Aubra EQ®
(Levonorgestrel and Ethinyl Estradiol Tablets USP)
0.1 mg/0.02 mg
Rx only

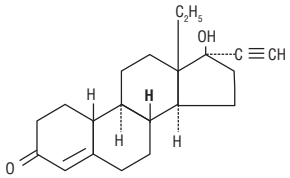
afaxys®

Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

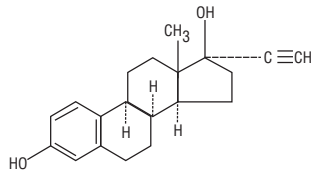
DESCRIPTION

Each active, white tablet (21) contains 0.1 mg of levonorgestrel USP, d(-)-13β-ethyl-17α- ethinyl-17β-hydroxygon-4-en-3-one, a totally synthetic progestogen, and 0.02 mg of ethinyl estradiol USP, 17α-ethinyl-1,3,5(10)-estratriene-3, 17β-diol. The inactive ingredients present are croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and povidone.

Each inactive, green tablet (7) contains the following inactive ingredients: croscarmellose sodium, FD & C Blue No. 2 Aluminum Lake, ferric oxide (sicovit yellow 10), lactose anhydrous, magnesium stearate, microcrystalline cellulose, and povidone.



Levonorgestrel



Ethinyl Estradiol

CLINICAL PHARMACOLOGY

Mode of Action

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).

Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of Aubra EQ in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first-pass metabolism. Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is between 38% and 48%.

After a single dose of Aubra EQ to 22 women under fasting conditions, maximum serum concentrations of levonorgestrel are 2.8 ± 0.9 ng/mL (mean ± SD) at 1.6 ± 0.9 hours. At steady state, attained from day 19 onwards, maximum levonorgestrel concentrations of 6.0 ± 2.7 ng/mL are reached at 1.5 ± 0.5 hours after the daily dose. The minimum serum levels of levonorgestrel at steady state are 1.9 ± 1.0 ng/mL. Observed levonorgestrel concentrations increased from day 1 (single dose) to days 6 and 21 (multiple doses) by 34% and 96%, respectively (Figure 1). Unbound levonorgestrel concentrations increased from day 1 to days 6 and 21 by 25% and 83%, respectively. The kinetics of total levonorgestrel are non-linear due to an increase in binding of levonorgestrel to sex hormone binding globulin (SHBG), which is attributed to increased SHBG levels that are induced by the daily administration of ethinyl estradiol.

Following a single dose, maximum serum concentrations of ethinyl estradiol of 62 ± 21 pg/mL are reached at 1.5 ± 0.5 hours. At steady state attained from at least day 6 onwards, maximum concentrations of ethinyl estradiol were 77 ± 30 pg/mL and were reached at 1.3 ± 0.7 hours after the daily dose. The minimum serum levels of ethinyl estradiol at steady state are 10.5 ± 5.1 pg/mL. Ethinyl estradiol concentrations did not increase from days 1 to 6, but did increase by 19% from days 1 to 21 (FIGURE I).

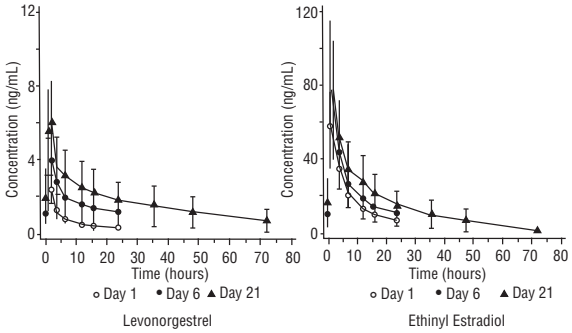


FIGURE I: Mean (SE) levonorgestrel and ethinyl estradiol serum concentrations in 22 subjects receiving Aubra EQ (100 mcg levonorgestrel and 20 mcg ethinyl estradiol)

TABLE I provides a summary of levonorgestrel and ethinyl estradiol pharmacokinetic parameters.

