

TRI-SPRINTEC- norgestimate and ethinyl estradiol
MedVantx, Inc.

Tri-Sprintec®

(norgestimate and ethinyl estradiol tablets - triphasic regimen)

PATIENTS SHOULD BE COUNSELED THAT THIS PRODUCT DOES NOT PROTECT AGAINST HIV INFECTION (AIDS) AND OTHER SEXUALLY TRANSMITTED DISEASES.

Rx only

DESCRIPTION

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

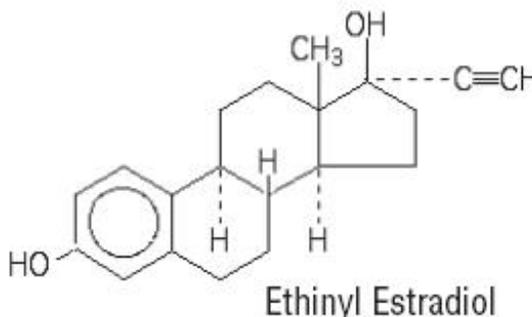
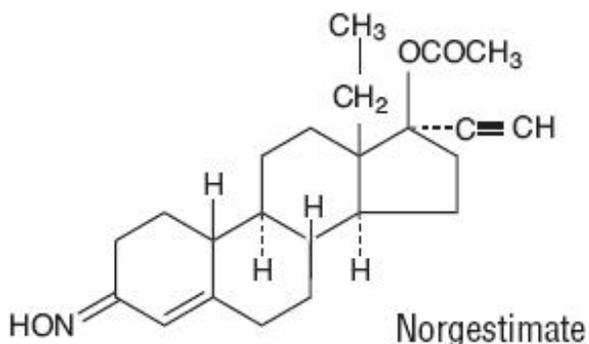
Each gray tablet contains 0.18 mg of the progestational compound, norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-oxime, (17 α)-(+) -) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17 α -pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients include anhydrous lactose, lactose monohydrate, lake blend black LB 636 (ingredients include aluminum sulfate solution, aluminum-chloride solution, FD&C blue no. 2, FD&C red no. 40, FD&C yellow no. 6, sodium bicarbonate and sodium carbonate), magnesium stearate, and pregelatinized starch.

Each light blue tablet contains 0.215 mg of the progestational compound norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α)-(+) -) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17 α -pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients include anhydrous lactose, FD&C blue no. 2 aluminum lake, (ingredients include aluminum sulfate solution, aluminum-chloride solution, sodium bicarbonate and sodium carbonate), lactose monohydrate, magnesium stearate, and pregelatinized starch.

Each blue tablet contains 0.25 mg of the progestational compound norgestimate (18, 19-Dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17 α)-(+) -) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17 α -pregna, 1,3,5(10)-trien-20-yne-3, 17-diol), and the inactive ingredients include anhydrous lactose, FD&C blue no. 2 aluminum lake, (ingredients include aluminum sulfate solution, aluminum-chloride solution, sodium bicarbonate and sodium carbonate), lactose monohydrate, magnesium stearate, and pregelatinized starch.

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

The structural formula is as follows:



CLINICAL PHARMACOLOGY

Oral Contraception

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

Receptor binding studies, as well as studies in animals and humans, have shown that norgestimate and 17-deacetyl norgestimate, the major serum metabolite, combine high progestational activity with minimal intrinsic androgenicity.⁹⁰⁻⁹³

Norgestimate, in combination with ethinyl estradiol, does not counteract the estrogen-induced increases in sex hormone binding globulin (SHBG), resulting in lower serum testosterone.^{90,91,94}

Acne

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

Norgestimate and ethinyl estradiol are well absorbed following oral administration of Tri-Sprintec. On the average, peak serum concentrations of norgestimate and ethinyl estradiol are observed within two hours (0.5 to 2 hr for norgestimate and 0.75 to 3 hr for ethinyl estradiol) after administration followed by a rapid decline due to distribution and elimination. Although norgestimate serum concentrations following single or multiple dosing were generally below assay detection within 5 hours, a major norgestimate serum metabolite, 17-deacetyl norgestimate, (which exhibits a serum half-life ranging from 12 to 30 hours) appears rapidly in serum with concentrations greatly exceeding that of norgestimate. The 17-deacetylated metabolite is pharmacologically active and the pharmacologic profile is similar to that of norgestimate. The elimination half-life of ethinyl estradiol ranged from approximately 6 to 14 hours.

