete filing letter: 9-12-94

Accepted for filing: 10-11-94

10. PHARMACOLOGICAL CATEGORY

Oral Contraceptive

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF

DMF

DMF _____
DMF _____

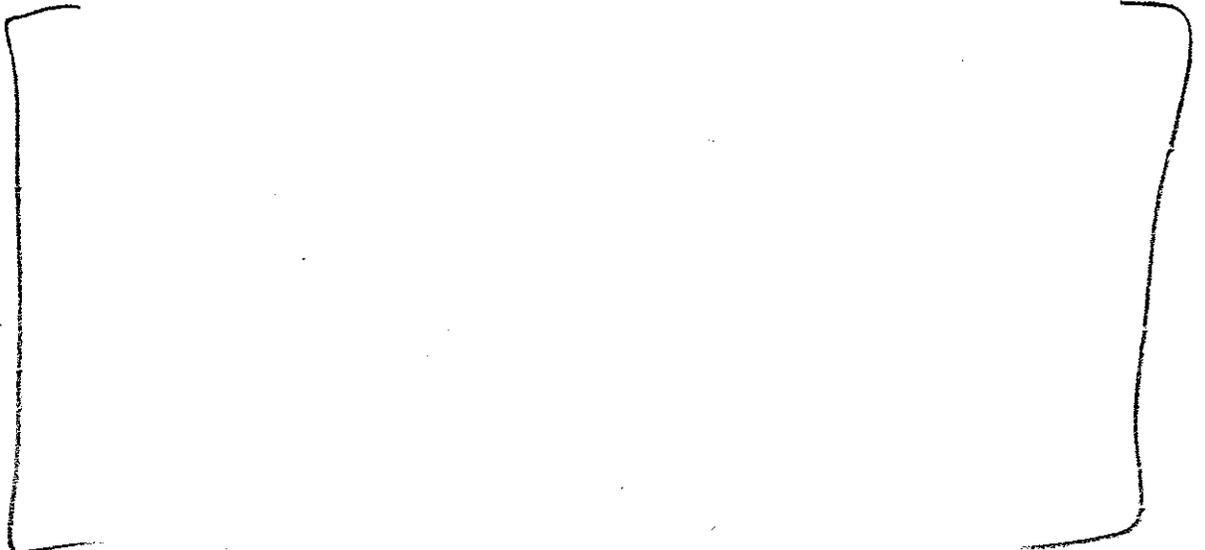
13. DOSAGE FORM
Tablet

14. POTENCY
21 Day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg
28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg;
and placebo

15. CHEMICAL NAME AND STRUCTURE
Listed in labeling insert per current USP

16. RECORDS AND REPORTS
N/A

17. COMMENTS
A. GENERAL COMMENTS:





B. COMMENTS TO BE INCLUDED IN NA LETTER:
All the comments listed in sections # 20, 23, 25, 27, 28, 29, 32, 33, and 34.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approved. A NA letter with major amendment is being sent to Syntex citing all the comments/deficiencies listed in this review.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
12-27-94
Revised on 1-4-95

cc: ANDA 74-538
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M.Shaikh/1-4-95
HFD-625/M.Smela/1-6-95
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F/T by dvw/3-13-95

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ISI 3/21/95

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1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-538

3. NAME AND ADDRESS OF APPLICANT

G. D. Searle & Co.
4901 Searle Parkway
Skokie, IL 60077

Former owner of the ANDA:

Syntex (F.P.), Inc.

HCO1 Box 16625, Bo. Mariana Road. 909, KM. 111

Humacao, Puerto Rico 00791

[This ANDA was transferred to G. D. Searle & Co. per NC dated 8-31-95]

4. BASIS OF SUBMISSION

Acceptable per CR # 1.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

TrivoraTM 21 and 28 Tablets

7. NONPROPRIETARY NAME

Levonorgestrel and Ethinyl Estradiol Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 8-19-94

Amendment: 9-27-94 & 10-7-94 (To submit response to OGD's letter dated 9-12-94)

NC: 3-28-95

NC: 8-31-95 (Transfer of ownership of this ANDA from Syntex)

NC: 9-18-95 (Transfer of ownership of this ANDA from Searle)

* ONC: 11-17-95 (Submission of updated FDA Form 356h after ownership change)

* NC (Bio): 11-30-95 (Response to bio letter dated 3-27-95)

* NC: 5-15-96

* Major Amendment: 6-10-96 (Response to NA - chemistry + labeling letter dated 3-23-95).

*NC (Bio): 7-19-96

FDA:

Incomplete filing letter: 9-12-94

Accepted for filing: 10-11-94

NA letter (Chemistry + Labeling): 3-23-95

NA letter (Bio): 3-27-95

Acknowledgement of transfer: 11-17-95

10. PHARMACOLOGICAL CATEGORY
Oral Contraceptive

11. Rx or OTC
Rx

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

13. DOSAGE FORM
Tablet

14. POTENCY

21 Day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg
28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg;
and placebo

15. CHEMICAL NAME AND STRUCTURE

Listed in labeling insert per current USP

16. RECORDS AND REPORTS

N/A

17. COMMENTS

A. GENERAL COMMENTS:



products for levonorgestrol and Ethinyl estradiol present in the drug product.

B. COMMENTS TO BE INCLUDED IN NA LETTER:

All the comments listed in sections # 21, 29, 32, 33, and 34.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approved. A NA letter with MINOR amendment is being sent to Searle citing all the comments/deficiencies listed in this review.

19. REVIEWER:

Mujahid L. Shaikh

DATE COMPLETED:

9-23-96

cc: ANDA 74-538

DUP File

Division File

Field Copy

Endorsements:

HFD-625/M. Shaikh/9-24-96

HFD-625/M. Smela/K. Furnranz for/9-25-96

x:new\firmnsz\searle\ltrs&rev\74538rev.

F/T by: bc/9-26-96

Handwritten initials and dates: |S|, |S|, 16/8/96, 10/8/96

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1. CHEMISTRY REVIEW NO. 3

2. ANDA # 74-538

3. NAME AND ADDRESS OF APPLICANT

G. D. Searle & Co.
4901 Searle Parkway
Skokie, IL 60077

Former owner of the ANDA:

Syntex (F.P.), Inc.

HCO1 Box 16625, Bo. Mariana Road. 909, KM. 111

Humacao, Puerto Rico 00791

[This ANDA was transferred to G. D. Searle & Co. per NC dated 8-31-95]

4. BASIS OF SUBMISSION

Acceptable per CR # 1.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

TrivoraTM 21 and 28 Tablets

7. NONPROPRIETARY NAME

Levonorgestrel and Ethinyl Estradiol Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 8-19-94

Amendment: 9-27-94 & 10-7-94 (To submit response to OGD's letter dated 9-12-94)

NC: 3-28-95

NC: 8-31-95 (Transfer of ownership of this ANDA from Syntex)

NC: 9-18-95 (Transfer of ownership of this ANDA from Searle)

ONC: 11-17-95 (Submission of updated FDA Form 356h after ownership change)

NC (Bio): 11-30-95 (Response to bio letter dated 3-27-95)

NC: 5-15-96

Major Amendment: 6-10-96 (Response to NA - chemistry + labeling letter dated 3-23-95).

NC (Bio): 7-19-96

* NC: 9-3-96

* Minor Amendment: 11-21-96

FDA:

Incomplete filing letter: 9-12-94

Accepted for filing: 10-11-94

NA letter (Chemistry + Labeling): 3-23-95



Additional information is required for containers/closure, and control and stability of the drug product.

B. COMMENTS TO BE INCLUDED IN NA LETTER:

All the comments listed in section nos. 26, 28, 29 and 34.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approved. A letter with minor amendment is being issued to the applicant including all the comments in section 17(B).

19. REVIEWER:

Mujahid L. Shaikh

DATE COMPLETED:

12-3-96

Revised on 12-9-96

cc: ANDA 74-538
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M. Shaikh/12-9-96

HFD-625/M. Smela/12-10-96

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F/T by: bc/12-18-96

1/31/96

12/20/96

12/23/96

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1. CHEMISTRY REVIEW NO. 4

2. ANDA # 74-538

3. NAME AND ADDRESS OF APPLICANT

G. D. Searle & Co.
4901 Searle Parkway
Skokie, IL 60077

Former owner of the ANDA:

Syntex (F.P.), Inc.
HCO1 Box 16625, Bo. Mariana Road. 909, KM. 111
Humacao, Puerto Rico 00791

[This ANDA was transferred to G. D. Searle & Co. per NC dated 8-31-95]

4. BASIS OF SUBMISSION

Acceptable per CR # 1.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

Trivora™ 21 and 28 Tablets

7. NONPROPRIETARY NAME

Levonorgestrel and Ethinyl Estradiol Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 8-19-94

Amendment: 9-27-94 & 10-7-94 (To submit response to OGD's letter dated 9-12-94)

NC: 3-28-95

NC: 8-31-95 (Transfer of ownership of this ANDA from Syntex)

NC: 9-18-95 (Transfer of ownership of this ANDA from Searle)

ONC: 11-17-95 (Submission of updated FDA Form 356h after ownership change)

NC (Bio): 11-30-95 (Response to bio letter dated 3-27-95)

NC: 5-15-96

Major Amendment: 6-10-96 (Response to NA - chemistry + labeling letter dated 3-23-95).

NC (Bio): 7-19-96

NC: 9-3-96

Minor Amendment: 11-21-96

* New Submissions

* Minor Amendment: 2-14-97 (Response to NA letter dated 12-27-96)

* ONC (BIO): 2-20-97

* ONC (BIO): 2-25-97

* ONC (BIO): 7-27-97

FDA:

Incomplete filing letter: 9-12-94

Accepted for filing: 10-11-94

NA letter (Chemistry + Labeling): 3-23-95

NA letter (Bio): 3-27-95

Acknowledgment of transfer: 11-17-95

NA letter: 10-15-96 (Chemistry + Labeling)

NA letter: 12-27-96 (Chemistry + Labeling)

10. PHARMACOLOGICAL CATEGORY
Oral Contraceptive

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF _____

13. DOSAGE FORM
Tablet

14. POTENCY

21 Day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg

28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg;
and placebo

15. CHEMICAL NAME AND STRUCTURE

Listed in labeling insert per current USP

16. RECORDS AND REPORTS

N/A

17. COMMENTS

[]

18. CONCLUSIONS AND RECOMMENDATIONS
Approved pending acceptable EER.

19. REVIEWER: Mujahid L. Shaikh DATE COMPLETED: 3-4-97

cc: ANDA 74-538
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M. Shaikh/3-4-97
HFD-625/M. Smela/3-10-97
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F/T by: bc/3-18-97

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1. CHEMISTRY REVIEW NO. 5

2. ANDA # 74-538

3. NAME AND ADDRESS OF APPLICANT

G. D. Searle & Co.
4901 Searle Parkway
Skokie, IL 60077

Former owner of the ANDA:
Syntex (F.P.), Inc.

HCO1 Box 16625, Bo. Mariana Road. 909, KM. 111
Humacao, Puerto Rico 00791

[This ANDA was transferred to G. D. Searle & Co. per NC
dated 8-31-95]

4. BASIS OF SUBMISSION
Acceptable per CR # 1.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
Trivora™ 21 and 28 Tablets

7. NONPROPRIETARY NAME
Levonorgestrel and Ethinyl Estradiol Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

FIRM:

Original submission: 8-19-94

Amendment: 9-27-94 & 10-7-94 (To submit response to OGD's
letter dated 9-12-94)

NC: 3-28-95

NC: 8-31-95 (Transfer of ownership of this ANDA from Syntex)

NC: 9-18-95 (Transfer of ownership of this ANDA from Searle)

ONC: 11-17-95 (Submission of updated FDA Form 356h after
ownership change)

NC (Bio): 11-30-95 (Response to bio letter dated 3-27-95)

NC: 5-15-96

Major Amendment: 6-10-96 (Response to NA - chemistry +
labeling letter dated 3-23-95).

NC (Bio): 7-19-96

NC: 9-3-96

Minor Amendment: 11-21-96

New Submissions

Minor Amendment: 2-14-97 (Response to NA letter dated 12-27-
96)

ONC (BIO): 2-20-97

ONC (BIO): 2-25-97

* NC: 10-3-97

* Amendment: 10-24-97 (Response to 9-22-97 NA letter)

FDA:

Incomplete filing letter: 9-12-94

Accepted for filing: 10-11-94

NA letter (Chemistry + Labeling): 3-23-95

NA letter (Bio): 3-27-95

Acknowledgment of transfer: 11-17-95

NA letter: 10-15-96 (Chemistry + Labeling)

NA letter: 12-27-96 (Chemistry + Labeling)

Bio Acceptance letter: 2-24-97

ANDA NA letter: 9-22-97

10. PHARMACOLOGICAL CATEGORY

Oral Contraceptive

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF ~~_____~~

13. DOSAGE FORM

Tablet

14. POTENCY

21 Day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg

28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg;

and placebo

15. CHEMICAL NAME AND STRUCTURE

Listed in labeling insert per current USP

16. RECORDS AND REPORTS

N/A

17. COMMENTS

[]

18. CONCLUSIONS AND RECOMMENDATIONS
Approved.

19. REVIEWER:
Mujahid L. Shaikh

DATE COMPLETED:
12-5-97
Revised 12-11-97

cc: ANDA 74-538
DUP File
Division File
Field Copy

Endorsements:

HFD-625/M. Shaikh/12-8-97
HFD-625/M. Smela/12-8-97
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F/T by: ~~bc/12-9-97~~

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12/11/97

12/11/97

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**CENTER FOR DRUG
EVALUATION AND RESEARCH**

APPLICATION NUMBER:

74-538

BIOEQUIVALENCE REVIEW

FEB 28 1995

Levonorgestrel/Ethinyl Estradiol,
Trivora™, Triphasic Regimen
0.050 mg / 0.030 mg
0.075 mg / 0.040 mg
0.125 mg / 0.030 mg
ANDA #74-538
Reviewer: L. Chuang
WP74-538.894

Syntex, Inc.
Palo Alto, CA
Submission Date:
August 19, 1994

**Review of Two Bioequivalence Studies, Dissolution Data and a
Waiver Request**

Introduction:

Levonorgestrel is a totally synthetic progestin; ethinyl estradiol is a semisynthetic estrogen. The combination product acts as a birth control agent through inhibition of ovulation.

A. Levonorgestrel (LNG)

LNG is well absorbed and completely available, with no evidence of a first-pass effect. Mean T_{max} ranges from 0.5 - 2 hours. Following a single dose, elimination is biphasic with mean terminal half-lives ranging from 12 - 45 hours. Peak plasma levels are in the low ng/mL range.

LNG is 93 - 95% bound to plasma proteins. The majority of this binding is to sex hormone binding globulin (SHBG). Lesser binding to serum albumin also occurs. Binding is of high affinity, low capacity and low affinity, high capacity types, respectively. Binding to alpha₁-glycoprotein may also occur. LNG dosed alone lowers SHBG binding capacity, whereas EE dosed alone increases SHBG binding capacity. The effect of co-administration of both drugs may be an increase in SHBG levels, possibly combined with changes in the clearance and/or volume of distribution of LNG. As a result, LNG plasma levels increase during the first dosing cycle greater than would be expected from single dose pharmacokinetics. In addition, the biologic half-life is increased upon multiple dosing.

Following oral dosing, LNG appears in the plasma principally as unmetabolized LNG, with lower levels of a reduced metabolite, 3 α ,5 β -tetrahydronorgestrel. LNG occurs principally in the unconjugated form in the plasma, although low concentrations of sulfate and glucuronide conjugates are found. The reduced metabolite occurs principally in sulfated form. Additional metabolites are found in the urine. Cumulative seven day excretion following a large oral dose of labeled LNG resulted in 45% of labeled drug in the urine and 32 % of labeled drug in the feces.

B. Ethinyl Estradiol (EE)

Peak EE levels occur within 1-2 hours following an oral dose. Mean C_{max} levels due to a 70 mcg EE dose are in the 170-200 pg/mL range. Kinetics obey a two compartment model following oral dosing, with the terminal linear segment of the profile beginning about 8 hours postdose. The biologic half-life of EE is 6-20 hours.

EE exhibits a large first-pass effect, with an absolute bioavailability of about 43%. About 65% of the first-pass metabolism is due to sulfate conjugation of EE in the gut wall. The drug occurs predominantly as the sulfate conjugate in the blood, with conjugated levels about 10 times greater than unconjugated levels. Unconjugated drug is 97-98% plasma protein bound. Binding is to albumin, not to SHBG. However, daily doses of EE as low as 30 mcg induce SHBG. The drug undergoes biliary recycling subsequent to sulfate and glucuronide conjugation.