TABLE I: MEAN (SD) PHARMACOKINETIC PARAMETERS OF AUBRA EQ OVER A 21-DAY DOSING PERIOD

Levonorgestrel						
Day	C_{max} ng/mL	T_{max} h	AUC ng•h/mL	CL/F mL/h/kg	Vλz/F L/kg	SHBG nmol/L
1	2.75 (0.88)	1.6 (0.9)	35.2 (12.8)	53.7 (20.8)	2.66 (1.09)	57 (18)
6	4.52 (1.79)	1.5 (0.7)	46.0 (18.8)	40.8 (14.5)	2.05 (0.86)	81 (25)
21	6.00 (2.65)	1.5 (0.5)	68.3 (32.5)	28.4 (10.3)	1.43 (0.62)	93 (40)
Unbound Levonorgestrel						
	pg/mL	h	pg•h/mL	L/h/kg	L/kg	fu %
1	51.2 (12.9)	1.6 (0.9)	654 (201)	2.79 (0.97)	135.9 (41.8)	1.92 (0.30)
6	77.9 (22.0)	1.5 (0.7)	794 (240)	2.24 (0.59)	112.4 (40.5)	1.80 (0.24)
21	103.6 (36.9)	1.5 (0.5)	1177 (452)	1.57 (0.49)	78.6 (29.7)	1.78 (0.19)
Ethinyl Estradiol						
	pg/mL	h	pg•h/mL	mL/h/kg	L/kg	
1	62.0 (20.5)	1.5 (0.5)	653 (227)	567 (204)	14.3 (3.7)	
6	76.7 (29.9)	1.3 (0.7)	604 (231)	610 (196)	15.5 (4.0)	
21	82.3 (33.2)	1.4 (0.6)	776 (308)	486 (179)	12.4 (4.1)	

Distribution

Levonorgestrel in serum is primarily bound to SHBG. Ethinyl estradiol is about 97% bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis.

Metabolism

Levonorgestrel: The most important metabolic pathway occurs in the reduction of the Δ4-3-oxo group and hydroxylation at positions 2α, 1β, and 16β, followed by conjugation. Most of the metabolites that circulate in the blood are sulfates of 3α,5β-tetrahydro-levonorgestrel, while excretion occurs predominantly in the form of glucuronides. Some of the parent levonorgestrel also circulates as 17β-sulfate. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

Ethinyl estradiol: Cytochrome P450 enzymes (CYP3A4) in the liver are responsible for the 2-hydroxylation that is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion. Levels of Cytochrome P450 (CYP3A) vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and undergoes enterohepatic circulation.

Excretion

The elimination half-life for levonorgestrel is approximately 36 ± 13 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40% to 68%) and about 16% to 48% are excreted in feces. The elimination half-life of ethinyl estradiol is 18 ± 4.7 hours at steady state.

Special Populations

Race

Based on the pharmacokinetic study with Aubra EQ, there are no apparent differences in pharmacokinetic parameters among women of different races.

Hepatic Insufficiency

No formal studies have evaluated the effect of hepatic disease on the disposition of Aubra EQ. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

Renal Insufficiency

No formal studies have evaluated the effect of renal disease on the disposition of Aubra EQ.

Drug-Drug Interactions

See **PRECAUTIONS section – Drug Interactions**

INDICATIONS AND USAGE

Aubra EQ is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Oral contraceptives are highly effective. Table II 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, the IUD, and Norplant® System, depends upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

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

Emergency Contraceptive Pills: The FDA has concluded that certain combined oral contraceptives containing ethinyl estradiol and norgestrel or levonorgestrel are safe and effective for use as postcoital emergency contraception. Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.[9]

Lactation Amenorrhea Method: LAM is a highly effective, temporary method of contraception.[10]

Source: Trussell J. Contraceptive efficacy. In: Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowel D, Guest F. Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers; 1998.

1. Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
2. Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
3. Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.
4. The percents becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within one year. This estimate was lowered slightly (to 85%) to represent the percent who would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
5. Foams, creams, gels, vaginal suppositories, and vaginal film.
6. Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
7. With spermicidal cream or jelly.
8. Without spermicides.
9. The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The FDA has declared the following dosage regimens of oral contraceptives to be safe and effective for emergency contraception: for tablets containing 50 mcg of ethinyl estradiol and 500 mcg of norgestrel 1 dose is 2 tablets; for tablets containing 20 mcg of ethinyl estradiol and 100 mcg of levonorgestrel 1 dose is 5 tablets; for tablets containing 30 mcg of ethinyl estradiol and 150 mcg of levonorgestrel 1 dose is 4 tablets.
10. However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

In a clinical trial with levonorgestrel and ethinyl estradiol tablets, 1,477 subjects had 7,720 cycles of use and a total of 5 pregnancies were reported. This represents an overall pregnancy rate of 0.84 per 100 woman-years. This rate includes patients who did not take the drug correctly. One or more pills were missed during 1,479 (18.8%) of the 7,870 cycles; thus all tablets were taken during 6,391 (81.2%) of the 7,870 cycles. Of the total 7,870 cycles, a total of 150 cycles were excluded from the calculation of the Pearl index due to the use of backup contraception and/or missing 3 or more consecutive pills.