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

INDICATIONS AND USAGE

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

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

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

TABLE I: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST

**YEAR OF TYPICAL USE AND THE FIRST YEAR OF
PERFECT USE OF CONTRACEPTION AND THE
PERCENTAGE CONTINUING USE AT THE END OF THE
FIRST YEAR. UNITED STATES.**

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

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

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

† 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.

- ‡ 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.
- § The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
- ¶ Foams, creams, gels, vaginal suppositories, and vaginal film.
- # Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
- Ⓟ With spermicidal cream or jelly.
- Ⓠ Without spermicides.

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

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

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

	Norgestimate and Ethinyl Estradiol	Placebo
	N=163	N=161
Mean Age at Enrollment	27.3 years	28
Inflammatory Lesions -	56.6	36.6
Mean Percent Reduction		
Total Lesions -	49.6	30.3
Mean Percent Reduction		

CONTRAINDICATIONS

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

- Thrombophlebitis or thromboembolic disorders
- A past history of deep vein thrombophlebitis or thromboembolic disorders

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

WARNINGS

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

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

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

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

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

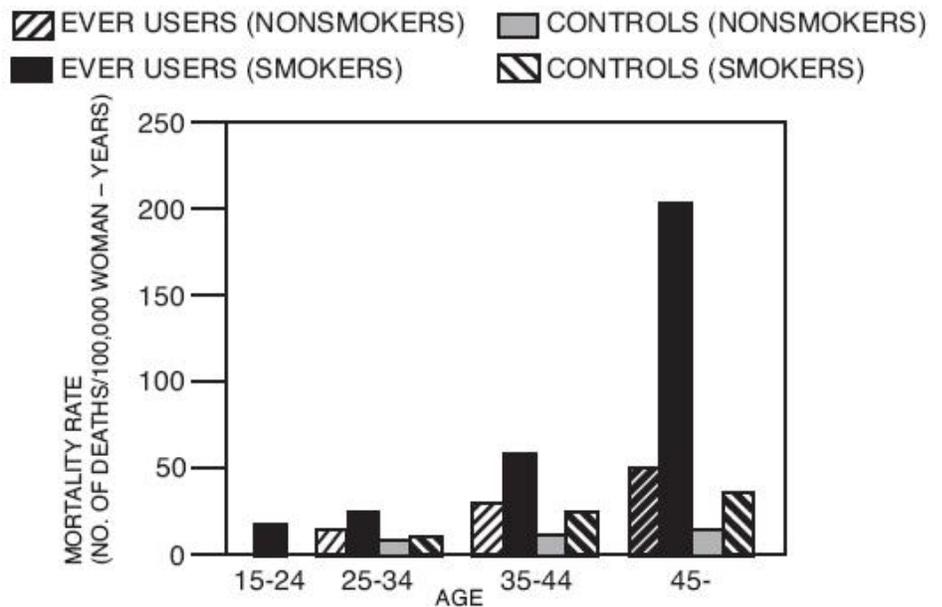
1. Thromboembolic Disorders and Other Vascular Problems

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

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

TABLE III.

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



Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity.¹³ In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism.¹⁴⁻¹⁸

Oral contraceptives have been shown to increase blood pressure among users (see Section 9 in WARNINGS). Similar effects on risk factors have been associated with an increased risk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Norgestimate has minimal androgenic activity (see CLINICAL PHARMACOLOGY), and there is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater⁹⁷.

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

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

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

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

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

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

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

2. Estimates of Mortality from Contraceptive Use

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

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

TABLE IV: ANNUAL NUMBER OF BIRTH-RELATED OR METHOD-RELATED DEATHS ASSOCIATED WITH

**CONTROL OF FERTILITY PER 100,000 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	7.4	9.1	14.8	25.7	28.2
Oral contraceptives nonsmoker†	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	1	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

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

* Deaths are birth-related

† Deaths are method-related

3. Carcinoma of the Reproductive Organs and Breasts

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. While there are conflicting reports, most studies suggest that use of oral contraceptives is not associated with an overall increase in the risk of developing breast cancer. Some studies have reported an increased relative risk of developing breast cancer, particularly at a younger age. This increased relative risk has been reported to be related to duration of use.^{36-44,79-89}

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.⁹⁵

Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia in some populations of women.⁴⁵⁻⁴⁸ However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

4. Hepatic Neoplasia

Benign hepatic adenomas are associated with oral contraceptive use, although the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attributable risk to be in the range of 3.3 cases/100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher dose.⁴⁹ Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.^{50,51}

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

5. Ocular Lesions

There have been clinical case reports of retinal thrombosis associated with the use of oral

contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

6. Oral Contraceptive Use Before or During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy.^{56,57} The majority of recent studies also do not indicate a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned,^{55,56,58,59} when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion.