A variety of phase 1 metabolites are formed from EE, primarily aromatic hydroxylation. A major metabolite is 2-hydroxyethyl estradiol.

C. Marketed Products

The triphasic combination is marketed by the innovator firm, Wyeth-Ayerst, in a triphasic regimen product consisting of the following three strengths of tablets:

- Phase 1 - 6 tablets: 50 mcg LNG/30 mcg EE
- Phase 2 - 5 tablets: 75 mcg LNG/40 mcg EE
- Phase 3 - 10 tablets: 125 mcg LNG/30 mcg EE

Only the innovator products, Triphasil^R-21 and Triphasil^R-28 (Wyeth-Ayerst) are available.

Bioequivalence Study - Phase 1 Tablet (Low Dose 0.050 mg LNG / 0.030 mg EE)

The purpose of this study (protocol #30-6106) is to determine the bioequivalence of the phase 1 tablet of Triphasil^R and the firm's similar product in healthy female subjects.

The clinical portion of the study was conducted by _____ The plasma analysis was conducted by _____ The study was conducted during May 24-October 10, 1993. The _____ approved the protocol and subject informed consent form for this study on April 29, 1993.

The study design was single-dose, single-center, randomized, two-period crossover. Thirty-one (31) female volunteers were recruited. The reported demography of these volunteers included

age (20-33 years old), weight (48.0-73.0 kg) and height (152-175 cm).

The inclusion criteria stated in the protocol are:

1. healthy women 18-35 years old
2. women who have not used oral contraceptive for at least 60 days.
3. women who have regular normal menstrual cycles
4. women whose weight are within 10% of normal body weight for their heights and frames.
5. women who are non-smokers for the past 6 months
6. women who agree to use effective means of birth control throughout the duration of the study.

The exclusion criteria stated in the protocol are:

1. women who are pregnant or suspect of being pregnant
2. women who have donated blood within the past 30 days
3. women who have taken enzyme inducing drugs within the past 28 days
4. women who have known sensitivity to the test formulation

None of the 31 subjects took any drug for 14 days prior to each study phase or had any alcohol and xanthine containing food and beverages for 48 hours prior to and during the study and all of them signed the informed consent forms. They were fasted overnight and assigned to one of the following treatments according to a randomly assigned sequence:

Treatment A - Reference Drug: Two Triphasil^R phase 1 tablets, 2 x 0.05 mg LNG/2 x 0.03 mg EE, Wyeth-Ayerst batch #3816-007-12058, formulation #F3816-017, potency 99.1%/99.0%, expires 02/95.

Treatment B - Test Drug: Two LNG/EE tablets, 2 x 0.05 mg/2 x 0.03 mg, Syntex batch #3816-007-12055, formulation #F3816-010, potency 98.7%/100.2%, batch size _____ tablets.

Each treatment was taken with 240 mL of water. Subjects continued to fast until 4 hours after dosing. Blood samples (15 mL each) were collected at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 30, 48 and 72 hours post-dose. Plasma samples were prepared and stored at -20°C until analysis. There was at least 4 weeks washout time between the 2 periods.

Analytical Method:

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acceptable ranges upon entry and exit from the study with few exceptions which were deemed not clinically significant by the investigator.

Six subjects experienced 8 adverse events. These events included stomach cramps, abdominal cramps, breast tenderness, nausea, fatigue, and pallor.

As expected from the protocol, 928 plasma samples were collected from the 29 subjects who completed the study. The results of standard curves were not reported, only the results of 30 sets of QC samples were reported as discussed in the analytical method section. Four samples were reassayed for EE due to pharmacokinetic anomaly, 2 of them the reassay confirmed the original values and the other 2 were each repeated twice and the repeated values were consistent and therefore reported.

The firm reported in Appendix D, Plasma Assay Data Report, that "the week 1 (presumably period 1, treatment B)), 0.5 hr, sample for EE from subject #27 was lost and was reported as "quantity not sufficient for analysis (QNS)". However, in the following Table 2, the EE concentration for the same subject at same time point was reported as 57.6 pg/mL. Instead, the EE concentration of subject #3 at the same time point of the same period was listed as QNS.

The mean plasma concentrations of EE and LNG at each sampling point after each treatment in 29 subjects and the mean pharmacokinetic parameters are presented below in Tables 1&2. The terminal elimination rate constant was computed by log linear regression analysis over 10 hours (for EE) or 12 hours (for LNG) through 72 hours.

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Table 1
Mean (C.V.%) Plasma EE Concentrations (pg/mL) at Each
Sampling Time Point and Least Square Means of Pharmacokinetic
Parameters (n = 29* -- Low Dose Study)

| Time (hour) | Treatment B (Syntex) | | Treatment A (Wyeth-Ayerst) | |
|-----------------------------------|----------------------|-------|----------------------------|-------|
| 0.00 | 0 | | 0 | |
| 0.50 | | | | |
| 1.00 | | | | |
| 1.50 | | | | |
| 2.00 | | | | |
| 4.00 | | | | |
| 6.00 | | | | |
| 8.00 | | | | |
| 10.00 | | | | |
| 12.00 | | | | |
| 16.00 | | | | |
| 24.00 | | | | |
| 30.00 | | | | |
| 36.00 | | | | |
| 48.00 | | | | |
| 72.00 | | | | |
| AUC _{0-t} (pg*h/mL) | 1383.0 | (30) | 1288.0 | (25) |
| AUC _{0-inf} (pg*h/mL) | 1576.0 | (28) | 1469.0 | (24) |
| C _{max} | 146.0 | (25) | 140.0 | (28) |
| LNAUC _{0-t} | 7.19 | (4.3) | 7.13 | (3.7) |
| LNAUC _{0-inf} | 7.32 | (3.9) | 7.26 | (3.6) |
| LNC _{max} | 4.95 | (5.0) | 4.90 | (5.9) |
| T _{max} (hr) | 1.62 | (38) | 1.69 | (31) |
| T _{1/2} | 15.0 | (24) | 14.4 | (27) |

* = unless otherwise indicated
a = (n = 28)

subject within sequence, period and treatment. Not any significant period, sequence or treatment effect was observed in the parameters of EE, however, there were significant period effects for both $LNAUC_{0-t}$ and $LNAUC_{0-inf}$ of LNG and significant period and treatment effects for LNC_{max} of LNG.

The LS means of all 3 untransformed and log transformed pharmacokinetic parameters of both EE and LNG, ratio of these means and the 90% confidence interval of test product versus reference product are presented in Tables 3&4.

Table 3

Statistical Analysis -- EE -- Low Dose Study

| Parameter | LS Means (Syntex) | LS Means (Wyeth-Ayerst) | T/R | 90% Confid. Interval |
|--------------------------|-------------------|-------------------------|-------|----------------------|
| AUC_{0-t} (pg*hr/mL) | 1386 | 1291 | 1.07 | 101.0; 111.3 |
| $LNAUC_{0-t}$ | 7.19 | 7.13 | 1.06 | 99.9; 112.6 |
| AUC_{0-inf} (pg*hr/mL) | 1579 | 1471 | 1.07 | 101.5; 113.2 |
| $LNAUC_{0-inf}$ | 7.33 | 7.26 | 1.07 | 101.0; 112.5 |
| C_{max} (pg/mL) | 146 | 140 | 1.04 | 95.4; 112.2 |
| LNC_{max} | 4.954 | 4.902 | 1.052 | 97.1; 113.2 |

Table 4

Statistical Analysis -- LNG -- Low Dose Study

| Parameter | LS Means (Syntex) | LS Means (Wyeth-Ayerst) | T/R | 90% Confid. Interval |
|--------------------------|-------------------|-------------------------|------|----------------------|
| AUC_{0-t} (ng*hr/mL) | 29.1 | 28.1 | 1.04 | 98.7; 108.6 |
| $LNAUC_{0-t}$ | 3.30 | 3.27 | 1.02 | 97.7; 107.0 |
| AUC_{0-inf} (ng*hr/mL) | 36.2 | 34.3 | 1.05 | 99.2; 111.7 |
| $LNAUC_{0-inf}$ | 3.49 | 3.46 | 1.04 | 98.6; 109.2 |
| C_{max} (ng/mL) | 3.23 | 2.87 | 1.13 | 107.3; 118.2 |
| LNC_{max} | 1.11 | 1.10 | 1.11 | 105.9; 116.6 |

Comments:

1. The firm did not provide the frame size of individual subjects in order for the reviewer to determine if their weights were within 10% of normal weight as described in the table of "Desirable Weight for Adults from the Metropolitan Life Insurance Company".
2. Assay validation information supporting the quantitation limits for both EE and LNG were not provided by the firm.
3. The concentration range of the standard curve was not provided.
4. The acceptance criteria for the standard curve and the QC samples of each run were not provided.
5. The subject number for the subject whose hour 0.5, period 1, plasma sample was lost during analytical process, was inconsistent in the text (#27) and Table 2 (#3) of Appendix 4, the "Plasma Assay Data Report".
6. The 90% confidence interval for log transformed AUC_{0-t} , AUC_{0-inf} , and C_{max} are all within 80-125% acceptable range.

Bioequivalence Study - Phase 3 Tablet (High Dose: 0.125 mg LNG / 0.030 mg EE)

The purpose of this study (protocol #32-6106) is to determine the bioequivalence of the phase 3 tablet of Triphasil^R and the firm's similar product in healthy female subjects.

The clinical portion of the study was conducted by _____
_____ The plasma analysis was conducted by _____
_____ The study was conducted during June 25-September 20, 1993. The Investigational Review Board of _____ approved the protocol and subject informed consent form for this study on June 11, 1993.

The study design was single-dose, single-center, randomized, two-period crossover. Thirty-two (32) female volunteers were recruited. The reported demography of these volunteers included age (19-34 years old), weight (47.7-78.2 kg) and height (151-177 cm).

The inclusion and exclusion criteria and the restrictions were the same as those in the above study. All subjects were fasted overnight and assigned to one of the following treatments according to a randomly assigned sequence:

Treatment A - Reference Drug: Two TriphasilR phase 3 tablets, 2 x 0.125 mg LNG/2 x 0.03 mg EE, Wyeth-Ayerst batch #3816-007-12060, formulation #F3816-017, potency 102.2%/103.1%, expires 02/95.

Treatment B - Test Drug: Two LNG/EE tablets, 2 x 0.125 mg/2 x 0.03 mg, Syntex batch #3816-007-12057, formulation #F3816-015, potency 102.0%/103.3%, batch size tablets.

Each treatment was taken with 240 mL of water. Subjects continued to fast until 4 hours after dosing. Blood samples (15 mL each) were collected at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 30, 48 and 72 hours post-dose. Plasma samples were prepared and stored at -20°C until analysis. There was at least 4 weeks washout time between the 2 periods.

Analytical Method:

Results:

Four (4) subjects (#1, #2, #21 and #29) failed to complete the study. One did not show up and 3 voluntarily withdrew before beginning of period 2.

All subjects' blood and urine chemistries were in the normal acceptable ranges upon entry and exit from the study with few exceptions which were deemed not clinically significant by the investigator.

Forty-seven (47) adverse events were reported by 29 subjects during treatment A and 43 events were reported by 27 subjects during treatment B. Only 17 of these events were considered by the investigator as being possibly drug related. They included headache, nausea, breast tenderness, abdominal bloating, dizziness, increased blood pressure, spotting and vomiting.

As expected from the protocol, 896 plasma samples were collected from the 28 subjects who completed the study. The results of standard curves were not reported, only the results of 29 sets of QC samples were reported as discussed in the analytical method section. Nine (9) plasma samples were reassayed for EE due to pharmacokinetic anomaly, the reassay confirmed the original values in 6 of these samples, 2 were each repeated twice and the repeated

values were consistent and therefore reported, and 1 had quite different repeated value than the original value (152 pg/mL versus 91.5 pg/mL) but insufficient sample precluded a third assay and the repeated value was reported since it fitted the pharmacokinetic profile. Two (2) plasma samples had processing errors and were reported as "quantity not sufficient" for both EE and LNG values.

The mean plasma concentrations of EE and LNG at each sampling point after each treatment in 28 subjects and the mean pharmacokinetic parameters are presented below in Tables 5&6. The terminal elimination rate constant was computed by log linear regression analysis over 10 hours (for EE) or 12 hours (for LNG) through 72 hours.

**APPEARS THIS WAY
ON ORIGINAL**

Table 6
Mean (C.V.%) Plasma LNG Concentrations (ng/mL) at Each
Sampling Time Point and Least Square Means of Pharmacokinetic
Parameters (n = 28* -- High Dose Study)

| Time (hour) | Treatment B (Syntex) | Treatment A (Wyeth-Ayerst) |
|-----------------------------------|------------------------|----------------------------|
| 0.00 | 0 | 0 |
| 0.50 | 3.62 (57) | 2.48 (83) |
| 1.00 | 5.95 (40) | 6.13 (36) |
| 1.50 | 5.73 (36) | 6.02 (33) |
| 2.00 | 4.89 (33) | 5.17 (34) |
| 4.00 | 2.64 (37) | 2.73 (35) |
| 6.00 | 1.95 (44) | 2.02 (46) |
| 8.00 | 1.62 (50) | 1.69 (49) |
| 10.00 | 1.41 ^a (53) | 1.50 (52) |
| 12.00 | 1.31 (55) | 1.35 (48) |
| 16.00 | 1.13 (53) | 1.15 (50) |
| 24.00 | 0.861 (57) | 0.88 (52) |
| 30.00 | 0.783 (58) | 0.789 ^a (48) |
| 36.00 | 0.676 (57) | 0.742 (51) |
| 48.00 | 0.514 (54) | 0.525 (51) |
| 72.00 | 0.279 (56) | 0.307 (54) |
| | | |
| AUC _{0-t} (ng*h/mL) | 69.1 (47) | 71.3 (43) |
| AUC _{0-inf} (ng*h/mL) | 82.0 (47) | 86.0 (44) |
| C _{max} | 6.44 (34) | 6.33 (36) |
| LNAUC _{0-t} | 4.13 (11) | 4.17 (11) |
| LNAUC _{0-inf} | 4.30 (11) | 4.35 (11) |
| LNC _{max} | 1.78 (21) | 1.80 (19) |
| T _{max} (hr) | 1.33 (23) | 1.26 (25) |
| T _{1/2} | 30.0 (34) | 31.2 (34) |

* = unless otherwise indicated
a = (n = 27)

Table 2
Mean (C.V.%) Plasma LNG Concentrations (ng/mL) at Each
Sampling Time Point and Least Square Means of Pharmacokinetic
Parameters (n = 29 -- Low Dose Study)

| Time (hour) | Treatment B (Syntex) | Treatment A (Wyeth-Ayerst) |
|-----------------------------------|----------------------|----------------------------|
| 0.00 | 0 | 0 |
| 0.50 | 2.58 (55) | 1.95 (58) |
| 1.00 | 2.97 (37) | 2.82 (32) |
| 1.50 | 2.46 (34) | 2.44 (32) |
| 2.00 | 1.90 (32) | 1.99 (34) |
| 4.00 | 0.998 (40) | 1.02 (38) |
| 6.00 | 0.731 (37) | 0.757 (42) |
| 8.00 | 0.636 (48) | 0.614 (43) |
| 10.00 | 0.562 (39) | 0.582 (41) |
| 12.00 | 0.530 (46) | 0.509 (40) |
| 16.00 | 0.473 (51) | 0.444 (45) |
| 24.00 | 0.346 (54) | 0.331 (47) |
| 30.00 | 0.316 (48) | 0.300 (44) |
| 36.00 | 0.291 (49) | 0.288 (45) |
| 48.00 | 0.224 (64) | 0.206 (57) |
| 72.00 | 0.131 (75) | 0.121 (67) |
| | | |
| AUC _{0-t} (ng*h/mL) | 29.2 (43) | 28.1 (25) |
| AUC _{0-inf} (ng*h/mL) | 36.2 (52) | 34.3 (47) |
| C _{max} | 3.25 (36) | 2.87 (32) |
| LNAUC _{0-t} | 3.30 (12) | 3.27 (11) |
| LNAUC _{0-inf} | 3.49 (12) | 3.45 (11) |
| LNC _{max} | 1.12 (33) | 1.00 (32) |
| T _{max} (hr) | 0.934 (34) | 1.02 (24) |
| T _{1/2} | 32.6 (41) | 31.2 (35) |

Analysis of Variance was performed on each pharmacokinetic parameter for both EE and LNG, with terms included sequence,

Analysis of Variance was performed on each pharmacokinetic parameter for both EE and LNG, with terms included sequence, subject within sequence, period and treatment. No significant ($p < 0.05$) period, sequence or treatment effect was observed in any log transformed pharmacokinetic parameters of either EE or LNG.