CONTRAINDICATIONS

Combination oral contraceptives should not be used in women with any of the following conditions:
Thrombophlebitis or thromboembolic disorders
A history of deep-vein thrombophlebitis or thromboembolic disorders
Cerebrovascular or coronary artery disease (current or past history)
Valvular heart disease with thrombogenic complications
Thrombogenic rhythm disorders
Hereditary or acquired thrombophilias
Major surgery with prolonged immobilization
Diabetes with vascular involvement
Headaches with focal neurological symptoms
Uncontrolled hypertension
Known or suspected carcinoma of the breast or personal history of breast cancer
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, or active liver disease
Known or suspected pregnancy
Hypersensitivity to any of the components of Aubra EQ

Are receiving Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations (see **WARNINGS, RISK OF LIVER ENZYME ELEVATIONS WITH CONCOMITANT HEPATITIS C TREATMENT).**

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular side effects from oral-contraceptive use. This risk increases with age and with the extent of smoking (in epidemiologic studies, 15 or more cigarettes per day was associated with a significantly increased risk) 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 venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension, 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 certain inherited or acquired thrombophilias, hypertension, hyperlipidemias, obesity, diabetes, and surgery or trauma with increased risk of thrombosis (see **CONTRAINDICATIONS**).

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 doses of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with lower doses 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 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. 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. 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 infarction in women in their mid-thirties or older with smoking accounting for the majority of excess cases. Mortality rates associated with circulatory disease have been shown to increase substantially in smokers over the age of 35 and nonsmokers over the age of 40 (FIGURE II) among women who use oral contraceptives.

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

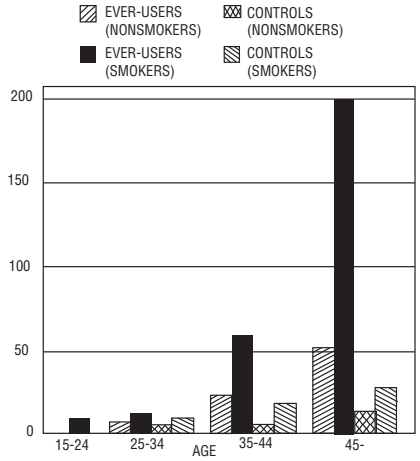


FIGURE II. (Adapted from P.M. Layde and V. Beral, Lancet, 1:541-546, 1981.)

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

b. Venous Thrombosis and Thromboembolism

An increased risk of venous 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. 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. The approximate incidence of deep-vein thrombosis and pulmonary embolism in users of low dose (less than 50 mcg ethinyl estradiol) combination oral contraceptives is up to 4 per 10,000 woman-years compared to 0.5 to 3 per 10,000 woman-years for non-users. However, the incidence is less than that associated with pregnancy (6 per 10,000 woman-years). The excess risk is highest during the first year a woman ever uses a combined oral contraceptive. Venous thromboembolism may be fatal. The risk of thromboembolic disease due to oral contraceptives is not related to length of use and gradually disappears after pill use is stopped.

A two- to four-fold increase in relative risk of postoperative 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. 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 after a midtrimester pregnancy termination.

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 (greater than 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, while smoking interacted to increase the risk for hemorrhagic strokes.

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. 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. The attributable risk is also greater in older women. Oral contraceptives also increase the risk for stroke in women with other underlying risk factors such as certain inherited or acquired thrombophilias. Women with migraine (particularly migraine/headaches with focal neurological symptoms, see **CONTRAINDICATIONS**) who take combination oral contraceptives may be at an increased risk of stroke.

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. A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents. 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 nature and absolute amount of progestogen used in the contraceptive. The 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 the lowest estrogen content which is judged appropriate for the individual patient.

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.

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. However, both studies were performed with oral contraceptive formulations containing 50 mcg or higher of estrogens.

2. Estimates of Mortality from Contraceptive Use

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral-contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is less than 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 1970's — but not reported until 1983. 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, 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 nonsmoking 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 nonsmoking 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.

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

Method of control and outcome	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44
No fertility-control methods*	7.0	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	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/ spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related
** Deaths are method related
Adapted from H.W. Ory, Family Planning Perspectives, *15*:57-63, 1983.

3. Carcinoma of the Reproductive Organs and Breasts

Numerous epidemiological studies have examined the association between the use of oral contraceptives and the incidence of breast and cervical cancer.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to decrease over time after combination oral contraceptive discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have reported a small increase in risk for women who first use combination oral contraceptives at a younger age. Most studies show a similar pattern of risk with combination oral contraceptive use regardless of a woman's reproductive history or her family breast cancer history.

Breast cancers diagnosed in current or previous OC users tend to be less clinically advanced than in nonusers.

Women with known or suspected carcinoma of the breast or personal history of breast cancer should not use oral contraceptives because breast cancer is usually a hormonally-sensitive tumor. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. 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 combination oral contraceptive use and breast and 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 these 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. Rupture of rare, benign, hepatic adenomas may cause death through intra abdominal hemorrhage.

Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (greater than 8 years) oral-contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral-contraceptive users approaches less than one per million users.

RISK OF LIVER ENZYME ELEVATIONS WITH CONCOMITANT HEPATITIS C TREATMENT

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications such as COCs. Discontinue Aubra EQ prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (see **CONTRAINDICATIONS**). Aubra EQ can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

5. Ocular Lesions

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives that may lead to partial or complete loss of vision. 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 infants born to women who have used oral contraceptives prior to pregnancy. 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 (see **CONTRAINDICATIONS** section).

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. 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 if pregnancy is confirmed.

7. Gallbladder Disease

Combination oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women. Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral-contraceptive users may be minimal. 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 glucose intolerance in a significant percentage of users. Oral contraceptives containing greater than 75 mcg of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance. Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the nondiabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed 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.; PRECAUTIONS, 3**.), changes in serum triglycerides and lipoprotein levels have been reported in oral-contraceptive users.

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. Data from the Royal College of General Practitioners and subsequent randomized trials have shown that the incidence of hypertension increases with increasing quantities 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 with hypertension elect to use oral contraceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued (see **CONTRAINDICATIONS** section). 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.

10. Headache

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause. (See **WARNINGS, 1c.** and **CONTRINDICATIONS.**)

11. Bleeding Irregularities

Breakthrough bleeding and spotting are sometimes encountered in patients on oral contraceptives, especially during the first three months of use. The type and dose of progestogen may be important. If bleeding persists or recurs, 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 (possibly with anovulation), especially when such a condition was preexistent.

12. Ectopic Pregnancy

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

PRECAUTIONS

1. General

Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

2. Physical Examination and Follow-Up

A periodic personal and family medical history and complete physical examination are appropriate for all women, 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 diagnostic 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.

3. 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. (See **WARNINGS, 1a., 1d.,** and **8.**)

A small proportion of women will have adverse lipid changes while taking oral contraceptives. Nonhormonal contraception should be considered in women with uncontrolled dyslipidemias. Persistent hypertriglyceridemia may occur in a small population of combination oral contraceptive users. Elevations of plasma triglycerides may lead to pancreatitis and other complications.

4. 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.

5. 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.

6. Emotional Disorders

Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree.

7. Contact Lenses

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

8. Gastrointestinal

Diarrhea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations.

9. Drug Interactions

Changes in Contraceptive Effectiveness Associated with Coadministration of Other Products: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, carbamazepine, felbamate, oxcarbazepine, topiramate, griseofulvin, and modafinil. In such cases a back-up nonhormonal method of birth control should be considered.

Several cases of contraceptive failure and breakthrough bleeding have been reported in the literature with concomitant administration of antibiotics such as ampicillin and other penicillins, and tetracyclines. However, clinical pharmacology studies investigating drug interactions between combined oral contraceptives and these antibiotics have reported inconsistent results.

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of oral contraceptive products may be affected with coadministration of anti-HIV protease inhibitors. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

Herbal products containing St. John's Wort (*Hypericum perforatum*) may induce hepatic enzymes (cytochrome P 450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

Increase in Plasma Levels Associated with Co-Administered Drugs

Co-administration of atorvastatin and certain oral contraceptives containing ethinyl estradiol increases AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid

and acetaminophen increase the bioavailability of ethinyl estradiol since these drugs act as competitive inhibitors for sulfation of ethinyl estradiol in the gastrointestinal wall, a known pathway of elimination for ethinyl estradiol. CYP 3A4 inhibitors such as indinavir, itraconazole, ketoconazole, fluconazole, and troleandomycin may increase plasma hormone levels. Troleandomycin may also increase the risk of intrahepatic cholestasis during coadministration with combination oral contraceptives.

Changes in Plasma Levels of Co-Administered Drugs

Combination hormonal contraceptives containing some synthetic estrogens (e.g., ethinyl estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone and other corticosteroids, and theophylline have been reported with concomitant administration of oral contraceptives. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine, and clofibric acid, due to induction of conjugation (particularly glucuronidation), have been noted when these drugs were administered with oral contraceptives.

The prescribing information of concomitant medications should be consulted to identify potential interactions.

Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer Aubra EQ with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations (see **WARNINGS, RISK OF LIVER ENZYME ELEVATIONS WITH CONCOMITANT HEPATITIS C TREATMENT**).

10. 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 i.e., corticosteroid binding globulin (CBG), sex hormone-binding globulins (SHBG) leading to increased levels of total circulating corticosteroids and sex steroids respectively. Free or biologically active hormone concentrations are unchanged.
d. Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
e. Glucose tolerance may be decreased.
f. 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.

11. Carcinogenesis

See **WARNINGS** section.