It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued until pregnancy is ruled out.

7. Gallbladder Disease

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

8. Carbohydrate and Lipid Metabolic Effects

Oral contraceptives have been shown to cause a decrease in glucose tolerance in a significant percentage of users.¹⁷ This effect has been shown to be directly related to estrogen dose.⁶⁵ Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.^{17,66} However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose.⁶⁷ Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored while taking oral contraceptives.

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS, 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

In clinical studies with norgestimate and ethinyl estradiol there were no clinically significant changes in fasting blood glucose levels. Minimal statistically significant changes were noted in glucose levels over 24 cycles of use. Glucose tolerance tests showed no clinically significant changes from baseline to cycles 3, 12, and 24.

9. Elevated Blood Pressure

An increase in blood pressure has been reported in women taking oral contraceptives⁶⁸ and this increase is more likely in older oral contraceptive users⁶⁹ and with extended duration of use.⁶¹ Data from the Royal College of General Practitioners¹² and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity.

Women with a history of hypertension or hypertension-related diseases, or renal disease⁷⁰ should be encouraged to use another method of contraception. If women elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.⁶⁸⁻⁷¹

10. Headache

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

11. Bleeding Irregularities

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. Nonhormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorrhea, pregnancy should be ruled out.

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

12. Ectopic Pregnancy

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS

1. Physical Examination and Follow-Up

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

2. Lipid Disorders

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

3. Liver Function

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

4. Fluid Retention

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

5. Emotional Disorders

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

6. Contact Lenses

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

7. Drug Interactions

Reduced efficacy and increased incidence of breakthrough bleeding and menstrual irregularities have

been associated with concomitant use of rifampin. A similar association, though less marked, has been suggested with barbiturates, phenylbutazone, phenytoin sodium, carbamazepine, and possibly with griseofulvin, ampicillin and tetracyclines.⁷²

8. Interactions with Laboratory Tests

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

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

9. Carcinogenesis

See WARNINGS section.

10. Pregnancy

Pregnancy Category X: See CONTRAINDICATIONS and WARNINGS sections.

11. Nursing Mothers

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

12. Pediatric Use

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

13. Sexually Transmitted Diseases

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

INFORMATION FOR THE PATIENT

See Patient Labeling printed below.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives (See WARNINGS section).

• Thrombophlebitis and venous thrombosis with or without embolism	• Myocardial infarction	• Hepatic adenomas or benign liver tumors
	• Cerebral hemorrhage	
	• Cerebral thrombosis	
• Arterial thromboembolism	• Hypertension	
• Pulmonary embolism	• Gallbladder disease	

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

• Nausea	• Edema	• Migraine
• Vomiting	• Melasma which may persist	• Rash (allergic)
• Gastrointestinal symptoms (such as abdominal cramps and bloating)	• Breast changes: tenderness, enlargement, secretion	• Mental depression
• Breakthrough bleeding	• Change in weight (increase or decrease)	• Reduced tolerance to carbohydrates
• Spotting	• Change in cervical erosion and secretion	• Vaginal candidiasis
• Change in menstrual flow	• Diminution in lactation when given immediately postpartum	• Change in corneal curvature (steepening)
• Amenorrhea	• Cholestatic jaundice	• Intolerance to contact lenses
• Temporary infertility after discontinuation of treatment		

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

• Pre-menstrual syndrome	• Hirsutism	• Impaired renal function
• Cataracts	• Loss of scalp hair	• Hemolytic uremic syndrome
• Changes in appetite	• Erythema multiforme	• Acne
• Cystitis-like syndrome	• Erythema nodosum	• Changes in libido
• Headache	• Hemorrhagic eruption	• Colitis

- Nervousness
 - Vaginitis
 - Budd-Chiari Syndrome
 - Dizziness
 - Porphyria
-

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.