The LS means of all 3 untransformed and LN-transformed pharmacokinetic parameters of both EE and LNG, ratio of these means and the 90% confidence interval of test product versus reference product are presented in Tables 7&8.

Table 7

Statistical Analysis -- EE -- High Dose Study

| Parameter | LS Means (Syntex) | LS Means (Wyeth-Ayerst) | T/R | 90% Confid. Interval |
|---------------------------------|-------------------|-------------------------|------|----------------------|
| AUC _{0-t} (pg*hr/mL) | 1398 | 1360 | 1.03 | 96.8; 108.8 |
| LNAUC _{0-t} | 7.19 | 7.19 | 1.01 | 95.6; 105.8 |
| AUC _{0-inf} (pg*hr/mL) | 1535 | 1493 | 1.03 | 97.5; 108.22 |
| LNAUC _{0-inf} | 7.29 | 7.28 | 1.01 | 96.1; 105.5 |
| C _{max} (pg/mL) | 150 | 141 | 1.06 | 96.7; 115.7 |
| LNC _{max} | 4.94 | 4.92 | 1.02 | 94.5; 110.0 |

Table 8

Statistical Analysis -- LNG -- High Dose Study

| Parameter | LS Means (SYNTEX) | LS Means (Wyeth-Ayerst) | T/R | 90% Confid. Interval |
|---------------------------------|-------------------|-------------------------|------|----------------------|
| AUC _{0-t} (ng*hr/mL) | 69.7 | 72.1 | 0.97 | 90.1; 103.3 |
| LNAUC _{0-t} | 4.14 | 4.18 | 0.96 | 90.0; 101.7 |
| AUC _{0-inf} (ng*hr/mL) | 82.5 | 87.0 | 0.95 | 89.1; 100.6 |
| LNAUC _{0-inf} | 4.31 | 4.37 | 0.94 | 88.7; 99.9 |
| C _{max} (ng/mL) | 6.37 | 6.50 | 0.98 | 92.7; 103.3 |
| LNC _{max} | 1.79 | 1.82 | 0.97 | 91.6; 103.1 |

2. Three (3) of the 12 high dose tablets tested had dissolution results less than Q, but none was less than Q —. This is acceptable according to the Acceptance Table of Dissolution in USP 23, p. 1793.

Waiver Request for Phase 2 Tablet (Mid-Dose 0.075 mg LNG/0.040 mg EE):

The firm is requesting a waiver of in vivo bioavailability study for the firm's mid-dose LNG/EE tablet, 0.075 mg/0.040 mg, based on the results of bioequivalence studies conducted above on both low dose and high dose tablets. The comparative formulations of all 3 strengths of products are listed below in Table 11.

Table 11: Comparative Formulations of Low, Mid and High Dose Tablets Manufactured by Syntex Inc.

| <u>Ingredient</u> | <u>Weight Per Tablet (mg)</u> | | |
|---------------------------|-------------------------------|-----------|-----------|
| | Low Dose | Mid Dose | High Dose |
| Levonorgestrel | 0.05 | 0.075 | 0.125 |
| Ethinyl Estradiol | 0.03 | 0.04 | 0.03 |
| Lactose, H ₂ O | — | — | — |
| Providone | — | — | — |
| Starch (Corn) | — | — | — |
| FD&C Blue #1 | — | — | — |
| FD&C Red #40 | — | — | — |
| Magnesium Stearate | — | — | — |
| Total Tablet Weight | 100.00 mg | 100.00 mg | 100.00 mg |

The firm has submitted dissolution data on its mid-dose LNG/EE 0.075/0.040 mg Tablet, lot #3816-007-12056, compared to the reference product, Triphasil Phase 2 Tablet, lot #3816-007-12059. The method and results are presented in Table 12.

4. The waiver in vivo bioequivalence study for the mid dose tablet can not be granted until the results of both bioequivalence studies on the low and high dose tablets are found acceptable by the Division of Bioequivalence.

Deficiencies:

1. The firm should provide the frame size of all subjects in both studies.
2. The firm should submit the validation information for the lowest quantitation limit of the assay methodology.
3. The firm should provide the concentration range and the results of all standard curves performed during the analysis of study samples.
4. The firm should provide the acceptance criteria for the results of standard curves and QC samples.
5. The firm should clarify the subject number whose plasma sample at 0.5 hour, period 1, low dose study, was lost during analytical process.

Recommendation:

1. The bioequivalence studies conducted by Syntex, Inc. on its Levonorgestral/Ethinyl Estradiol tablets, 0.050 mg/ 0.030 mg and 0.125 mg/0.030 mg, batch #3816-007-12055 and #3816-007-12057 respectively, comparing them to Triphasil^R 0.050 mg/0.030 mg and 0.125 mg/0.030 mg respectively, have been found incomplete due deficiencies stated above.
2. The waiver of in vivo bioequivalence study requirement for the firm's Levonorgestrel/Ethinyl Estradiol tablet, 0.075 mg/ 0.040 mg, can not be granted until both bioequivalence studies have been found acceptable by the Division of Bioequivalence.
3. The dissolution testings conducted by Syntex Inc. on all three strengths of the test products, batch #3816-007-12055, #3816-007-12056 and #3816-007-12057, are acceptable. The dissolution testings should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of 5 ppm polysorbate solution in water at 37°C using USP XXIII apparatus 2 at 75 rpm. The test products should meet the following specifications:

"not less than —, and not less than ~ of the labeled amount of both of both levonorgestrel and ethinyl estradiol in the dosage form are dissolved in 30 minutes, and 60 minutes respectively."

The above recommendation and deficiencies should be forwarded to the firm.

ISI
Lin-whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED RMHATRE
FT INITIALED RMHATRE

ISI

RAM

Concur:

ISI

Date:

2/28/95

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA 74-538 (original, duplicate), HFD-600 (Hare), HFD-630, HFC-130 (JAllen), HFD-344 (CViswanathan), HFD-652 (Mhatre, Chuang), Drug File, Division File

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-538

**ADMINISTRATIVE
DOCUMENTS**

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

ANDA Number: 74-538 Date of Submission: November 21, 1996

Applicant's Name: G.D. Searle & Co.

Proprietary Name: Trivora[®] - 21 Tablets and Trivora[®]
- 28 Tablets

Established Name: Levonorgestrel and Ethinyl Estradiol
Tablets USP,
0.05 mg/0.03 mg, 0.075 mg/0.04 mg,
0.125 mg/0.03 mg

Labeling Deficiencies:

1. BLISTER PACK CONTAINER (1 x 21 and 1 x 28)

Satisfactory in final print.

2. STICKER AND BLISTER CARD (1 x 21 and 1 x 28)

The directions in step 1 allow for a "day 1" start only. Revise so the "Sunday start" directions are also included.

3. CARTON (6 x 21 or 6 x 28 tablets)

Satisfactory in final print.

4. INSERT

- I. BRIEF SUMMARY INSERT

Satisfactory in draft.

- II. DETAILED PATIENT LABELING INSERT

Satisfactory in draft.

- III. PHYSICIAN INSERT

Satisfactory in draft.

Please revise your sticker and blister card labels as instructed above, and submit final printed sticker and blister card container labels, brief summary, detailed patient and professional insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

Do you have 12 Final Printed Labels and Labeling? Yes

Blister Pack Container: November 21, 1996 (21s and 28s)

Sticker and Blister Card:

Carton Labeling: November 21, 1996 (6 x 21 or 6 x 28).

Brief Patient Summary Insert Labeling:

Professional Package Insert Labeling:

Detailed Patient Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Triphasil[®]

NDA Number: 19-190 (21) and 19-192 (28)

NDA Drug Name: Triphasil[®] -21 or Triphasil[®] - 28 Tablets

NDA Firm: Wyeth Laboratories

However, this insert was based on the labeling of NDA 18-977/S-019 - Tri-Norinyl[®]; Approved August 30, 1995; Revised April 1995. Syntex See FTR.

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Approved Tri-Norinyl[®] labeling in file folder.

Basis of Approval for the Carton Labeling: Approved Tri-Norinyl[®] carton labeling.

Other Comments: See FTR regarding model.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

| Established Name | Yes | No | N.A. |
|---|-----|----|------|
| Different name than on acceptance to file letter? | | X | |
| Is this product a USP item? If so, USP supplement in which verification was assured. USP 23 | X | | |
| Is this name different than that used in the Orange Book? | | X | |

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

| | | | |
|--|--|---|---|
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |
| Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? | | X | |
| Do any of the inactives differ in concentration for this route of administration? | | X | |
| Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? | | X | |
| Is there a discrepancy in inactives between DESCRIPTION and the composition statement? | | X | |
| Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported? | | X | |
| Failure to list the coloring agents if the composition statement lists e.g., Opacoda, Opaspray? | | | X |
| Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION? | | | X |
| Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) | | | X |
| USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) | | | |
| Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? | | X | |
| 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. | | | |

FOR THE RECORD:

1. This review was based on the Labeling of Tri-Norinyl 21 & 28 day Tablets (Syntex; Approved August 30, 1995; Revised April 1995).
2. The RLD for this drug product is Tri-phasil (Wyeth). This firm modeled their labeling after Tri-Norinyl (Syntex). After discussion with Yana Mille it was determined this was acceptable. Yana gave me some background information on the labeling of BCP's. If a generic firm has an NDA approved for another birth control product and wanted to market a different generic product, it was determined that the generic firm could use their NDA's labeling for the generic. She explained that even though there is a class labeling guidance for these drug products, a majority of times the NDA's add much more information in order to not be sued. This information is approved in new drugs. However, each company differs in the amount of

information they submit in the labeling and in turn the labeling is not consistent for all birth control products. It would not be fair to a company who has an NDA with all this information in it to not be able to use it in their generic insert because the RLD does not have the same information in it. The DOSAGE AND ADMINISTRATION must remain the same for the type of dosing regimen.

3. Patent/Exclusivities

There are no patents or exclusivities listed in the 16th edition of the Orange Book or supplement nine.

4. Storage/Dispensing Recommendations

USP: Preserve in well closed containers.

NDA: Store at controlled room temperature 15° - 30° C (59° - 86° F).

ANDA: Store at controlled room temperature 15° - 30° C (59° - 86° F).

5. Product Line

The innovator packages this product in 21 or 28 day cycle packs. The generic is proposing the same packaging size.

6. All inactives are listed in the DESCRIPTION section of the labeling. See pages 1337, 1406, 1474 and 1546.1.

Date of Review: December 16, 1996

Date of Submission: November 21, 1996
Minor Amendment/3rd cycle/Draft

Primary Reviewer:

|S|

Date: 12/16/96

Secondary Reviewer:

|S|

Date: 12/17/96

Team Leader:

|S|

Date: 12/17/96

CC:

ANDA 74-538
DUP/DIVISION FILE
HFD-613/CHolquist/AVezza/JGrace (no cc)
njg/12/17/96/x:\new\firmnsz\ltrs&rev\searle\74538na3.1
Review

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

| | | | |
|--|--|-----------------------------|---|
| REQUEST TYPE <i>(Check One)</i> <input type="checkbox"/> Original <input checked="" type="checkbox"/> FollowUp <input type="checkbox"/> FUR | DATE December 20, 1996 | PHONE NO. (301) 594-0370 | EER ID # |
| REQUESTORS NAME: M.Shaikh/S.O'Keefe | DIVISION: Office of Generic Drugs | | MAIL CODE: HFD-625 |
| APPLICATION AND SUPPLEMENT NUMBER: ANDA 74-538 | | | |
| BRAND NAME: | ESTABLISHED NAME: Levonorgestrel and Ethinyl Estradiol Tablets USP | | |
| DOSAGE STRENGTH: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg 21 and 28 day | | | STERILE <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| PROFILE CLASS:: TCM | PRIORITY CLASSIFICATION <i>(See SMG CDER-4820.3)</i> | | |
| APPLICANT'S NAME: Syntex (F.P.) Inc. | | | |
| APPLICANT'S ADDRESS: 3401 Hillview Avenue, M/S S1-200 Palo Alto, California 94304 | | | |
| COMMENTS : FUR and addition of an alternate packaging and testing facility (No. 5.) | | | |

FACILITIES TO BE EVALUATED

(Name and Complete Address)

| | RESPONSIBILITY | DMF NUMBER/ PROFILE CODE | FKEY CIRTS ID | HFD-324 USE ONLY | |
|--|--|-----------------------------|------------------|------------------|--|
| | | | | | |
| 1. Syntex S.A. de C.V., Division Quimica Km. 4 Carretera Federal Cuernavaca-Cuautla 62500 Jiutepec, Morelos MEXICO | Manufacturer of Drug Substance | CCS | | | |
| 2. _____ | _____ | CCS | | | |
| 3. Syntex (F.P.) Inc. Bo. Mariana Rd. 909, Km. 1.1 Humacao, Puerto Rico 00791 | Manufacturer of Drug Product | NEC | | | |
| 4. Syntex Research 3401 Hillview Avenue Palo Alto, California 94304 | Testing Facility | NEC | | | |
| 5. Searle & Co. <i>WD 2/14/97 Amend</i> State Road Highway 189, KM. 2.0 Caguas, PR 00725 <i>OC notified by EHA</i> | Alternate final packaging, labeling, stability testing for DP | NEC | | | |

| | | |
|--------------------------|------------------------|---------------|
| FOR HFD-324 USE ONLY: | CSD | DATE RECEIVED |
| | CGMP COMPLIANCE STATUS | DATE |

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.
cc: ANDA 74-538 HFD-625/Div File

x:\wpfile\eerforms\74538

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

Date of Review: July 8, 1996

Date of Submission: June 10, 1996

Primary Reviewer: Carol Holquist

Secondary Reviewer: Adolph Vezza

ANDA Number: 74-538

Review Cycle: 2 - Draft

Applicant's Name [as seen on 356(h)]: G. D. Searle & Co.

Manufacturer's Name (If different than applicant): Syntex
(F.P.)
Inc.

Proprietary Name: Trivora™ - 21 Tablets and Trivora™ - 28
Tablets

Established Name: Levonorgestrel and Ethinyl Estradiol Tablets
USP, 0.05 mg/0.03 mg, 0.075 mg/0.04 mg,
0.125 mg/0.03 mg

**LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE
CHEMISTRY COMMENTS TO THE FIRM:**

B. LABELING DEFICIENCIES

1. BLISTER PACK CONTAINER (1 x 21 and 1 x 28)

a. Include the STD warning statement.

b. If space permits include the "Usual Dosage"
statement.

2. STICKER AND BLISTER CARD (1 x 21 and 1 x 28)

Satisfactory in draft.

3. CARTON 6 Blisters (21 or 28 tablets) and 6 Tablet
Dispensers

Satisfactory in draft.

4. INSERT

I. BRIEF SUMMARY INSERT

- a. Delete the last sentence of the fourth paragraph after the boxed warning.

b.

II. DETAILED PATIENT LABELING INSERT

- a. INTRODUCTION - Revise the first sentence to read:

...contraceptives (the birth control pill or the pill)...

- b. EFFECTIVENESS OF ORAL CONTRACEPTIVES

- i. Revise paragraph one to read:

Oral contraceptives or "_____"
_____ are used to prevent pregnancycontrol. When they are taken correctly, _____

Typical...

- ii. Table - Insert the following text above "Adapted with permission as follows:



Adapted...

- c. WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES - Revise the first paragraph after the boxed warning to read:

...stroke.

- Blood clots in the legs

iii. Number 5 - Insert the following text as the title:

Sexually transmitted diseases

i.

ii

j.

...may provide information

III. PHYSICIAN INSERT

Revise this insert to be in accord with the enclosed Labeling Guidance Text For Combination Oral Contraceptives Prescribing Information (PI) Physician Labeling; Revised August 1994.