12. Pregnancy

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

13. Nursing Mothers

Small amounts of oral-contraceptive steroids and/or metabolites 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.

14. Pediatric Use

Safety and efficacy of Aubra EQ 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 Aubra EQ before menarche is not indicated.

15. Geriatric Use

Aubra EQ has not been studied in women over 65 years of age and is not indicated in this population.

16. Information for the Patient

See Patient Labeling Printed Below.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions (see **WARNINGS** section for additional information) has been associated with the use of oral contraceptives:

Thromboembolic and thrombotic disorders and other vascular problems (including thrombophlebitis and venous thrombosis with or without pulmonary embolism, mesenteric thrombosis, arterial thromboembolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis), carcinoma of the reproductive organs and breasts, hepatic neoplasia (including hepatic adenomas or benign liver tumors), ocular lesions (including retinal vascular thrombosis), gallbladder disease, carbohydrate and lipid effects, elevated blood pressure, and headache including migraine.

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

Acne
Amenorrhea
Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.
Breast changes: tenderness, pain, enlargement, secretion
Budd-Chiari syndrome
Cervical erosion and secretion, change in
Cholestatic jaundice
Chorea, exacerbation of
Colitis
Contact lenses, intolerance to
Corneal curvature (steepening), change in
Dizziness
Edema/fluid retention
Erythema multiforme
Erythema nodosum
Gastrointestinal symptoms (such as abdominal pain, cramps, and bloating)
Hirsutism
Infertility after discontinuation of treatment, temporary
Lactation, diminution in, when given immediately postpartum
Libido, change in
Melasma/chloasma which may persist
Menstrual flow, change in
Mood changes, including depression
Nausea
Nervousness
Pancreatitis
Porphyria, exacerbation of
Rash (allergic)
Scalp hair, loss of
Serum folate levels, decrease in
Spotting
Systemic lupus erythematosus, exacerbation of
Unscheduled bleeding
Vaginitis, including candidiasis
Varicose veins, aggravation of
Vomiting
Weight or appetite (increase or decrease), change in

The following adverse reactions have been reported in users of oral contraceptives:
Cataracts
Cystitis-like syndrome
Dysmenorrhea
Hemolytic uremic syndrome
Hemorrhagic eruption
Optic neuritis, which may lead to partial or complete loss of vision
Premenstrual syndrome
Renal function, impaired

OVERDOSAGE

Symptoms of oral contraceptive overdosage in adults and children may include nausea, vomiting, and drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms.

NONCONTRACEPTIVE HEALTH BENEFITS

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

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, Aubra EQ® (levonorgestrel and ethinyl estradiol tablets) must be taken exactly as directed and at intervals not exceeding 24 hours. The dosage of Aubra EQ is one white tablet daily for 21 consecutive days, followed by one green inert tablet daily for 7 consecutive days, according to prescribed schedule. It is recommended that Aubra EQ tablets be taken at the same time each day.

The blister pack should be kept in the pouch supplied to avoid possible fading of the pills. If the pills fade, patients should continue to take them as directed.

During The First Cycle of Use

The possibility of ovulation and conception prior to initiation of medication should be considered. The patient should be instructed to begin taking Aubra EQ on either the first Sunday after the onset of menstruation (Sunday Start) or on Day 1 of menstruation (Day

1 Start).

Sunday Start

The patient is instructed to begin taking Aubra EQ on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (white) is taken that day. One white tablet should be taken daily for 21 consecutive days, followed by one green inert tablet daily for 7 consecutive days. Withdrawal bleeding should usually occur within 3 days following discontinuation of white tablets and may not have finished before the next pack is started. During the first cycle, contraceptive reliance should not be placed on Aubra EQ until a white tablet has been taken daily for 7 consecutive days, and a nonhormonal back-up method of birth control should be used during those 7 days.

Day 1 Start

During the first cycle of medication, the patient is instructed to begin taking Aubra EQ during the first 24 hours of her period (day one of her menstrual cycle). One white tablet should be taken daily for 21 consecutive days, followed by one green inert tablet daily for 7 consecutive days. Withdrawal bleeding should usually occur within 3 days following discontinuation of white tablets and may not have finished before the next pack is started. If medication is begun on day one of the menstrual cycle, no back-up contraception is necessary. If Aubra EQ tablets are started later than day one of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on Aubra EQ tablets until after the first 7 consecutive days of administration, and a nonhormonal back-up method of birth control should be used during those 7 days.

After the First Cycle of Use

The patient begins her next and all subsequent courses of tablets on the day after taking her last green tablet. She should follow the same dosing schedule: 21 days on white tablets followed by 7 days on green tablets. If in any cycle the patient starts tablets later than the proper day, she should protect herself against pregnancy by using a nonhormonal back-up method of birth control until she has taken a white tablet daily for 7 consecutive days.