NONCONTRACEPTIVE HEALTH BENEFITS

The following noncontraceptive health benefits related to the use of combination oral contraceptives are supported by epidemiological studies which largely utilized oral contraceptive formulations containing estrogen doses exceeding 0.035 mg of ethinyl estradiol or 0.05 mg mestranol.⁷³⁻⁷⁸

Effects on menses:

- Increased menstrual cycle regularity
- Decreased blood loss and decreased incidence of iron deficiency anemia
- Decreased incidence of dysmenorrhea

Effects related to inhibition of ovulation:

- Decreased incidence of functional ovarian cysts
- Decreased incidence of ectopic pregnancies

Other effects:

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

DOSAGE AND ADMINISTRATION

Oral Contraception

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

28-Day Regimen (Sunday Start)

When taking Tri-Sprintec 28 Tablets, the first tablet should be taken on the first Sunday after menstruation begins. If period begins on Sunday, the first tablet should be taken that day. Take one active tablet daily for 21 days followed by one white tablet daily for 7 days. After 28 tablets have been taken, a new course is started the next day (Sunday). For the first cycle of a Sunday Start regimen, another method of contraception should be used until after the first seven consecutive days of administration.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should continue taking one tablet every day until Sunday. On Sunday the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has

sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling (“How to Take the Pill” section).

28-Day Regimen (Day 1 Start)

The dosage of Tri-Sprintec 28 Tablets, for the initial cycle of therapy is one active tablet administered daily from the 1st day through the 21st day of the menstrual cycle, counting the first day of menstrual flow as “Day 1” followed by one white tablet daily for 7 days. Tablets are taken without interruption for 28 days. After 28 tablets have been taken, a new course is started the next day.

If the patient misses one (1) active tablet in Weeks 1, 2, or 3, the tablet should be taken as soon as she remembers. If the patient misses two (2) active tablets in Week 1 or Week 2, the patient should take two (2) tablets the day she remembers and two (2) tablets the next day; and then continue taking one (1) tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills. If the patient misses two (2) active tablets in the third week or misses three (3) or more active tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a backup method of birth control if she has sex in the seven (7) days after missing pills.

Complete instructions to facilitate patient counseling on proper pill usage may be found in the Detailed Patient Labeling (“How to Take the Pill” section).

The use of Tri-Sprintec for contraception may be initiated 4 weeks postpartum in women who elect not to breastfeed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. (See CONTRAINDICATIONS and WARNINGS concerning thromboembolic disease. See also PRECAUTIONS for “Nursing Mothers.”) The possibility of ovulation and conception prior to initiation of medication should be considered.

(See Discussion of Dose-Related Risk of Vascular Disease from Oral Contraceptives.)

ADDITIONAL INSTRUCTIONS FOR ALL DOSING REGIMENS

Breakthrough bleeding, spotting, and amenorrhea are frequent reasons for patients discontinuing oral contraceptives. In breakthrough bleeding, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, adequate diagnostic measures are indicated to rule out pregnancy or malignancy. If pathology has been excluded, time or a change to another formulation may solve the problem. Changing to an oral contraceptive with a higher estrogen content, while potentially useful in minimizing menstrual irregularity, should be done only if necessary since this may increase the risk of thromboembolic disease.

Use of oral contraceptives in the event of a missed menstrual period:

1. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period and oral contraceptive use should be discontinued until pregnancy is ruled out.
2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out before continuing oral contraceptive use.

Acne

The timing of initiation of dosing with Tri-Sprintec for acne should follow the guidelines for use of Tri-Sprintec as an oral contraceptive. **Consult the DOSAGE AND ADMINISTRATION section for oral contraceptives.** The dosage regimen for Tri-Sprintec for treatment of facial acne, as available in the Blister Pack Tablet Dispenser, utilizes a 21-day active and a 7-day placebo schedule. Take one active tablet daily for 21 days followed by one white tablet for 7 days. After 28 tablets have been taken,

a new course is started the next day.

HOW SUPPLIED

Tri-Sprintec[®] (norgestimate and ethinyl estradiol tablets) 0.18 mg/0.035 mg are gray, round, unscored tablets debossed with stylized **b** on one side and **985** on the other side; 0.215 mg/0.035 mg are light blue, round, unscored tablets debossed with stylized **b** on one side and **986** on the other side; 0.25 mg/0.035 mg are blue, round, unscored tablets debossed with stylized **b** on one side and **987** on the other side.