Please revise your labels and labeling, as instructed above, and submit final printed blister stickers and blister card, blister pack labels and carton labeling and draft insert labeling. 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. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

Do you have 12 Final Printed Labels and Labeling? Yes

Blister Stickers and Card:

Blister cards:

Carton Labeling:

Professional Package Insert Labeling:

Detailed Patient Package Insert Labeling:

Brief Summary Patient Package Insert:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Triphasil

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance?
No, but on class labeling guidance from NDA.

If yes, give date of labeling guidance:

August 1994

Basis of Approval for the Container Labels:

Basis of Approval for the Carton Labeling:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

| 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 | | | |
| <i>PROPRIETARY NAME</i> | | | |
| Has the firm proposed a proprietary name? If yes, complete this subsection. | X | | |
| Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? | | X | |

| | | | |
|---|------------|-----------|-------------|
| Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? | | X | |
| <i>PACKAGING</i> -See applicant's packaging configuration in FTR | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | | X | |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | X | |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | X | |
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | X | | |
| Are there any other safety concerns? | | X | |
| <i>LABELING</i> | | | |
| 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 | |
| Error Prevention Analysis: LABELING (Continued) | Yes | No | N.A. |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | X | |
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | X | |
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | X | |
| Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR | | | |
| Is the scoring configuration different than the RLD? | | X | |
| Has the firm failed to describe the scoring in the HOW SUPPLIED section? | | X | |
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |

| | | | |
|---|--|---|---|
| Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? | | X | |
| Do any of the inactives differ in concentration for this route of administration? | | X | |
| Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)? | | X | |
| Is there a discrepancy in inactives between DESCRIPTION and the composition statement? | | X | |
| Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported? | | X | |
| Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray? | | X | |
| Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION? | | | X |
| Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed) | | | X |
| USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations) | | | |
| Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable? | | X | |
| Does USP have labeling recommendations? If any, does ANDA meet them? | | X | |
| Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container? | | X | |
| Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling. | | X | |
| Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable) | | | |
| Insert labeling references a food effect or a no-effect? If so, was a food study done? | | X | |
| Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why. | | X | |
| Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state. | | | |

NOTES/QUESTIONS TO THE CHEMIST:

Enclose Labeling Guidance with the chemistry letter.

FOR THE RECORD:

1. This review was based on the Labeling Guidance Text For Combination Oral Contraceptives Prescribing Information (PI); Revised August 1994.
2. Patent/Exclusivities
There are no patents or exclusivities listed in the 16th edition of the Orange Book or supplement five.
3. Storage/Dispensing Recommendations

USP: Preserve in well closed containers.

NDA: Store at controlled room temperature 15° - 30° C
(59° - 86° F).

ANDA: Store at controlled room temperature 15° -
30° C (59° - 86° F).

4. Product Line

The innovator packages this product in 21 or 28 day
cycle packs. The generic is proposing the same
packaging size.

5. All inactives are listed in the DESCRIPTION section of
the labeling. See pages 1337, 1406, 1474 and 1546.

ISI
Primary Reviewer

7/24/96
Date

ISI
Acting Team Leader
Labeling Review Branch

7/24/96
Date

cc:

ANDA 74-538
Dup/Division File
HFD-613/CHolquist/AVezza (no cc)
njg/7/24/96/firmsnz/searle/ltrs&rev/74538NA2.L
Review

Enclose Labeling Guidance

SYNTEX
3401 HILLVIEW AVE
PALO ALTO

CA 94303

ANDA #: N074538

Dear Sir/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 for the following:

NAME OF DRUG:

LEVONORGESTREL; ETHINYL ESTRADIOL

Dosage Form: TAB Potency: TRIPHASIC 21; 28 DAY

USP:

DATE OF APPLICATION: 19-AUG-94

7x 0.05 mg / 0.03 mg
7x 0.75 mg / 0.04 mg
7x 0.125 mg / 0.3 mg - 21 day

DATE OF RECEIPT: 25-AUG-94

7x 0.05 mg / 0.03 mg
7x 0.75 mg / 0.04 mg 7x 0.125 mg / 0.03 mg
7x Placebo 28 day

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

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the ~~analytical methods~~ and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

If the above methodology is not submitted, the review of the application will be delayed.

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

Sincerely yours,

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Smela
Randon II
HFD - 625
Refused
file 505(j)(2)(A)
KK
8/26/94

MEMO OF TELCON

DATE: August 16, 1994

BETWEEN: Tracy Lin/Syntex (415-354-2286)

SUBJECT: Combining 21 day and 28 day birth control (BC) tablets
in one application or separate applications

-Background: Syntex was preparing an ANDA for a 21 day & 28 day BC product to be combined in one application. The firm wanted confirmation that one application would be acceptable. There were several phone calls with Ms Lin pressing for a definitive answer. PPG #20-90 does not spell out a definitive answer for combining the 21 day and the 28 day products. The intent of PPG #20-90 is to combine similar tablet products into a single application. The Orange Book lists examples of birth control products with one and two applications for the 21 and 28 day products. Conversations with HFD-510 offered no additional insight. OGD labeling people had no objections for one application. OGD chemists also saw no problems with combining both packaging into one application.

In my final telephone conversation of August 16, 1994 with concurrence with Gordon, I told the firm that it appears that one application is acceptable, however OGD reserves the right to change its decision if new information comes to light once the application is submitted.

-Please note the application was submitted as one application and was accepted.

Harvey Greenberg
May 12, 1995

(This a summary from my telephone log and Syntex file regarding 21 and 28 day BC tablets in one application)

bcpills.tel

Redacted 3

pages of trade

secret and /or

confidential

commercial

information

REVIEW OF PROFESSIONAL LABELING #1

ANDA

DRAFT

DATE OF REVIEW: January 23, 1995

ANDA #: 74-538

NAME OF FIRM: Syntex (F.P.) Inc.

NAME OF DRUG: Trade: Trivora™-21 Tablets
Trivora™-28 Tablets

Generic: Levonorgestrel and Ethinyl
Estradiol Tablets, USP

DATE OF SUBMISSION: August 19, 1994

COMMENTS:

BLISTER PACK CONTAINER: 1 x 21 tablets and 1 x 28 tablets

There are two starting options to choose from when you begin taking birth control pills. A Day 1 (first day of the menstrual flow) or a Sunday start (Sunday after your menstrual flow begins). Your package design, with the stamped days of the week, allows for a Sunday start only. We believe this package design could be confusing to the patient. The directions instruct the patient to take the "first pill of the first pack". However, if the patient chooses the Day 1 option, she must choose the day of the week, the menstrual flow begins (not necessarily Sunday) and continue through the cycle not receiving all 21 or 28 tablets. We believe stickers should be available to place over the pre-printed days or propose some other type of system that will ensure the patient receives the pill on the proper day and for the proper amount of days in each phase. We refer you to the innovator's product for guidance.

CARTON: 6 Blisters (21 or 28 tablets) and 6 Tablet Dispensers

1. "Usual Dosage" rather than _____
2. Delete " _____ This information appears in the Usual Dosage statement.
3. Revise your carton contents statement as follows:

6 Blisters containing 21 (or 28) tablets each and 6
Tablet Dispensers

AUXILIARY LABEL: Satisfactory in draft.

INSERT:

GENERAL COMMENTS

1. The model you have used in your side-by-side comparison is not the most currently approved innovator's labeling. There are numerous changes needed throughout the text of your insert. Please refer to Triphasil®-21 [Wyeth Laboratories Inc; Approved April 20, 1994; Revised September 15, 1993 (professional labeling); Revised June 1, 1993, (patient labeling)] for guidance.

In addition, to the above changes please note the following:

2. Revise your subsection headings so that they do not appear to have the same prominence as the section headings.
3. Inactive ingredients, lactose - Please note that there are two USP/NF monographs for lactose. Please revise accordingly.
4. Please include the molecular weight and formula of each active ingredient in the DESCRIPTION section.

RECOMMENDATIONS:

1. Inform the firm of the above comments.
2. Request the firm revise their blister tablet container labels, carton, package insert, and patient labeling, then prepare and submit final printed container and auxiliary labels and carton labeling and draft professional and patient labeling.

FOR THE RECORD:

1. We have asked the firm to start over and submit new professional and patient insert labeling. Review revealed extensive changes needed.
2. Upon resubmission, the review will be based on Triphasil® -21 Approved April 20, 1994.

NOTE: Carol Zimmermann REVIEWED THIS DOCUMENT - FOR THIS REVIEW ONLY

Adolph Vezza

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: November 4, 1994

FROM: Cecelia Parise
CSO, RSB

SUBJECT: Random Assignment

TO: The Record
ANDA 74-453

This is an application for a drug product with a strength of 1 mg or less. Usually, our policy states that these drug products are assigned directly to Steve Sherken. However, since M. Shaikh reviewed a related application before this policy was in effect, the application will be assigned to Random II and the Branch Chief will assign the application to the appropriate reviewer.

*Mr. Shaikh has renewed ANDAs
for the same drug / dosage form /
applicant and is assigned this
ANDA pursuant to OGD
random assignment exceptions.
PSI, 1/3/95*

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: September 28, 1995
FROM: Bill Russell, CSO, RSB
SUBJ: Telecon
TO: ANDAs 74-538 and 73-597

I spoke with Donna Helms at Searle to request in-date 356h's for these applications.

I also spoke with Lynn Hansen at Syntex to request in-date 356h's with original signatures. Also I requested her to revise the letter transferring 74-538 dated August 31, 1995, using Syntex USA letterhead and original signatures. I also requested they include an explanation why the letter for 74-538 was signed by Dan Zabrowski instead of the designated agent, Katy Morton. I was told Katy was no longer with the firm and suggested they include that information.

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: 5/9/96
FROM: Bill Russell, CSO, RSB
SUBJECT: Telecon
TO: ANDA 74-538

I spoke with Doran Frano who will investigate and get back to me.

5/13: Doran says they should have the data soon. She'll have a conference tomorrow to get a definite date and get back with us.

5/15 - Doran called back to say they'll commit to respond within 30 days or w/d.

Jason

Levonorgestrel/Ethinyl Estradiol,
Trivora™, Triphasic Regimen
0.050 mg / 0.030 mg
0.075 mg / 0.040 mg
mg
ANDA #74-538
Reviewer: L. Chuang

Searl

Slokie, IL
Submission Date:
November 30, 1995

Please request the
info for us.
0.125 mg / 0.030

Thank,

YCH
4/4/96

The following items are required for completion of the review:

1. Results of standard curves from all assays, including means and CV.
2. Clarification of QC concentrations, whether they are _____ (they were shown differently in the original submission and in the amendment).
3. Medical records/case reports and clinical records (entrance screening, post-study examination, etc.)

These information can either be faxed to the firm or requested by telephone.

~~Add SAS data format for their future submission~~

Scott
P. Searl

review, and the clock will be restarted.

**APPEARS THIS WAY
ON ORIGINAL**

CDEK Establishment Evaluation Report
for November 03, 1997

Application: ANDA 74538/000
Stamp: 25-AUG-1994 Regulatory Due:
Applicant: SEARLE
4901 SEARLE PKY
SKOKIE, IL 60077

Priority: Org Code: 600
Action Goal: District Goal: 25-OCT-1995
Brand Name:
Established Name: LEVONORGESTREL; ETHINYL
ESTRADIOL
Generic Name:
Dosage Form: TAB (TABLET)
Strength: TRIPHASIC 21; 28 DAY

FDA Contacts: J. WILSON III (HFD-617) 301-827-5848 , Project Manager
M. SHAIKH (HFD-625) 301-827-5848 , Review Chemist
S. OKEEFE (HFD-617) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 28-OCT-1997 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 08-SEP-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____

DMF No: _____
AADA No: _____

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 28-OCT-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: _____

Establishment: 2623450
GD SEARLE AND CO
HWY 189 KM 2
CAGUAS, PR 00625

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-MAY-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY
TESTER

Establishment: 2650097
SYNTEX FP INC
BO MARIANA RD 909 KM 1.1
HUMACAO, PR 00661

DMF No:
AADA No:

Profile: TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION

Responsibilities: FINISHED DOSAGE
MANUFACTURER

CDER Establishment Evaluation Report
for November 03, 1997

Milestone Date: **05-MAY-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **2911044**
SYNTEX INC / OREAD LABS
3401 HILLVIEW AVENUE
PALO ALTO, CA 94304

DMF No:
AADA No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **17-JAN-1997**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE RELEASE
TESTER**

Establishment: **9610327**
SYNTEX SA

DMF No:
AADA No:

62000 CUERNAVACA, MORELOS, , M

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **21-AUG-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE
MANUFACTURER**

APPROVAL SUMMARY PACKAGE

ANDA NUMBER: 74-538

FIRM: G. D. Searle & Co,

DOSAGE FORM: Tablet

STRENGTH: 21 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; and
0.125 mg/0.03 mg
28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125
mg/0.03 mg plus placebo.

DRUG: Levonorgestrel and Ethinyl Estradiol Tablet USP
Trivora-21 and Trivora-28 Tablets

cGMP STATEMENT/EIR UPDATED STATUS:

EER submitted on 11-3-97 for all the facilities listed in Section # 33 of CR # 5 is acceptable per Egas on 10-28-97.

BIO STUDY:

Acceptable per bio letter to the firm dated 2-24-97.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not required.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?

Containers used in the stability studies are identical to those listed in container section.

Expiration dating period of 24 months for the drug product is acceptable based on the stability data for the exhibit batches generated at CRT and under accelerated stability conditions.

LABELING:

Satisfactory per C. Holquist's review completed on 3-5-97.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.):

Levonorgestrel/Ethinyl Estradiol
0.05 mg/0.03 mg - lot # 18678; Size: _____ tablets).
0.075 mg/0.04 mg - lot # 98679; Size: _____ tablets).
0.125 mg/0.03 mg - lot # 38680; Size: _____ tablets).

Placebo: lot # 57454; Size: _____ tablets).

NDS Source:

Referenced DMF _____ for Syntex Corporation was found adequate per M. Shaikh's review completed on 1-11-95. This DMF remains adequate after review of 4-25-97 amendment. This reviewer completed the review on 12-11-97.

Referenced DMF _____ is adequate per M. Shaikh's review dated 12-4-97.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA SAME PROCESS?)

Size of bio/stability Batch:

Levonorgestrel/Ethinyl estradiol

0.05 mg/0.03 mg - lot # 18678; Size: _____ tablets).

0.075 mg/0.04 mg - lot # 98679; Size: _____ tablets).

0.125 mg/0.03 mg - lot # 38680; Size: _____ tablets).

Placebo: lot # 57454; Size: _____ tablets).

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

Production batch size post-approval of the application is _____ Tablets) for each color tablet and for the placebo tablets.