Switching from Another Hormonal Method of Contraception

When the patient is switching from a 21-day regimen of tablets, she should wait 7 days after her last tablet before she starts Aubra EQ. She will probably experience withdrawal bleeding during that week. She should be sure that no more than 7 days pass after her previous 21-day regimen. When the patient is switching from a 28-day regimen of tablets, she should start her first pack of Aubra EQ on the day after her last tablet. She should not wait any days between packs. The patient may switch any day from a progestin-only pill and should begin Aubra EQ the next day. If switching from an implant or injection, the patient should start Aubra EQ on the day of implant removal or, if using an injection, the day the next injection would be due. In switching from a progestin-only pill, injection, or implant, the patient should be advised to use a nonhormonal back-up method of birth control for the first 7 days of tablet-taking.

If Spotting or Breakthrough Bleeding Occurs

If spotting or breakthrough bleeding occur, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician.

Risk of Pregnancy if Tablets are Missed

While there is little likelihood of ovulation occurring if only one or two white tablets are missed, the possibility of ovulation increases with each successive day that scheduled white tablets are missed. Although the occurrence of pregnancy is unlikely if Aubra EQ is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out.

The risk of pregnancy increases with each active (white) tablet missed. For additional patient instructions regarding missed tablets, see the **WHAT TO DO IF YOU MISS PILLS** section in the **DETAILED PATIENT LABELING** below.

Use after Pregnancy, Abortion or Miscarriage

Aubra EQ may be initiated no earlier than day 28 postpartum in the nonlactating mother or after a second trimester abortion due to the increased risk for thromboembolism (see **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** concerning thromboembolic disease). The patient should be advised to use a nonhormonal back-up method for the first 7 days of tablet taking.

Aubra EQ may be initiated immediately after a first trimester abortion or miscarriage. If the patient starts Aubra EQ immediately, back-up contraception is not needed.

HOW SUPPLIED

Aubra EQ® (Levonorgestrel and ethinyl estradiol tablets USP) 0.1 mg/0.02 mg is available in a carton of 3 pouches, each containing 28 tablets:

21 active tablets: White to off-white, round, biconvex, beveled-edge tablets, debossed with "S" on one side and "59" on other side of the tablet.

7 inert tablets: Green, round, mottled, biconvex, beveled-edge uncoated tablets, debossed with "S" on one side and "61" on other side of the tablet.

1 Pouch of 28 tablets	NDC 50102-220-21
Carton of 3 Pouches	NDC 50102-220-23

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

Brief Summary Patient Package Insert

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

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 approximately 1.0% per year (1 pregnancy per 100 women per year of use) when used without missing any pills. The average failure rate of large numbers of pill users is approximately 5% per year (5 pregnancies per 100 women per year of use) 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 or death. The risks associated with taking oral contraceptives increase significantly if you:

- smoke.
- have high blood pressure, diabetes, high cholesterol, or a tendency to form blood clots.
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice, malignant or benign liver tumors, or major surgery with prolonged immobilization.
- have headaches with neurological symptoms.

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

Although cardiovascular disease risks may be increased with oral-contraceptive use after age 40 in healthy, nonsmoking women, there are also greater potential health risks associated with pregnancy in older women.

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 do not smoke. 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) and lungs (pulmonary embolism), blockage 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. Women with migraine also may be at increased risk of stroke with pill use.
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 health-care provider if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, as well as some anticonvulsants and some antibiotics, herbal preparations containing St. John's Wort (*Hypericum perforatum*), and HIV/AIDS drugs may decrease oral-contraceptive effectiveness.

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use.

Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.

After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill. It may be that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

You should have regular breast examinations by a health-care provider and examine your own breasts monthly. Tell your health-care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone sensitive tumor.

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.

Taking the 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 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 appropriate 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 AUBRA EQ

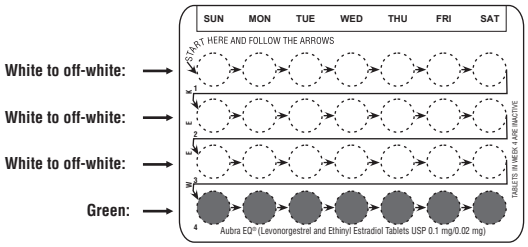
IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING AUBRA EQ:

1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking Aubra EQ.
   And
   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. See "WHAT TO DO IF YOU MISS PILLS" below.
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 feel sick to your stomach, do not stop taking Aubra EQ. The problem will usually go away. If it doesn't go away, check with your health-care provider.
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 (within 4 hours after you take your pill), you should follow the instructions for WHAT TO DO IF YOU MISS PILLS. IF YOU HAVE DIARRHEA or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up nonhormonal method (such as condoms or spermicide) until you check with your health-care provider.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your health-care provider 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 health-care provider.