Tri-Sprintec 28 (norgestimate and ethinyl estradiol tablets) are packaged in cartons of six blister cards. Each card contains 28 tablets as follows: Each gray tablet contains 0.18 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each light blue tablet contains 0.215 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. Each blue tablet contains 0.25 mg of the progestational compound, norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol, and the 7 white placebo tablets contain inert ingredients (Placebo tablets are white, round, unscored tablets, debossed with stylized **b** on one side and **143** on the other side). (NDC 0555-9018-58).

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

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BRIEF SUMMARY PATIENT PACKAGE INSERT

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

For the majority of women, oral contraceptives can be taken safely. But there are some women who are at high risk of developing certain serious diseases that can be fatal or may cause temporary or permanent disability. The risks associated with taking oral contraceptives increase significantly if you:

- smoke
- have high blood pressure, diabetes, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, or malignant or benign liver tumors

Although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy, nonsmoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women.

You should not take the pill if you suspect you are pregnant or have unexplained vaginal bleeding.

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

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, bleeding between menstrual periods, weight gain, breast tenderness, and difficulty wearing contact lenses. These side effects, especially nausea and vomiting may subside within the first three months of use.

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

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

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

There is conflict among studies regarding breast cancer and oral contraceptive use. Some studies have reported an increase in the risk of developing breast cancer, particularly at a younger age. This increased risk appears to be related to duration of use. The majority of studies have found no overall increase in the risk of developing breast cancer. Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

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

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

Tri-Sprintec Tablets (like all oral contraceptives) are intended to prevent pregnancy. Tri-Sprintec Tablets are also used to treat moderate acne in females who are able to take oral contraceptives.

Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DETAILED PATIENT LABELING

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

Tri-Sprintec Tablets: Each gray tablet contains 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. Each light blue tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. Each blue tablet contains 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. Each white tablet contains inert ingredients.

INTRODUCTION

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

EFFECTIVENESS OF ORAL CONTRACEPTIVES FOR CONTRACEPTION

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, the chance of becoming pregnant is less than 1% (1 pregnancy per 100 women per year of use) when used perfectly, without missing any pills. Typical failure rates are actually 3% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

In comparison, typical failure rates for other nonsurgical methods of birth control during the first year of use are as follows:

Implant: <1%

Injection: <1%

IUD: 1 to 2%

Diaphragm with spermicides: 20%

Spermicides alone: 26%

Vaginal sponge: 20 to 40%

Female sterilization: <1%

Male sterilization: <1%

Cervical Cap with spermicides: 20 to 40%

Condom alone (male): 14%

Condom alone (female): 21%

Periodic abstinence: 25%

Withdrawal: 19%

No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

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

Some women should not use the pill. For example, you should not take the pill if you are pregnant or think you may be pregnant. You should also not use the pill if you have any of the following conditions:

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

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

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your healthcare provider if you have or have had:

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

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

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

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risk of Developing Blood Clots

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

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

GENERAL PRECAUTIONS.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills and may be greater with longer duration of oral contraceptive use. In addition, some of these increased risks may continue for a number of years after stopping oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages. For women aged 20 to 44 it is estimated that about 1 in 2,000 using oral contraceptives will be hospitalized each year because of abnormal clotting. Among nonusers in the same age group, about 1 in 20,000 would be hospitalized each year. For oral contraceptive users in general, it has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for nonusers the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.

2. Heart Attacks and Strokes

Oral contraceptives may increase the tendency to develop strokes (stoppage or rupture of blood vessels in the brain) and angina pectoris and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability. Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.

3. Gallbladder Disease

Oral contraceptive users probably have a greater risk than nonusers of having gallbladder disease, although this risk may be related to pills containing high doses of estrogens.

4. Liver Tumors

In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.

5. Cancer of the Reproductive Organs and Breasts

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

A meta-analysis of 54 studies found a small increase in the frequency of having breast cancer diagnosed for women who were currently using combined oral contraceptives or had used them within the past ten years. This increase in the frequency of breast cancer diagnosis, within ten years of stopping use, was generally accounted for by cancers localized to the breast. There was no increase in the frequency of having breast cancer diagnosed ten or more years after cessation of use.

Some studies have found an increase in the incidence of cancer of the cervix in women who use oral contraceptives. However, this finding may be related to factors other than the use of oral contraceptives. There is insufficient evidence to rule out the possibility that pills may cause such cancers.