Manufacturing process for intended production size batch is same as used for the stability batch except for tooling for which a pre-market commitment has been made.

cc: ANDA 74-538
Division File
Field Copy

Endorsements:

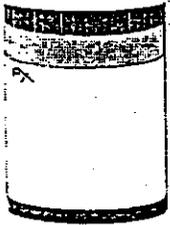
HFD-625/M.Shaikh/12-11-97

HFD-625/M.Smela/12-11-97

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F/T by:

75/ 12/11/97
15/ 12/11/97

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

Date: 18 December 1997

TO: DORANNE FRANCO -8152

Phone: (847) 982-7691 Fax: (847) 982-8090

From: Bob West

Phone: (301) 827-~~5846~~ 5841 Fax: (301) 443-3847

Number of Pages: 3
(Including Cover Sheet)

Comments: Copy of Approval letter - TRIVORA-21
and Trivora-28

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CDER Establishment Evaluation Report
for December 14, 1997

Application: **ANDA 74538/000**
Stamp: **25-AUG-1994** Regulatory Due:
Applicant: **SEARLE**
4901 SEARLE PKY
SKOKIE, IL 60077

Priority: _____ Org Code: **600**
Action Goal: _____ District Goal: **25-OCT-1995**
Brand Name: _____
Established Name: **LEVONORGESTREL; ETHINYL ES**
Generic Name: _____
Dosage Form: **TAB (TABLET)**
Strength: **TRIPHASIC 21; 28 DAY**

FDA Contacts: **J. WILSON III (HFD-617) 301-827-5848 , Project Manager**
M. SHAIKH (HFD-625) 301-827-5848 , Review Chemist
S. OKEEFE (HFD-617) 301-827-5848 , Team Leader

Overall Recommendation:

ACCEPTABLE on 28-OCT-1997 by M. EGAS (HFD-322) 301-594-0095
WITHHOLD on 08-SEP-1997 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: _____ MF No: _____

_____ AADA No: _____

Profile: **CSN** OAI Status: **NONE** Responsibilities: _____
Last Milestone: **OC RECOMMENDAT 28-OCT-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **2623450** DMF No: _____
GD SEARLE AND CO
HWY 189 KM 2 AADA No: _____
CAGUAS, PR 00625

Profile: **TCM** OAI Status: **NONE** Responsibilities: _____
Last Milestone: **OC RECOMMENDAT 05-MAY-1997** **FINISHED DOSAGE PACKAGER**
Decision: **ACCEPTABLE** **FINISHED DOSAGE STABILITY TESTER**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **2650097** DMF No: _____
SYNTEX FP INC
BO MARIANA RD 909 KM 1.1 AADA No: _____
HUMACAO, PR 00661

Profile: **TCM** OAI Status: **NONE** Responsibilities: _____
Last Milestone: **OC RECOMMENDAT 05-MAY-1997** **FINISHED DOSAGE MANUFACTURER**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **2911044** DMF No: _____

CDER Establishment Evaluation Report
for December 14, 1997

Page 2 of 2

2911044
SYNTEX INC / OREAD LABS
3401 HILLVIEW AVENUE
PALO ALTO, CA 94304

AADA No:

Responsibilities:

FINISHED DOSAGE RELEASE TESTER

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDAT 17-JAN-1997
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: 9610327
SYNTEX SA

62000 CUERNAVACA, MORELOS,,

DMF No: _____

AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDAT 21-AUG-1997
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities:

DRUG SUBSTANCE MANUFACTURER

**APPEARS THIS WAY
ON ORIGINAL**

**CENTER FOR DRUG
EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

74-538

CORRESPONDENCE

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

October 24, 1997

Douglas Sporn, MD
Office of Generic Drugs
Center for Drug Evaluation and Research (HFD-600)
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

SEARLE

AMENDMENT

RE: ANDA 74-538
Trivora® (levonorgestrel and
ethinyl estradiol tablets USP)
Triphasic Regimen
MINOR AMENDMENT

N/AM

Dear Mr. Sporn:

In accordance with 21 CFR 314.120 and in response to your letter of September 22, 1997, G.D. Searle and Co. hereby submits a MINOR AMENDMENT to the above mentioned ANDA.

Searle has been notified by ~~_____~~ at the cGMP-related deficiencies associated with the ~~_____~~ have been corrected.

If you have any questions regarding this matter, please do not hesitate to contact me.

Sincerely,



Doranne Frano
Associate Director
Regulatory Affairs
(847) 982-7691
(847) 982-8090 (fax)

DF/sai ANDA74-538.doc

RECEIVED

OCT 27 1997

GENERIC DRUGS

Madue
10-3-97

9/5/97
1 hrs

Redacted

4

Page(s) of trade

secret and /or

confidential

commercial

information

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 708 982 7000
Fax 708 982 4701

February 25, 1997

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II (HFD-600)
7500 Standish Place
Rockville, MD 20855

SEARLE

NEW COPY
yrmw
BIOEQUIVALENT

NC BIO noted
NHT
8/12/97

RE: ANDA #74-538
Trivora®
(levonorgestrel and
ethinyl estradiol
tablets, USP)
triphasic regimen

PHONE REQUEST

Dear Mr. Sporn:

Per a phone request from Ms. Lizzie Sanchez enclosed are the Case Report Forms for the Trivora Bioequivalence Study LAB 32-6106 (High Dose).

If you have any questions regarding this matter, please do not hesitate to contact me.

Sincerely,

for *Quita Piergiovanni*
Doranne Frano
Regulatory Affairs
(847) 982-7691
(847) 982-8090 fax

DF/j
trivora2.feb

RECEIVED
FEB 26 1997
GENERIC DRUGS

Nadine
3-5-97

Searle
Box 5110
Chicago, Illinois 60680-5110
Telephone 847 982 7000
Fax 847 470 1480

BIDENABILITY

February 20, 1997

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II (HFD-600)
7500 Standish Place
Rockville, MD 20855

SEARLE

RE: ANDA #74-538
Trivora®
(levonorgestrel and
ethinyl estradiol
tablets, USP)
triphasic regimen

ORIGINAL

PHONE REQUEST

Dear Mr. Sporn:

Per a phone request from Ms. Lizzie Sanchez enclosed are the Case Report Forms for the Trivora Bioequivalence Study LAB 30-6106 (Low Dose). Searle is obtaining the requested Case Report Forms for LAB 32-6106 (High Dose), and we expect to submit them.

If you have any questions regarding this matter, please do not hesitate to contact me.

Sincerely,



Doranne Frano
Regulatory Affairs
(847) 982-7691
(847) 982-8090 fax

RECEIVED

FEB 21 1997

trivora1.feb **GENERIC DRUGS**

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

January 3, 1997

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II (HFD-600)
7500 Standish Place
Rockville, MD 20855

SEARLE

NEW CORRESP

RE: ANDA #74-538
Trivora®
(levonorgestrel and
ethinyl estradiol
tablets, USP)
triphasic regimen

Dear Mr. Sporn:

Reference is made to your letter dated December 27, 1996 regarding the above-mentioned ANDA.

G.D. Searle & Co. hereby notifies you of our intent to amend this application in accordance with 21 CFR 314.120.

If you have any questions concerning this matter, please do not hesitate to contact me.

Sincerely,



Doranne Frano
Regulatory Affairs
(847) 982-7691
(847) 982-8090 fax

trivora.jan

RECEIVED

JAN 06 1997

GENERIC DRUGS

G. D. Searle & Co.
Attention: Doranne Frano
4901 Searle Parkway
Skokie, IL 60077

DEC 27 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated August 19, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Levonorgestrel and Ethinyl Estradiol Tablets USP, 21 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; and 0.125 mg/0.03 mg and 28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg; placebo.

Reference is also made your amendments dated September 3, and November 21, 1996.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1.

batches. Please provide a commitment to submit the following information for the first commercial batch of each strength:

- Certificate of Analysis of the batch; and
- Comparative dissolution profile data for the batch vs. the ANDA exhibit batch.

Please include a statement that you will not release the drug product to the market until the requested information is reviewed and found satisfactory. We will review the data on receipt. This data should be submitted as a supplement marked "Expedited Review Requested." If you have this data, then it may be provided in lieu of the commitment.

2.



3. We have the following comments regarding the stability of the drug product.

- a. You have requested an expiration dating period of 36 months for the drug product. Please use a tentative expiration dating period of 24 months. An extension will require full term data for three production batches.
- b. Please revise your post-approval stability commitment to use storage conditions of $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60 \pm 5\% \text{RH}$, or $25 - 30^{\circ}\text{C}$.
- c. Please provide three months stability data under accelerated conditions for product packaged into the newly proposed blister film.

B. Labeling Deficiencies:

1. BLISTER PACK CONTAINER (1 x 21 and 1 x 28)

Satisfactory in final print.

2. STICKER AND BLISTER CARD (1 x 21 and 1 x 28)

The directions in step 1 allow for a "day 1" start only. Revise so the "Sunday start" directions are also included.

3. CARTON (6 x 21 or 6 x 28 tablets)

Satisfactory in final print.

4. INSERT

I. BRIEF SUMMARY INSERT

Satisfactory in draft.

II. DETAILED PATIENT LABELING INSERT

Satisfactory in draft.

III. PHYSICIAN INSERT

Satisfactory in draft.

Please revise your sticker and blister card labels as instructed above, and submit final printed sticker and blister card container labels, brief summary, detailed patient and professional insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

The CGMP compliance of the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

The file on this application is now closed. You are required to take an action described under 21 CFR 3124.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your response to this letter will be considered a MINOR AMENDMENT and should be plainly marked as such in your cover letter. Please note that if the pending bioequivalence review is not received prior to completion of the chemistry and/or labeling review of your amendment, issuance of our subsequent action letter may be delayed. Further, if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/s/ *W/22/21*
Rasmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

Labels
Am
NDA 74-538 AMENDMENT

November 21, 1996

Mr. Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II (HFD-600)
7500 Standish Place
Rockville, MD 20855

Counselor (rev)
Comp. label
C. H. Johnson
12/16/96

SEARLE

RE: ANDA #74-538
Trivora®
(levonorgestrel and
ethinyl estradiol
tablets, USP)
triphasic regimen

MINOR AMENDMENT

Dear Mr. Sporn:

In response to your letter dated October 15, 1996 and in accordance with 21 CFR 314.120, G.D. Searle & Co. hereby submits this minor amendment to the above-mentioned ANDA. Your comments are written below in italics followed by our responses.

A. Chemistry Deficiencies:

I.

[]

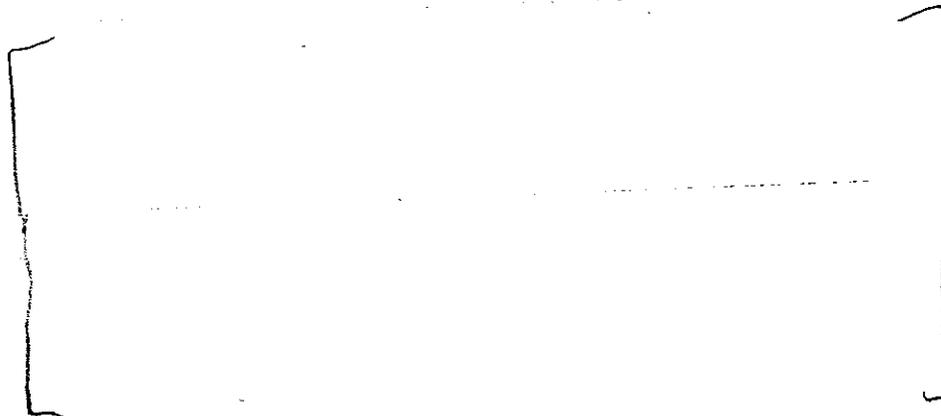
Response:

[]

Mr. Douglas Sporn
Office of Generic Drugs
November 21, 1996
Page 2

2.

Response:



B. Labeling Deficiencies:

1. BLISTER PACK CONTAINER (1 X 21 and 1 X 28)

a. *Include the STD warning statement.*

Response:

The blister container has been modified from a plastic compact to a printed foil blister pack and a cardboard pocket (envelope). This configuration is identical to the envelopes used originally when the Norethin® 1/35-21&28 ANDA 71-480 & 71-481 was marketed by G.D. Searle & Co.. An example of the Trivora packaging configuration is included in Attachment 3. Final printed copy of the Trivora blister pack foil and pocket is included in Attachment 4.

b. *If space permits include "Usual Dosage" statement.*

Response:

The "Usual Dosage" statement has been included on the Trivora pocket.

2. STICKER AND BLISTER CARD (1 X 21 and 1 X 28)

Satisfactory in draft.

Mr. Douglas Sporn
Office of Generic Drugs
November 21, 1996
Page 3

Response:

The sticker card has been modified to combine the text for 21 and 28 day instructions into one label that will be printed on the back of the sticker card.

Final printed copy of the sticker card and text is included in Attachment 5.

3. CARTON 6 Blisters (21 or 28 tablets) and 6 Tablet Dispensers

Satisfactory in draft.

Response:

The carton has been modified to G.D. Searle & Co. format and is identical to the approved carton format for Searle's Demulen, NDA 18-168. The blisters will be inserted into the Trivora pocket with all required patient labeling before being packaged into the cartons (see Attachment 3). The text copy has been revised to reflect this modified packaging configuration.

Final printed copy of the carton is included in Attachment 6.

4. INSERT

The inserts were modified as requested if the suggested change strengthened the current statements and were not in conflict with currently approved labeling for other O.C. products.

I. BRIEF SUMMARY INSERT

- a. *Delete the last sentence of the fourth paragraph after the boxed warning. [Some studies have reported an increase...]*

This change was not made, the current text is felt to be adequate.

- b. *Finally, if you are still not sure what to do about the pills you have missed: Delete numbers six thru twelve.*

The numbers 6 through 12 were deleted but the text provides information and has therefore not been deleted.

II. DETAILED PATIENT LABELING INSERT

a. INTRODUCTION - Revise the first sentence to read:

...contraceptives (the birth control pill or the pill)...

The current text is felt to be adequate.

b. EFFECTIVENESS OF ORAL CONTRACEPTIVES

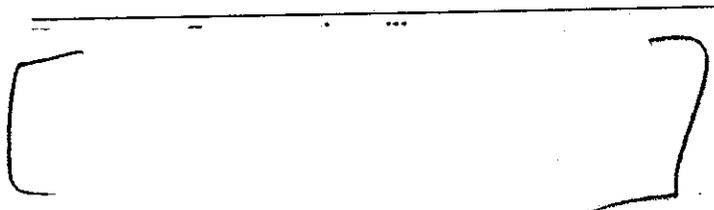
i. Revise paragraph one to read:

Oral contraceptives: _____
_____ are used to prevent pregnancy...control. When
they are taken correctly, _____

_____. Typical...

The current text is felt to be adequate.

ii. Table - Insert the following text above "Adapted with permission as follows:



Adapted...

The current text is felt to be adequate.

c. WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES -
Revise the first paragraph after the boxed warning to read:

...stroke.

- Blood clots in the legs (thrombophlebitis), lungs...

The current text is felt to be adequate.

- d. *OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES - Insert a space between the penultimate paragraph and the last item listed in paragraph one.*

A space has been added.

- e. RISKS OF TAKING ORAL CONTRACEPTIVES

- i. *Revise the first sentence of number 3 to read:*

...users probably have a...

The current text is felt to be adequate.

- ii. *Revise the title of number 5 read:*

Cancer of the reproductive organs and breasts.

In addition, revise paragraph one to read:

...should be closely followed by their doctors.

The text has been revised as suggested.

- f. ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL METHOD OR PREGNANCY, Second paragraph - *...of death was highest...*

The text has been revised as suggested.

- g. SIDE EFFECTS OF ORAL CONTRACEPTIVES

- i. *Number one - ...any serious problems it...*

The text has been revised as suggested.

- ii. *Number four - Delete "(_____)" from the title.*

The text has been revised as suggested.

h. GENERAL PRECAUTIONS

- i. *Number one - Revise the first paragraph to read:*

~~_____~~ you may not
menstruate...so. If you...instructed and missed a
menstrual period, or if you missed two..

The current text is felt to be adequate.

- ii. *Number 2 - Revise to read:*

...If possible do not use oral contraceptives, _____
~~_____~~ use another method of
contraception _____



The text has been revised as suggested.

- iii. *Number 5 - Insert the following text as the title:*

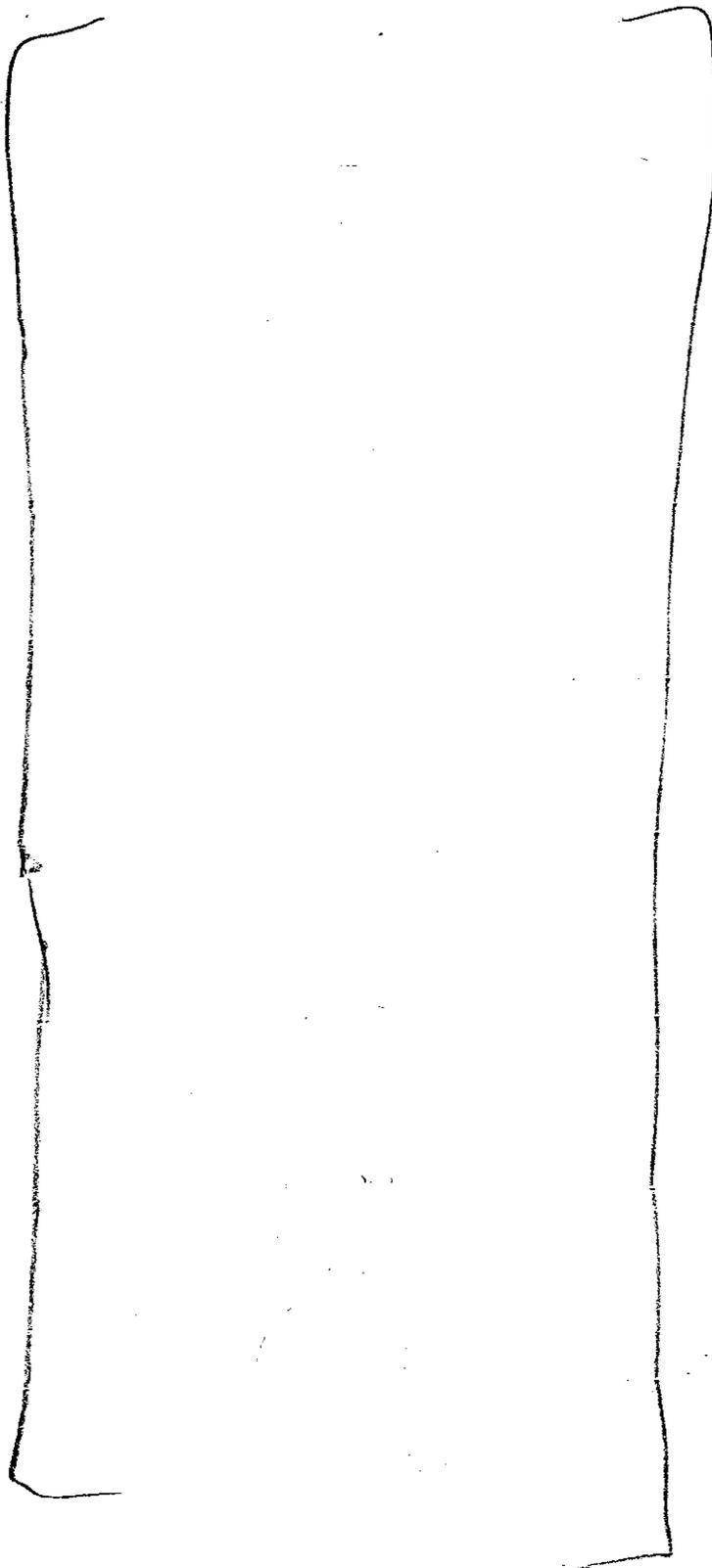
Sexually transmitted diseases

The title has been added.

i.