***BEFORE* YOU START TAKING AUBRA EQ**

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.
   The pill pack has 21 "active" white pills (with hormones) to take for 3 weeks, followed by 1 week of reminder green pills (without hormones).
3. FIND:
   1. where on the pack to start taking pills, and
   2. in what order to take the pills (follow the arrow).



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

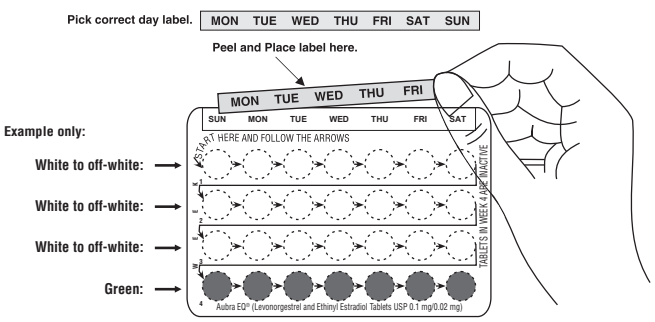
WHEN TO START THE *FIRST* PACK OF PILLS

You have a choice of which day to start taking your first pack of pills.

Decide with your health-care provider which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START

1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet blister pack.



   Note: if the first day of your period is a Sunday, you can skip step#1.
2. Take the first "active" white pill of the first pack during the *first 24 hours of your period.*
3. You will not need to use a back-up nonhormonal method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START

1. Take the first "active" white pill of the first pack on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. *Use a nonhormonal method of birth control* (such as condoms or spermicide) as a backup method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

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

IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS

If your previous brand had 21 pills: Wait 7 days to start taking Aubra EQ. You will probably have your period during that week. Be sure that no more than 7 days pass between the 21-day pack and taking the first white Aubra EQ pill ("active" with hormone).

If your previous brand had 28 pills: Start taking the first white Aubra EQ pill ("active" with hormone) on the day after your last reminder pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

Aubra EQ may not be as effective if you miss white "active" pills, and particularly if you miss the first few or the last few white "active" pills in a pack.

If you **MISS 1** white "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 COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.

If you **MISS 2** 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 COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.

If you **MISS 2** white "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 health-care provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.

If you **MISS 3 OR MORE** white "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 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 health-care provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills.
   You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.

If you forget any of the 7 green "reminder" pills in Week 4:

THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up nonhormonal birth-control method if you start your next pack on time.

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

Use a BACK-UP NONHORMONAL BIRTH-CONTROL METHOD anytime you have sex.

KEEP TAKING ONE PILL EACH DAY until you can reach your health-care provider.

BIRTH CONTROL AFTER STOPPING THE PILL

If you do not wish to become pregnant after stopping the pill, speak to your health-care provider about another method of birth control.

DETAILED PATIENT LABELING

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

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 leaflet 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 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 revisits. You should also follow your health-care provider's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than most other nonsurgical methods of birth control. When they are taken correctly, without missing any pills, the chance of becoming pregnant is approximately 1% per year (1 pregnancy per 100 women per year of use). Typical failure rates are approximately 5% per year (5 pregnancies per 100 women per year of use) when women who miss pills are included. The chance of becoming pregnant increases with each missed pill during each 28-day cycle of use.

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

IUD: 0.1 to 2%	Female condom alone: 21%
Depo-Provera® (injectable progestogen): 0.3%	Cervical cap
Norplant® System (levonorgestrel implants): 0.05%	Never given birth: 20%
Diaphragm with spermicides: 20%	Given birth: 40%
Spermicides alone: 26%	Periodic abstinence: 25%
Male condom alone: 14%	No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels from oral-contraceptive use. This risk increases with age and with the amount of smoking (15 or more cigarettes per day has been associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use oral contraceptives should not smoke.

Some women should not use the pill. For example, you should not take the pill if you have any of the following conditions:

- 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, or certain hormonally-sensitive cancers.
- Unexplained vaginal bleeding (until a diagnosis is reached by your health-care provider).
- Liver tumor (benign or cancerous) or active liver disease.
- Yellowing of the whites of the eyes or of the skin (jaundice) during pregnancy or during previous use of the pill.
- Known or suspected pregnancy.
- A need for surgery with prolonged bedrest.
- Heart valve or heart rhythm disorders that may be associated with formation of blood clots.
- Diabetes affecting your circulation.
- Headaches with neurological symptoms.
- Uncontrolled high blood pressure.
- Allergy or hypersensitivity to any of the components of Aubra EQ (levonorgestrel and ethinyl estradiol tablets).
- If you take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.