ESTIMATED RISK OF DEATH FROM A BIRTH-CONTROL METHOD OR PREGNANCY

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

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	7.4	9.1	14.8	25.7	28.2
Oral contraceptives nonsmoker†	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	1	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth-related

† Deaths are method-related

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

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

WARNING SIGNALS

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

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

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. Vaginal Bleeding

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

2. Contact Lenses

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

3. Fluid Retention

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

4. Melasma

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

5. Other Side Effects

Other side effects may include nausea and vomiting, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, and vaginal infections. If any of these side effects bother you, call your doctor or healthcare provider.

GENERAL PRECAUTIONS

1. Missed Periods and Use of Oral Contraceptives Before or During Early Pregnancy

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

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

2. While Breast-Feeding

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

oral contraceptives only after you have weaned your child completely.

3. Laboratory Tests

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

4. Drug Interactions

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

5. Sexually Transmitted Diseases

Tri-Sprintec Tablets (like all oral contraceptives) are intended to prevent pregnancy. Tri-Sprintec Tablets are also used to treat moderate acne in females who are able to take oral contraceptives. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

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 TO 3 PACKS OF PILLS. If you do feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your doctor or clinic.

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

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

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

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

BEFORE YOU START TAKING YOUR PILLS

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

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

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

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

Tri-Sprintec: There are 7 gray “active” pills, 7 light blue “active” pills, and 7 blue “active” pills.

3. ALSO FIND:

1) where on the pack to start taking pills,

2) in what order to take the pills

CHECK PICTURE OF THE FOLD-OVER-DOSE CARD AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE AT THE END OF THE BRIEF SUMMARY PATIENT PACKAGE INSERT.

4. BE SURE YOU HAVE READY AT ALL TIMES:

ANOTHER KIND OF BIRTH CONTROL (such as condoms, foam or sponge) to use as a back-up method in case you miss pills.

AN EXTRA, FULL PILL PACK

WHEN TO START THE *FIRST* PACK OF PILLS

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

SUNDAY START

1. Take the first “active” gray pill of the first pack on the Sunday *after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

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

DAY 1 START

1. Take the first “active” gray pill of the first pack during the *first 24 hours of your period*.

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

WHAT TO DO DURING THE MONTH

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

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

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

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

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

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** gray, light blue, or blue “active” pill:

1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** gray or light blue “active” pills in a row in **WEEK 1 OR WEEK 2** of your pack:

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

If you **MISS 2** blue “active” pills in a row in **THE 3rd WEEK:**

1. If you are a Sunday Starter:

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

If you are a Day 1 Starter

THROW OUT the rest of the pill pack and start a new pack that same day.

2. You may not have your period this month but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You **MAY BECOME PREGNANT** if you have sex in the *7 days* after you miss pills. You **MUST** use another birth control method (such as condoms, foam, or sponge) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** gray, light blue, or blue “active” pills in a row (during the first 3 weeks):

1. If you are a Sunday Starter:

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

If you are a DAY 1 Starter

THROW OUT the rest of the pill pack and start a new pack 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 method for those 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS

If you forget any of the 7 white “reminder” pills in Week 4:

THROW AWAY the pills you missed.

Keep taking one pill each day until the pack is empty.

You do not need a back-up method.

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

Use a **BACK-UP METHOD** anytime you have sex.

KEEP TAKING ONE “ACTIVE” PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately one percent (i.e., one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are about 3%. If failure does occur, the risk to the fetus is minimal.

PREGNANCY AFTER STOPPING THE PILL

There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.

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

OVERDOSAGE

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

OTHER INFORMATION

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

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

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

In addition to preventing pregnancy, use of combination oral contraceptives may provide certain

benefits. They are:

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

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

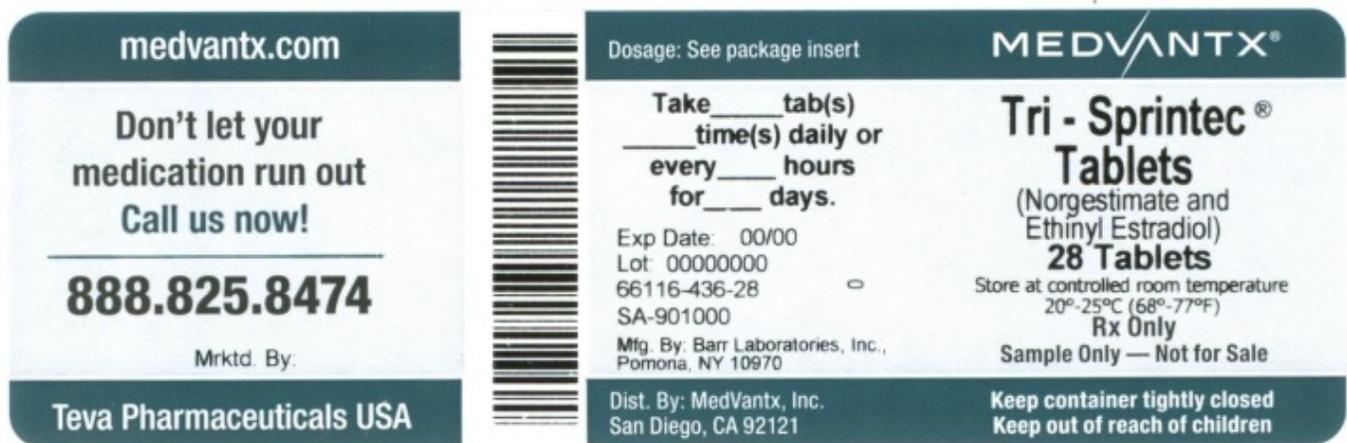
BARR LABORATORIES, INC.

Pomona, NY 10970

Issued MARCH 2009

BR-9018

PRINCIPAL DISPLAY PANEL



TRI-SPRINTEC

norgestimate and ethinyl estradiol kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:66116-436(NDC:0555-9018)
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66116-436-28	1 in 1 CARTON		
1		1 in 1 POUCH		
1		1 in 1 BLISTER PACK		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1		7
Part 2		7
Part 3		7
Part 4		7

Part 1 of 4

TRI-SPRINTEC TRIPHASIC REGIMEN

norgestimate and ethinyl estradiol tablet

Product Information

Route of Administration ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NORGESTIMATE (UNII: C291HFX4DY) (NORGESTIMATE - UNII:C291HFX4DY)	NORGESTIMATE	0.18 mg
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.035 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
ALUMINUM SULFATE (UNII: 34S289N54E)	
ALUMINUM CHLORIDE (UNII: 3CYT62D3GA)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
SODIUM BICARBONATE (UNII: 8MDF5V39QO)	
SODIUM CARBONATE (UNII: 45P3261C7T)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	GRAY	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	b;985
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075808	01/25/2011	

Part 2 of 4

TRI-SPRINTEC TRIPHASIC REGIMEN

norgestimate and ethinyl estradiol tablet

Product Information

Route of Administration ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NORGESTIMATE (UNII: C291HFX4DY) (NORGESTIMATE - UNII:C291HFX4DY)	NORGESTIMATE	0.215 mg
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.035 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
ALUMINUM OXIDE (UNII: LM26O6933)	
ALUMINUM SULFATE (UNII: 34S289N54E)	
ALUMINUM CHLORIDE (UNII: 3CYT62D3GA)	
SODIUM BICARBONATE (UNII: 8MDF5V39QO)	
SODIUM CARBONATE (UNII: 45P3261C7T)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	BLUE (light blue)	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	b;986
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075808	01/25/2011	

Part 3 of 4

TRI-SPRINTEC TRIPHASIC REGIMEN

norgestimate and ethinyl estradiol tablet

Product Information

Route of Administration ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
NORGESTIMATE (UNII: C291HFX4DY) (NORGESTIMATE - UNII:C291HFX4DY)	NORGESTIMATE	0.25 mg
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	0.035 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
ALUMINUM OXIDE (UNII: LM26O6933)	
ALUMINUM SULFATE (UNII: 34S289N54E)	
ALUMINUM CHLORIDE (UNII: 3CYT62D3GA)	
SODIUM BICARBONATE (UNII: 8MDF5V39QO)	
SODIUM CARBONATE (UNII: 45P3261C7T)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics

Color	BLUE	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	b;987
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075808	01/25/2011	

Part 4 of 4

INERT

inert tablet

Product Information

Route of Administration	ORAL
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Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
HYPROMELLOSES (UNII: 3NXW29V3WO)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	

Product Characteristics

Color	WHITE	Score	no score
Shape	ROUND	Size	6mm
Flavor		Imprint Code	b;143
Contains			

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075808	01/25/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA075808	01/25/2011	

Labeler - MedVantx, Inc. (806427725)

Establishment

Name	Address	ID/FEI	Business Operations
Blenheim Pharmacal, Inc.		171434587	REPACK

Revised: 8/2011

MedVantx, Inc.