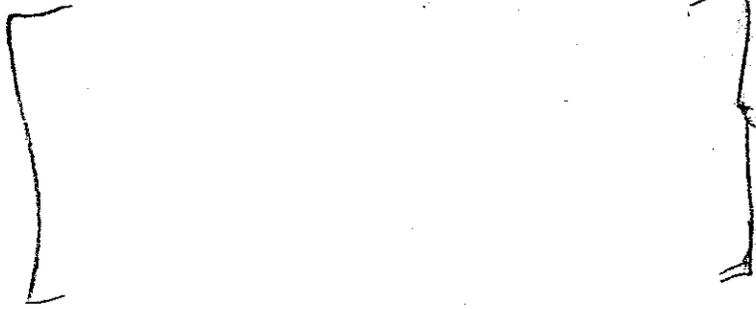


Mr. Douglas Sporn
Office of Generic Drugs
November 21, 1996
Page 7



Mr. Douglas Sporn
Office of Generic Drugs
November 21, 1996
Page 8

The paragraph has been relocated as suggested..



III. PHYSICIAN INSERT

Revise this insert to be in accord with the enclosed Labeling Guidance Text for Combination Oral Contraceptives Prescribing Information (PI) Physician Labeling; Revised August 1994.

The proposed Trivora labeling is identical to our other approved oral contraceptive products. A side-by-side comparison of the proposed Trivora inserts to the approved labeling for Tri-Norinyl NDA 18-977 and Levora ANDAs 73-592 and 73-594 has been provided in Attachment 7 for your reference. Revised Draft Physician Insert, Detailed Patient Labeling and Brief Summary of patient labeling is included in attachments 8, 9 & 10.

In addition, a side-by-side annotated comparison of the June 10, 1996 proposed labeling to the Revised Draft labeling, as requested in your Oct. 15, 1996, is included in Attachment 11.

Finally, Searle acknowledges that the cGMP compliance of the facilities referred to in our application will be evaluated by the FDA Office of Compliance and that a satisfactory evaluation is required prior to the approval of this application.

If you have any questions concerning this matter, please do not hesitate to contact me.

Sincerely,

Handwritten signature of Doranne Frano.

Doranne Frano
Regulatory Affairs
(847) 982-7691
(847) 982-8090 fax

Enc.
trivora.nov

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

November 21, 1996

Mr. Jeremiah Beckwith, Jr.
Director of Investigations
FDA San Juan District Office
Stop 8½ Fernández Juncos Avenue
Puerta de Tierra Station
San Juan, PR 00906

Re: ANDA 74-538
Trivora
(levonorgestrel and
ethinyl estradiol
tablets, USP)
triphasic regimen

SEARLE

MINOR AMENDMENT

Dear Mr. Beckwith:

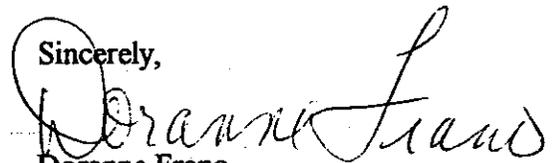
G. D. Searle & Co. hereby submits a field copy of the above-mentioned ANDA amendment dated November 22, 1996.

G.D. Searle & Co. certifies that this is true copy of the amendment submitted to FDA headquarters in Rockville, Maryland.

Please note that the packaging information for adding ~~_____~~ REPLACES the information provided in our September 3, 1996 submission. This is the only information that has changed from that submission.

If you have any questions concerning this submission, please do not hesitate to contact me.

Sincerely,



Doranne Frano
Regulatory Affairs
(847) 982-7691
(847) 982-8090 fax

RECEIVED

NOV 23 1996

cc: Office of Generic Drugs

GENERIC DRUGS

sanjuan.nov

G. D. Searle & Co.
Attention: Doranne Frano
4901 Searle Parkway
Skokie, IL 60077

OCT 15 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated August 19, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Levonorgestrel and Ethinyl Estradiol Tablets USP, 21 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; and 0.125 mg/0.03 mg and 28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg; placebo.

Reference is also made your amendments dated November 17 and 30, 1995, and May 15, June 10 and July 19, 1996.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1.

2.

Handwritten brackets on the right side of the page, corresponding to items 1 and 2. Item 1 has a large bracket that spans most of the page height. Item 2 has a smaller bracket that spans about one-third of the page height.

B. Labeling Deficiencies:

1. BLISTER PACK CONTAINER (1 x 21 and 1 x 28)
 - a. Include the STD warning statement.
 - b. If space permits include the "Usual Dosage" statement.
2. STICKER AND BLISTER CARD (1 x 21 and 1 x 28)

Satisfactory in draft.
3. CARTON 6 Blisters (21 or 28 tablets) and 6 Tablet Dispensers

Satisfactory in draft.

4. INSERT

I. BRIEF SUMMARY INSERT

- a. Delete the last sentence of the fourth paragraph after the boxed warning. [Some studies have reported an increase...]
- b. Finally, If you are still not sure what to do about the pills you have missed: Delete numbers six thru twelve.

II. DETAILED PATIENT LABELING INSERT

- a. INTRODUCTION - Revise the first sentence to read:

...contraceptives (the birth control pill or the pill)...

- b. EFFECTIVENESS OF ORAL CONTRACEPTIVES

- i. Revise paragraph one to read:

Oral contraceptives are used to prevent pregnancycontrol. When they are taken correctly,

Typical...

- ii. Table - Insert the following text above "Adapted with permission as follows:

Adapted...

- c. WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES -
Revise the first paragraph after the boxed
warning to read:
- ...stroke.
- Blood clots in the legs
(thrombophlebitis), lungs...
- d. OTHER CONSIDERATIONS BEFORE TAKING ORAL
CONTRACEPTIVES - Insert a space between the
penultimate paragraph and the last item
listed in paragraph one.
- e. RISKS OF TAKING ORAL CONTRACEPTIVES
- i. Revise the first sentence of number 3 to
read:

...users probably have a...
 - ii. Revise the title of number 5 to read:

Cancer of the reproductive organs and
breasts.

In addition, revise paragraph one to
read:

...should be closely followed by their
doctors.
- f. ESTIMATED RISK OF DEATH FROM A BIRTH CONTROL
METHOD OR PREGNANCY, Second paragraph - ...of
death was highest...
- g. SIDE EFFECTS OF ORAL CONTRACEPTIVES
- i. Number one - ...any serious problems
it...
 - ii. Number four - Delete " "
 from the title.

h. GENERAL PRECAUTIONS

- i. Number one - Revise the first paragraph to read:

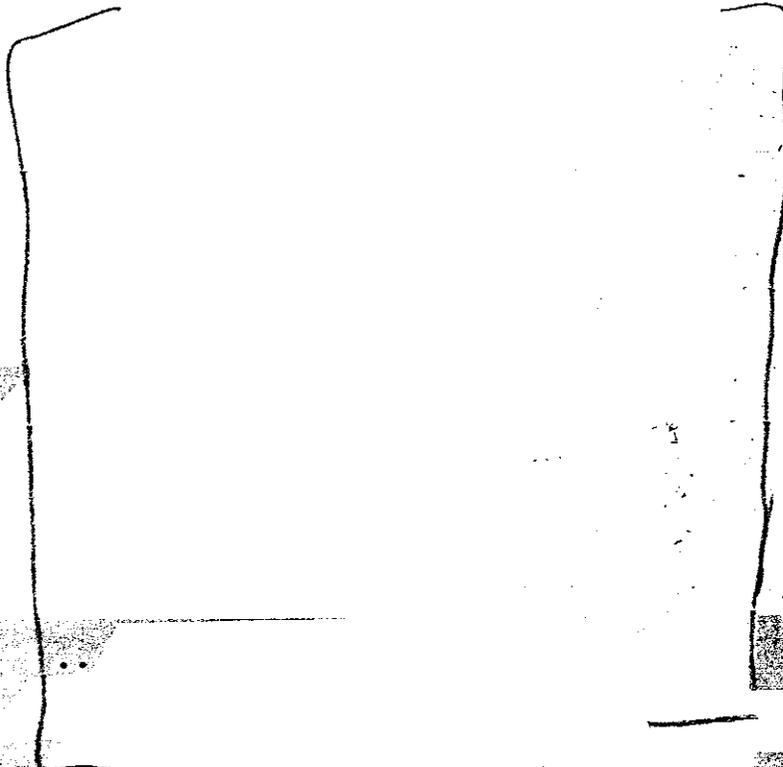
_____ when you may not menstruate...so. If you...instructed and missed a menstrual period, or if you missed two...

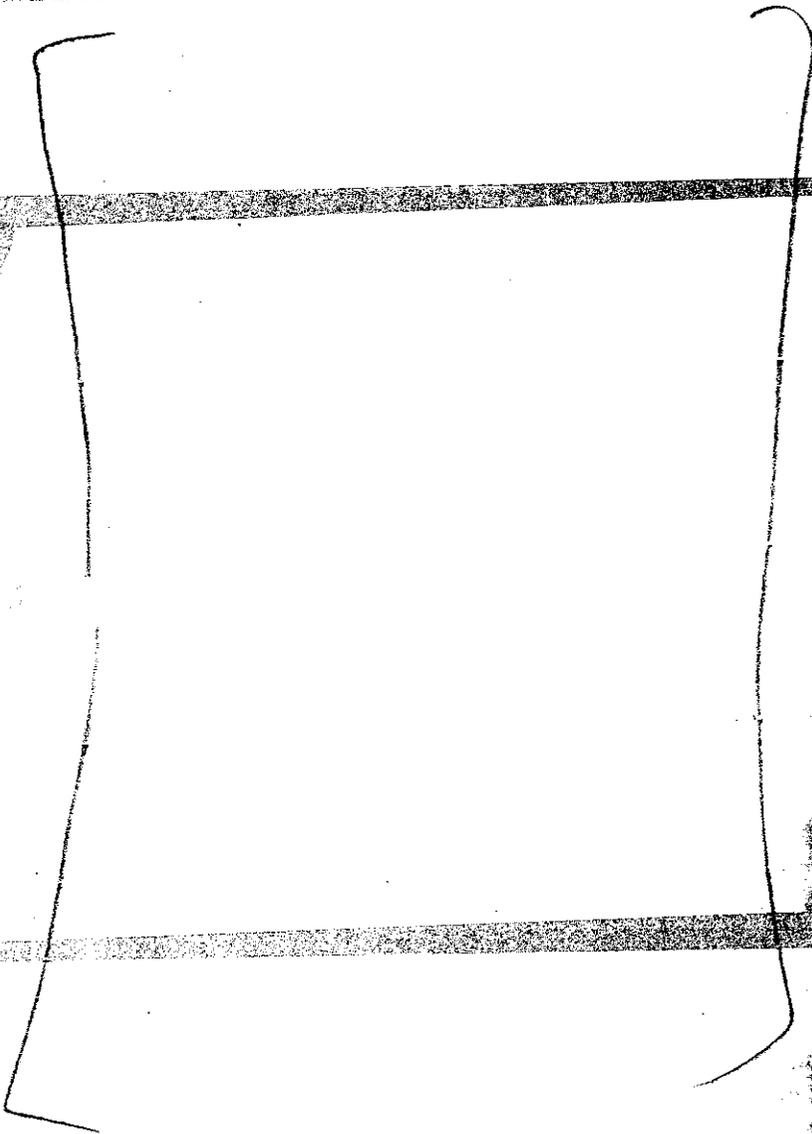
- ii. Number 2 - Revise to read:

...If possible do not use oral contraceptives
_____ use another method of contraception

- iii. Number 5 - Insert the following text as the title:

Sexually transmitted diseases





III. PHYSICIAN INSERT

Revise this insert to be in accord with the enclosed Labeling Guidance Text For Combination Oral Contraceptives Prescribing Information (PI) Physician Labeling; Revised August 1994.

Please revise your labels and labeling, as instructed above, and submit final printed blister stickers and blister card, blister pack labels and carton labeling and draft insert labeling. 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. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon

further review of the application prior to approval.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

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 the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely Yours,

RSI

10/11/96

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

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

NEW CORRESP
NC
noted NAT
JDK/ef 6/27/96

June 10, 1996

RECEIVED

JUN 12 1996

FDA San Juan District Office
Stop 8½ Fernández Juncos Avenue
Puerta de Tierra Station
San Juan, PR 00906

SEARLE

Re: ANDA 74-538 Trivora™ 21 and 28 Tablets
(levonorgestrel and ethinyl estradiol tablets, USP)
Triphasic Regimen

Dear Sir or Madam:

G. D. Searle & Co. hereby submits a field copy of the above-mentioned ANDA amendment.

G.D. Searle & Co. certifies that this is true copy of the amendment submitted to FDA headquarters in Rockville, Maryland.

If you have any questions concerning this submission, please do not hesitate to contact me.

Sincerely,

Doranne Frano

Doranne Frano
Regulatory Affairs
(847) 982-7691
(847) 982-8090 fax

cc: Office of Generic Drugs

sanjuan.jun

RECEIVED

JUN 12 1996

GENERIC DRUGS

Madue

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

orig

DR. Label type
NDA ORIG AMENDMENT
AC

June 10, 1996

RECEIVED

JUN 11 1996

GENERIC DRUGS

*1 labeling reviewed
completed
7/23/96
/S/*

Douglas Sporn
Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room #154
Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

SEARLE

RE: ANDA 74-538, Trivora™ -21 and -28 Tablets
(levonorgestrel and ethinyl estradiol tablets, USP) Triphasic Regimen
MAJOR AMENDMENT: PENDING APPLICATION

Dear Mr. Sporn:

Reference is made to the ANDA cited above and to the non-approval letter dated March 23, 1995. G.D. Searle & Co. hereby amends the above-referenced ANDA. For ease of review, the comments included in the March 23, 1995 letter are reproduced below in bold type, followed by our responses.

A. **Chemistry Deficiencies:**

2.

[Redacted content]

Redacted

8

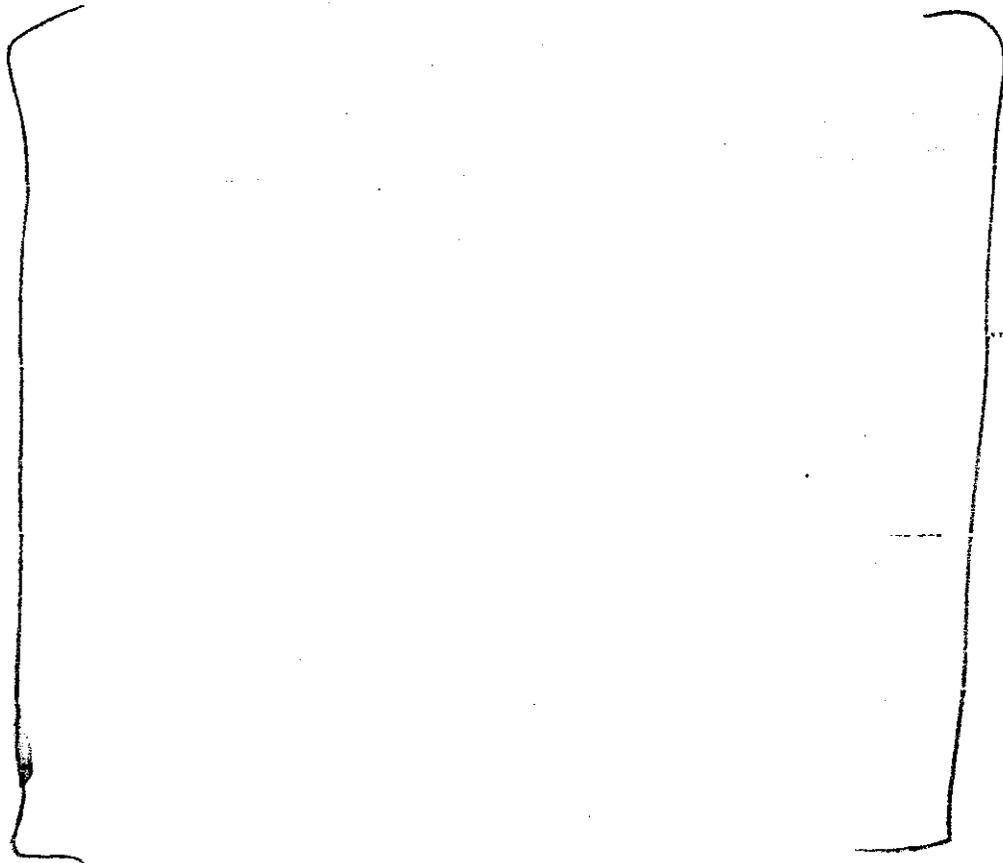
Page(s) of trade

secret and /or

confidential

commercial

information



B. Labeling Deficiencies:

BLISTER PACK CONTAINER: 1 x 21 tablets and 1 x 28 tablets

There are two starting options to choose from when a patient begins taking an oral contraceptive: A Day 1 (first day of the menstrual flow) or a Sunday start (Sunday after your menstrual flow begins). Your package design, with the stamped days of the week, allows for a Sunday start only. We believe this package design could be confusing to the patient. The directions instruct the patient to take the "first pill of the first pack". However, if the patient chooses the Day 1 option, she must choose the day of the week the menstrual flow begins (not necessarily Sunday) and continue through the cycle not receiving all 21 or 28 tablets. We believe stickers should be available to place over the pre-printed days or propose some other type of system that will ensure the patient receives the tablet on the proper day and for the proper amount of days in each phase. We refer you to the innovator's product for guidance.

We have provided stickers (Attachment 23) for the patient to place over the pre-printed days to indicate the starting date of their oral contraceptive use.

CARTON: 6 Blisters (21 or 28 tablets) and 6 Tablet Dispensers

1. "Usual Dosage" rather than "
2. Delete " this information appears in the Usual Dosage statement.
3. Revise your carton content statement as follows:
6 Blisters containing 21 (or 28) tablets each and 6 Tablet Dispensers

The carton labels have been revised to include all of the FDA comments. The final printed carton labels are provided in Attachment 24.

AUXILIARY LABEL: Satisfactory in draft.

INSERT:

GENERAL COMMENTS

1. The model you have used in your side-by-side comparison is not the most currently approved innovator's labeling. There are numerous changes needed throughout the text of your insert. Please refer to Triphasil® -21 [Wyeth Laboratories Inc; Approved April 20, 1994; Revised September 15, 1993 (professional labeling); Revised June 1, 1993, (patient labeling)] for guidance.

In addition to the above changes, please note the following:

2. Revise your subsection headings so that they do not appear to have the same prominence as the section headings.
3. Inactive ingredients, lactose - please note that there are two USP/NF monographs for lactose. Please revise accordingly.
4. Please include the molecular weight and formula of each active ingredient in the DESCRIPTION section.

Please revise your blister tablet container labels, carton, package insert, and patient labeling, then prepare and submit final printed container and auxiliary labels and carton labeling and draft professional and patient labeling.

We have incorporated all the FDA comments into the package insert. This revision reflects the update of the Brevicon, Norinyl and Tri-Norinyl inserts approved August 30, 1995). Container, auxiliary and carton labeling are provided in Attachments 23 and 24. Draft professional and patient labeling are provided in Attachment 25.

can't use different letters

Office of Generic Drugs
Food and Drug Administration
June 10, 1996
Page 12

In addition, all labeling has been revised to reflect the transfer of this ANDA (effective August 31, 1995) to G.D. Searle & Co. Trivora will be distributed by SCS Pharmaceuticals, a wholly owned subsidiary.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

- 1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.**

We acknowledge that a satisfactory evaluation of all the facilities listed in our application is required prior to approval.

- 2. The acceptance of the product specifications and expiration dating period of two years including the stability data is contingent on resolution of the issue of the proposed dissolution specification.**

As indicated in our responses to Items 6.e. and 7.c., the USP dissolution specification for uncoated Levonorgestrel/Ethinyl Estradiol Tablets has been adopted. We believe this resolves the issue of the proposed dissolution specification.

- 3. Please submit additional room temperature stability data for the executed batch if available.**

Updated stability data through 24 months is included in Attachment 14.

If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,



Doranne Frano
Regulatory Affairs
(847) 982-7691
(847) 982-8090 (Fax)

Enc.

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 847 982 7000
Fax 847 982 4701

May 15, 1996

NEW CORRESP
NC

NAT
M
5/21/96

Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II (HFD-600)
7500 Standish Place
Rockville, MD 20855

SEARLE

RECEIVED
MAY 17 1996
GENERIC DRUGS

Re: ANDA 74-538 Trivora™ 21 and 28 Tablets
(levonorgestrel and ethinyl estradiol tablets, USP)
Triphasic Regimen

Dear Mr. Sporn:

Reference is made to a telephone conference with Bill Russell, and a non-approval letter dated March 23, 1995 regarding the above-mentioned ANDA. G.D. Searle & Co. acquired this ANDA on August 31, 1995, following the acquisition of Syntex by Hoffmann-La Roche. The activities required to respond to the March 23, 1995 FDA non-approval letter were initiated by Searle following the transfer of the ANDA ownership in August of 1995 and are on-going. G.D. Searle & Co. hereby commits to providing a response by June 10, 1996 and understands that if this commitment is not met, the ANDA will be voluntarily withdrawn.

If you have any questions concerning this matter, please do not hesitate to contact me.

Sincerely,



Doranne Frano
Regulatory Affairs
(847) 982-7691
(847) 982-8090 fax

trivora.may

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 708 982 7000
Fax 708 982 4701

BIOAVAILABILITY

November 30, 1995

Rabindra N. Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP.

NC/BID

SEARLE

RE: ANDA 74-538, Trivora™ -21 and -28 Tablets
(levonorgestrel and ethinyl estradiol, USP)
Triphasic Regimen
AMENDMENT TO PENDING APPLICATION:
Response to Bioequivalence Comments

RECEIVED 1

DEC 01 1995

GENERIC DRUGS

Dear Dr. Patnaik:

In accordance with 21 CFR 314.120 and in response to your letter dated March 27, 1995, G.D. Searle & Co. hereby amends the above-mentioned ANDA. As requested, a copy of your letter is provided in Attachment 1. For ease of review, your comments are reproduced below in italics, followed by our responses.

1. *The frame size of all subjects in both studies was not submitted and is required to properly evaluate the \pm 10% of normal requirement specified in the study protocol.*

Response:

The frame size data were not collected on the case report forms for the subjects in the studies. However, each subject's body weight was within 10% of the average weight for their age and height, as determined by the Metropolitan Life Insurance Co. weight tables, which requires the frame size to determine inclusion. The weight and height information for each subject is provided in Table 1 of the study reports. For ease of review, copies of these tables are provided in Attachment 2.

2. *Assay validation information supporting the quantitation limits for both levonorgestrel and ethinyl estradiol was not provided.*

Response:

To assess the accuracy and precision of the RIA standard curves for EE₂ and LNG, the recovery of EE₂ added at each point of the standard curve was determined. The same procedure was also used for the standard curves for LNG. Each RIA standard curve is prepared using 3 aliquots of calibration standard at each of 10 concentrations for EE₂ and each of 9 concentrations for LNG. Standard curves are calculated by means of the four-parameter curve fitting procedure of Rodbard and Hutt. (Rodbard and Hutt, *Statistical Analysis of Radioimmunoassays and Immunometric (Labeled Antibody) Assays*, in "Radioimmunoassays and Related Procedures in Medicine", International Atomic Energy Agency, Vienna, 1974, 165-192).

For EE₂, the amount of 1.56 pg read off the standard curve corresponds to concentration of 5 pg/ml in a sample, and for LNG the amount of 3.13 pg (0.00313 ng) read off the standard curve corresponds to a concentration of 12.5 pg/ml in a sample. The relationship between the amount of EE₂ or LNG read off the standard curve for a sample (X) and the concentration of EE₂ or LNG in a sample of plasma (Y) is shown by the following equation:

$$X(\text{pg}) \times 1/R \times 1/F \times 1/V(\text{ml}) = Y(\text{pg/ml})$$

where R = Procedural recovery (approximately 50% to 60%)
F = Fraction of the final aliquot used in the RIA (1/3)
V = Volume of plasma used for analysis (2 ml)

Attachment 3 lists precision and accuracy data at the quantification limits for EE₂ and LNG from the first six curves of each of the two studies (Study 30-6106 and Study 32-6106), and Attachment 4 lists all the data for all curve points for the first six curves in each study. As shown in Attachment 3, the 1.56-pg point for EE₂ has a %CV of 16.2% and recovery of 95.5%, while the 3.13-pg point for LNG has a %CV of 6.08% and a recovery of 88.8%. These data support the quantification limits of 5 pg/ml for EE₂ and 12.5 pg/ml for LNG.

3. *The concentration range and the results of the standard curves used during the analysis of study samples were not provided.*

Response:

The concentration ranges and results of the standard curves, including tabulated data and plotted data for each curve, along with control and

Office of Generic Drugs
CDER, FDA
November 30, 1995
Page 3

study sample analysis data from the first six assays for LNG and EE₂ were provided in Volume 2, pages 275-381 ("Representative Raw Data for the Standards, Controls and Study Samples for the First Six Subjects for Study No. 30-6106") and Volume 3, pages 571-676 ("Representative Raw Data for the Standards, Controls, and Study Samples for the First Six Subjects for Study No. 32-6106").

For ease of review, we have included (Attachment 4) summarized data for the first six standard curves from each study for levonorgestrel and ethinyl estradiol in 4 tables.

Using the individual counts for the first six sets of standards and the resultant standard curves generated by each set, we provided the calculated concentrations of the calibration standards, along with the four curve parameters, A, B, C and D (Attachment 4). We also provided calculated values of the mean, standard deviation, precision (%CV) and accuracy (% recovery) for the calibrator concentrations and the parameters for the six representative curves. For these tables, all values have been rounded to the indicated values before use in any further calculation. Note that Parameter C, which describes the analyte mass at the midpoint of the curve, provides a measure of reproducibility of the curve from run to run.

Equation for the Four-Parameter Logistic Model

$$Y = \frac{(A-D)}{1 + (X/C)^B} + D$$

X is analyte mass; Y is response

Reference: Rodbard and Hutt, *Statistical Analysis of Radioimmunoassays and Immunometric (Labeled Antibody) Assays*, in "Radioimmunoassays and Related Procedures in Medicine", International Atomic Energy Agency, Vienna, 1974, 165-192.

4. *The acceptance criteria for the results of standard curves and QC samples was not provided.*

Office of Generic Drugs
CDER, FDA
November 30, 1995
Page 4

Response:

Assay run acceptance is based on SOPs which stipulate that quality control samples are prepared such that their concentrations correspond to approximately 20%, 50%, and 80% of the maximum displacement of the label. (For this assay the EE₂ concentrations in the quality controls were _____, and the LNG concentrations were _____). Two quality control samples at each concentration are analyzed in each run. The results from all quality control samples are recorded and monitored. For an assay to be accepted, no more than two quality control samples in the run and no two at a given concentration may deviate by more than 20% from the validated mean concentration established for the quality control.

- 5. In the low dose study, at 0.5 hr. of period 1, there are discrepancies in the report concerning a plasma sample that was lost during analytical processing. Please provide a detailed explanation that clarifies the subject involved and the circumstances.*

Response:

During the first robotic processing (11/2/93) of the samples from Subject 3, a robot processing error invalidated the run, and all samples were reprocessed for analysis. For Subject 3: 0.5 hr. of period 1, insufficient sample remained for the reprocessing and analysis; therefore, the result was reported as Quantity Not Sufficient (QNS).

We believe this response will enable you to complete your review of the bioequivalence study. If you have any questions regarding this submission, please do not hesitate to contact me.

Sincerely,



Donna K. Helms
Director, Regulatory Affairs
847 (708) 982-4751
(708) 982-8152 (FAX)

DKH/lpb



August 31, 1995

Center for Drug Evaluation and Research
Division of Generic Drug Products
HFD-230,17B-20
5600 Fishers Lane
Rockville, MD 20857

NEW SOURCE

Subject: Transfer of Ownership of Pending ANDA No. 74-538
Trivora™ 21 and 28 day Tablets, USP Triphasic Regimen
(levonorgestrel and ethinyl estradiol tablets)

Dear Sirs:

This is to notify the United States Food and Drug Administration that pursuant to an Agreement dated July 24, 1995, all rights to the subject pending Abbreviated New Drug Application No. 74-538 for levonorgestrel and ethinyl estradiol tablets have been transferred from Syntex (U.S.A.) Inc. to G.D. Searle and Co. pursuant to 21 CFR § 314.72, effective as of August 31, 1995. Searle will be given a complete copy of the NDA.

The regulatory agent for this ANDA is now Daniel L. Zabrowski, Vice President Drug Regulatory Affairs, Hoffman-La Roche Inc..

For any questions regarding this transfer, please contact Ms. Lynn Hansen, Regulatory Affairs, Syntex (415) 852-1476 or Ms. Donna Helms, Regulatory Affairs, Searle (708) 982-4751.

Sincerely,

A handwritten signature in black ink that reads 'Daniel L. Zabrowski / Lt'.

Daniel L. Zabrowski, Ph.D.
Vice President
Drug Regulatory Affairs
Hoffman-La Roche Inc.
acting as agent for
Syntex (U.S.A.) Inc.

cc: Ms. C. Nuechterlein Syntex (U.S.A.) Inc.
Ms. C. Zammuto G.D. Searle and Co.

RECEIVED

OCT 10 1995

GENERIC DRUGS

ANDA 74-538

G.D. Searle & Co.
Attention: Donna K. Helms
4901 Searle Parkway
Skokie, IL 60077

NOV 17 1995

Dear Madam:

We acknowledge receipt of your communication dated September 18, 1995, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for Levonorgestrel and Ethinyl Estradiol Tablets USP, 21 Day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; and 0.125 mg/0.03 mg and 28 Day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg; and placebo.

Your letter details the transfer of ownership of the ANDA from Syntex (F.P.), Inc. to G.D. Searle and Co.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the approved application. The material submitted is being retained as part of your application.

Sincerely yours,

JSI

11/16/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:ANDA 74-538
DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-613/Labeling

Endorsement: HFD-615/Prickman, Actg
HFD-615/WRussell, CS
HFD-610/CHoppes, Actg Chief, LRB
WP file\X:\new\firmnsz\searle\ltrs&rev\74538.f
F/T hrw 11-14-95
Transfer of Ownership!

JSI 11/17/95 *JSI* 11/18/95
---date

Searle
4901 Searle Parkway
Skokie, Illinois 60077
Telephone 708 982 7000
Fax 708 982 4701

September 18, 1995

NEW CORRESP
NC

Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products
HFD-510
5600 Fishers Lane
Rockville, MD 20857

SEARLE

RE: Acceptance of Ownership
ANDA No. 74-538
Trivora™ 21 and 28 day Tablets, USP Triphasic Regimen
(levonorgestrel and ethinyl estradiol tablets)

Dear Sirs:

The purpose of this communication is to notify the United States Food and Drug Administration that pursuant to 21 CFR § 314.72, G.D. Searle & Co. hereby accepts responsibility and ownership of the above mentioned Abbreviated New Drug Application, effective August 31, 1995. Enclosed is a signed FDA Form 356H and a copy of the letter reflecting transfer of ownership from Syntex (F.P.) Inc. to Searle.

Searle will comply with all commitments, agreements, promises and conditions made by Syntex (F.P.) Inc. and contained in this application. Searle will have a complete copy of the ANDA, including supplements and records that are required to be kept under 21 CFR § 314.80 and 21 CFR § 314.81. Revised labeling will be submitted separately to reflect the change in ownership. All changes to this ANDA will be made in accordance with 21 CFR § 314.70.

If you have any questions concerning this matter, please do not hesitate to contact me.

Sincerely,



Donna K. Helms
Director, Regulatory Affairs
(708) 982-4751
(708) 982-8152 FAX

ljp Syntex\ANDA 74-538

RECEIVED

SEP 21 1995

GENERIC DRUGS

99

NEW CORRESP

August 31, 1995

Center for Drug Evaluation and Research
Division of Generic Drug Products
HFD-230,17B-20
5600 Fishers Lane
Rockville, MD 20857

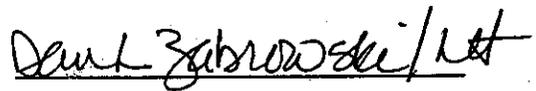
Subject: Transfer of Ownership of Pending ANDA No. 74-538
Trivora™ 21 and 28 day Tablets, USP Triphasic Regimen
(levonorgestrel and ethinyl estradiol tablets)

Dear Sirs:

This is to notify the United States Food and Drug Administration that pursuant to an Agreement dated July 24, 1995, all rights to the subject pending Abbreviated New Drug Application No. 74-538 for levonorgestrel and ethinyl estradiol tablets have been transferred from Syntex (F.P.) Inc. to G.D. Searle and Co. pursuant to 21 CFR § 314.72, effective as of August 31, 1995. Searle will be given a complete copy of the NDA.

For any questions regarding this transfer, please contact Ms. Lynn Hansen, Regulatory Affairs, Syntex (415) 852-1476 or Ms. Donna Helms, Regulatory Affairs, Searle (708) 982-4751.

Sincerely,



Dan L. Zabrowski, Ph.D.
Vice President
Drug Regulatory Affairs
Hoffman-La Roche Inc.
acting as agent for
Syntex (F.P.) Inc.

cc: Ms. C. Nuechterlein Syntex (U.S.A.) Inc.
Ms. C. Zammuto G.D. Searle and Co.

RECEIVED

SEP 19 1995

GENERIC DRUGS

Handwritten initials and signature

DUPLICATE

SYNTEX (U.S.A.) INC.
3401 HILLVIEW AVENUE, P.O. BOX 10850
PALO ALTO, CALIFORNIA 94303

(415) 855-5050
TELEX 4997273 SYNTEX PLA



*NAL
D. King
4-17-95*

NEW CORRESP

March 28, 1995

Mr. Douglas L. Sporn
Acting Director, Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: **Notice of Intent to File an Amendment**
ANDA 74-538 Trivora™ -21 and -28 Tablets
Levonorgestrol and Ethinyl Estradiol Tablets, USP Triphasic Regimen

Dear Mr. Sporn:

We acknowledge receipt of the non-approval letter issued by Dr. Rashmikant Patel dated March 23, 1995 regarding the subject ANDA. In accordance with 21 CFR § 314.120 (a), we wish to notify you of our intent to amend this ANDA.

If you have any questions, you may contact Ms. Katy Morton at (415) 354-2287 or myself at (415) 354-2286.

Sincerely,

Tracy Lin
Program Manager
Regulatory Agent for
Syntex (F.P.) Inc.

RECEIVED

APR 04 1995

GENERIC DRUGS

*13 APR 1995
P. [Signature]*

Levonorgestrel and Ethinyl Estradiol Tablets USP
ANDA 74-538

MAR 27 1995

Syntex (F.P.) Inc.
Attention: Katy Morton
3401 Hillview Avenue M/S S1-200
Palo Alto, CA 94304

Dear Ms., Morton

Reference is made to the Bioequivalence studies submitted August 19, 1994, for Levonorgestrel and Ethinyl Estradiol Tablets USP.

The Office of Generic Drugs has reviewed the referenced material and determined that the bioequivalence studies comparing the test product, Levonorgestrel and Ethinyl Estradiol Tablets USP, lots 3816-007-12055 and 3816-007-12057, manufactured by Syntex, with the reference listed drug Triphasil®, lots 3816-007-12058 and 3816-007-12060, manufactured by Wyeth-Ayerst are incomplete for the following reasons:

1. The frame size of all subjects in both studies was not submitted and is required to properly evaluate the $\pm 10\%$ of normal requirement specified in the study protocol.
2. Assay validation information supporting the quantitation limits for both levonorgestrel and ethinyl estradiol were not provided.
3. The concentration range and the results of the standard curves used during the analysis of study samples, was not provided.
4. The acceptance criteria for the results of standard curves and QC samples was not provided.
5. In the low dose study, at 0.5 hr, of period I, there are discrepancies in the report, concerning a plasma sample that was lost during analytical processing. Please provide a detail explanation that clarifies the subject involved and the circumstances.

The *in vivo* bioequivalence study waiver request for the mid dose tablet can not be considered until the results of bioequivalence studies on both the low and high dose tablets are found acceptable.

An action described under 21 CFR 314.96 which will amend this application is required, if you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290.

In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

^
|S|
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA 74-538

Syntex (F.P.) Inc.
Attention: Katy Morton
3401 Hillview Ave, M/S S1-200
Palo Alto, CA 94304

MAR 23 1995

Dear Madam:

This is in reference to your abbreviated new drug application dated August 19, 1994, and accepted for filing on October 11, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Levonorgestrel and Ethinyl Estradiol Tablets USP, 21 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; and 0.125 mg/0.03 mg and 28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg; placebo.

Reference is also made to your amendments dated September 27 and October 7, 1994.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

1.

2.

firm
dk

Redacted

2

Page(s) of trade

secret and /or

confidential

commercial

information



B. Labeling Deficiencies:

BLISTER PACK CONTAINER: 1 x 21 tablets and 1 x 28 tablets

There are two starting options to choose from when a patient begins taking an oral contraceptive: A Day 1 (first day of the menstrual flow) or a Sunday start (Sunday after your menstrual flow begins). Your package design, with the stamped days of the week, allows for a Sunday start only. We believe this package design could be confusing to the patient. The directions instruct the patient to take the "first pill of the first pack". However, if the patient chooses the Day 1 option, she must choose the day of the week ^(ok) the menstrual flow begins (not necessarily Sunday) and continue through the cycle not receiving all 21 or 28 tablets. We believe stickers should be available to place over the pre-printed days or propose some other type of system that will ensure the patient receives the tablet on the proper day and for the proper amount of days in each phase. We refer you to the innovator's product for guidance.

2. The acceptance of the product specifications and expiration dating period of two years including the stability data is contingent on resolution of the issue of the proposed dissolution specification.
3. Please submit additional room temperature stability data for the executed batch if available.

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 the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

RS/ 3/22/95

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

cc: ANDA 74-538
 DUP File
 Division File
 Field Copy
 HFD-600/Reading File

Endorsement:

HFD-625/M.Shaikh/1-4-95
 HFD-613/A.Vezza/3-14-95
 HFD-625/M.Smela/1-6-95
 HFD-617/D.Konigstein/CSO/1-11-95, 3-14-95
 X:\WPFILE\CARLOS\SHAIKH\74538LTR.1
 F/T by dvw/3-15-95

RS/ 3/21/95
RS/ 3/16/95
RS/ 3/21/95
TS/ 3/20/95

NOT APPROVABLE - MAJOR

OCT 25 1994

Syntex (F.P.) Inc.
Attention: Katy Morton
3401 Hillview Avenue, M/S S1-200
Palo Alto, CA 94304

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 our "Refuse to File" letter dated September 12, 1994, and your amendment dated October 7, 1994.

NAME OF DRUG: Levonorgestrel and Ethinyl Estradiol Tablets USP,
21 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; and
0.125 mg/0.03 mg
28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125
mg/0.03 mg; and placebo

DATE OF APPLICATION: August 19, 1994

DATE OF RECEIPT: August 25, 1994

DATE ACCEPTABLE FOR FILING: October 11, 1994

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

We remind you of your responsibility to submit a properly signed and executed 356(h) form with each submission. We refer you to 21 CFR 314.50(a) for further guidance.

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

Should you have questions concerning this application, contact:

David Konigstein
Consumer Safety Officer
(301) 594-0370

Sincerely yours,

/S/ for 10/24/94

Gordon R. Johnston
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA74-538

cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement:

HFD-615/PRickman, Acting Chie _____ date
HFD-615/KRoberts, CSO _____ date
HFD-625/MSmela, Sup. Chem. _____ ate
WP File B:\ackanda\74538.ack
F/T hrw 10-14-94
ANDA Acknowledgement Letter!

/S/ 10/21/94
/S/ 10/24/94 */S/ m*



ORIGINAL

(415) 855-5050

*File 505(f)(2)(A)
Kubler
10/12/94*

HUMAN PHARMACEUTICAL REGULATORY AFFAIRS

Mr. Gordon R. Johnston
Acting Director, Division of Labeling and Program Support
Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

October 7, 1994

M/A C
AMENDMENT

Re: **AMENDMENT**
ANDA 74-538 Levonorgestrel and Ethinyl Estradiol Tablets, USP, Triphasic Regimen

Dear Mr. Johnston,

Thank you for taking the time today to discuss with Dan Zabrowski and myself our concerns regarding your September 12, 1994 refusal to file letter. Although we are still not in agreement with the action taken on this ANDA, in the interest of avoiding further delays in filing this ANDA, we hereby amend the subject application to include the requested information. For ease of review, FDA's comments are reproduced below, followed by our response.

FDA Comment: You have failed to provide a letter of authorization from Syntex (U.S.A) Inc. granting the Agency permission to reference the drug master file for ethinyl estradiol in support of your application.

Response: A letter of authorization from Syntex Corporation, the holder of ethinyl estradiol DMF, granting FDA permission to reference DMF # — in support of the subject Syntex (F.P) Inc. ANDA is provided in Attachment 1.

FDA Comment: You are required to submit a certified copy of the technical section of the application to the FDA district office at the time of submission. In addition, you must include a certification in the archival copy of the application that the field copy is a "true" copy of the technical sections of the application. Refer to Sections 314.94 (d)(5) and 314.440 of the Final Rule, published in the Federal Register, September 8, 1993, pages 47351 and 47352. Please provide a revised third (field) copy certification.

Response: As requested, a revised Third Copy Certification pursuant to 21 CFR §314.94 (d)(5) is provided in Attachment 2. Also provided is a copy of the cover letter which accompanied the third copy sent to the district office.

We believe this ANDA is acceptable for filing. If you have any questions, you may contact Ms. Tracy Lin at (415) 354-2286 or myself at (415) 354-2287.

Sincerely,

Katy Morton

Katy Morton, Senior Manager
Regulatory Agent for Syntex (F.P.) Inc. **11**

GENERIC DRUGS

Syntex Research
Attention: Katy Morton
Agent For: Syntex (F.P.) Inc.
3401 Hillview Avenue, M/S S1-200
Palo Alto, California 94304

SEP 12 1994

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated August 19, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Levonorgestrel and Ethinyl Estradiol Tablets USP, 21 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; and 0.125 mg/0.03 mg and 28 day: 0.05 mg/0.03 mg; 0.075 mg/0.04 mg; 0.125 mg/0.03 mg; and placebo.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

You have failed to provide a letter of authorization from Syntex (U.S.A.) Inc. granting the Agency permission to reference the drug master file for ethinyl estradiol in support of your application.

You are required to submit a certified copy of the technical section of the application to the FDA district office at the time of submission. In addition, you must include a certification in the archival copy of the application that the field copy is a "true" copy of the technical sections of the application. Refer to Sections 314.94(d)(5) and 314.440 of the Final Rule, published in the Federal Register, September 8, 1993, pages 47351 and 47352. Please provide a revised third (field) copy certification.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Khyati Roberts
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

9/12/94
Gordon R. Johnston
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA#74-538.ref
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting Chief ISL *8/7/94* date
HFD-615/CParise, CSO ISL date
HFD-615/KRoberts, CSO ISL *8/3/94* date
HFD-625/MSmela, Chem Branch ISL *9/8/94* date
WP File B:\rtfanda\74538.ref ✓
F/T File hrw 8-30-94
ANDA Refuse to File!

*Refer to
File 305 (J)(A)
12/11/94
5/18/94
8/29/94*

HUMAN PHARMACEUTICALS REGULATORY AFFAIRS

August 19, 1994

*Labeling review completed
8/22/94*

Mr. Douglas L. Sporn
Acting Director, Office of Generic Drugs
CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

**Subject: New ANDA for Trivora™ - 21 and - 28 Tablets
(Levonorgestrel and Ethinyl Estradiol Tablets, USP) Triphasic Regimen**

Dear Mr. Sporn,

On behalf of Syntex (F.P.) Inc. and under the provisions of Section 505(j) of the Federal Food, Drug, and Cosmetic Act, and Section 314.55 of the Code of Federal Regulations, Title 21, we are submitting an Abbreviated New Drug Application for Trivora™ - 21 and - 28 Tablets (Levonorgestrel and Ethinyl Estradiol Tablets, USP) Triphasic Regimen. These oral contraceptive products consist of a triphasic regimen of three active tablets (Phase 1 - 0.05/0.03 mg, Phase 2 - 0.075/0.04 mg, and Phase 3 - 0.125/0.03 mg levonorgestrel and ethinyl estradiol, respectively) with and without placebo tablets.

The listed drugs, Triphasil® - 21 and 28 Tablets (Levonorgestrel and Ethinyl Estradiol Tablets, USP) Triphasic Regimen, are the subjects of Wyeth Ayerst' approved NDAs 19-192 and 19-190, respectively. Our decision to file both the 21 and 28 day presentations in a single ANDA was discussed with Mr. Harvey Greenberg at the Regulatory Support Branch of the OGD on August 15, 1994 and found acceptable.

The patent for Triphasil® - 21 and 28 Tablets has expired (May 18, 1993) and there is no unexpired exclusivity covering Triphasil tablets.

This ANDA meets the criteria for an ANDA in that the condition of use, active ingredients, route of administration, dosage form, and strength are identical to those of the listed drug.

The labeling for Trivora tablets is consistent with the innovator's labeling but is modeled after Syntex' OC class labeling and is identical to our recently approved Levora (Levonorgestrel and Ethinyl Estradiol Tablets) labeling except for the Description, Dosage and Administration and How Supplied sections. This labeling has included all FDA's recent requirements with respect to (1) new simplified instruction for the "How To Take the Pill" (HTTTP) section ("FDA PPI Instructions for OC Use" guideline, revised March 18, 1992), (2) warnings about HIV infection and other sexually transmitted diseases (FDA 4/8/93 letter), (3) delayed physical examination (FDA 6/29/93 letter).

Bioequivalence studies which demonstrate the bioequivalence between Syntex (F.P.) Inc.'s Trivora tablets and Wyeth's Triphasil tablets (Phase 1 and Phase 3) are provided in Section VI. The bioequivalence study protocols were discussed with Dr. Dighe, Dr. Nerurkar and Dr. Adams on September 4, 1992 and were found acceptable. A Letter of Understanding summarizing the bioequivalence study was submitted on September 15, 1992 (provided in Section VI.1). Pursuant to 21 CFR 320.22(d)(2), a waiver for the bioequivalence study for Phase 2 tablets is requested based on In Vitro dissolution data and evidence showing that all tablets are proportionally similar in their active and inactive ingredients.

RECEIVED

AUG 25 1994

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This ANDA contains 7 volumes. The organization of this ANDA follows the Table of Contents provided in the OGD Policy and Procedure Guide #30-91. The signed Regulatory Agent Authorization Letter, Certification Statement, Conviction Information and Third Copy Certification are also provided.

By copy of this letter, we would like to request comments from Mr. Jerry Phillips regarding the acceptability of the Trivora trade name. If you have any questions during your review of this ANDA, we would be pleased to respond by telephone, written communications, or in person. Please contact Ms. Tracy Lin at (415) 354-2286 or myself at (415) 354-2287.

Sincerely,



Katy Morton, Senior Manager
Regulatory Agent for Syntex (F.P.) Inc.

CC by Fax: Mr. Jerry Phillips