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

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health-care provider if you or any family member has ever had:

- Breast nodules, fibrocystic disease of the breast, an abnormal breast X-ray or mammogram.
- Diabetes.
- Elevated cholesterol or triglycerides.
- High blood pressure.
- A tendency to form blood clots.
- Migraine or other headaches or epilepsy.
- Depression.
- Gallbladder, liver, heart, or kidney disease.
- History of scanty or irregular menstrual periods.

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

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

RISKS OF TAKING ORAL CONTRACEPTIVES

1. Risks of developing blood clots

Blood clots and blockage of blood vessels are 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.

Users of combination oral contraceptives have a higher risk of developing blood clots compared to non-users. This risk is highest during the first year of combination oral-contraceptive use.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or injury, or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your health-care provider 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 or after a midtrimester pregnancy termination. 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 also the section *While breast-feeding* in **GENERAL PRECAUTIONS**.)

The risk of blood clots is greater in users of combination oral contraceptives compared to nonusers. This risk may be higher in users of high-dose pills (those containing 50 mcg or more of estrogen) and may also be greater with longer use. In addition, some of these increased risks may continue for a number of years after stopping combination oral contraceptives. The risk of abnormal blood clotting increases with age in both users and nonusers of combination oral contraceptives, but the increased risk from the oral contraceptive appears to be present at all ages.

The excess risk of blood clots is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is lower than blood clots associated with pregnancy. The use of combination oral contraceptives also increases the risk of other clotting disorders, including heart attack and stroke. Blood clots in veins cause death in 1% to 2% of cases. The risk of clotting is further increased in women with other conditions. Examples include: smoking, high blood pressure, abnormal lipid levels, certain inherited or acquired clotting disorders, obesity, surgery or injury, recent delivery or second trimester abortion, prolonged inactivity or bed rest. If possible, combination oral contraceptives should be stopped before surgery and during prolonged inactivity or bedrest.

Cigarette smoking increases the risk of serious cardiovascular events. This risk increases with age and amount of smoking and is quite pronounced in women over 35. Women who use combination oral contraceptives should be strongly advised not to smoke. If you smoke you should talk to your health care professional before taking combination oral contraceptives.

2. Heart attacks and Strokes

Oral contraceptives may increase the tendency to develop strokes or transient ischemic attacks (blockage 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.

Women with migraine (especially migraine/headache with neurological symptoms) who take oral contraceptives also may be at higher risk of stroke and must not use combination oral contraceptives (see section **WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES**).

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. Oral contraceptives may worsen existing gallbladder disease or accelerate the development of gallbladder disease in women previously without symptoms.

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 two 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

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use.

Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly if you started using hormonal contraceptives at a younger age.

After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go down and disappear 10 years after stopping use of the pill. It is not known whether this slightly increased risk of having breast cancer diagnosed is caused by the pill. It may be that women taking the pill were examined more often, so that breast cancer was more likely to be detected.

You should have regular breast examinations by a health-care provider and examine your own breasts monthly. Tell your health-care provider if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone sensitive tumor.

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.

6. Lipid Metabolism and Pancreatitis

There have been reports of increases of blood cholesterol and triglycerides in users of combination oral contraceptives. Increases in triglycerides have led to inflammation of the pancreas (pancreatitis) in some cases.

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 AND ACCORDING TO AGE

Method of control and outcome	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44
No fertility-control methods*	7.0	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	1.0	1.0	1.4	1.4
Condom*	1.1	1.6	0.7	0.2	0.3	0.4
Diaphragm/spermicide*	1.9	1.2	1.2	1.3	2.2	2.8
Periodic abstinence*	2.5	1.6	1.6	1.7	2.9	3.6

* Deaths are birth related
** Deaths are method related

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

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

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your health-care provider 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 health-care provider to show you how to examine your breasts).
- Severe pain or tenderness in the stomach area (indicating a possibly ruptured liver tumor).
- Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood (possibly indicating severe depression).
- Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-colored urine, or light-colored bowel movements (indicating possible liver problems).

SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. Unscheduled or breakthrough vaginal bleeding or spotting

Unscheduled vaginal bleeding or spotting may occur while you are taking the pills. Unscheduled bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Unscheduled 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 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 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 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 nausea, breast tenderness, change in appetite, headache, nervousness, depression, dizziness, loss of scalp hair, rash, vaginal infections, inflammation of the pancreas, and allergic reactions.

If any of these side effects bother you, call your health-care provider.

GENERAL PRECAUTIONS

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

There may be times when you may not menstruate regularly after you have completed taking a cycle of pills. If you have taken your pills regularly and miss one menstrual period, continue taking your pills for the next cycle but be sure to inform your health-care provider before doing so. If you have not taken the pills daily as instructed and missed a menstrual period, or if you missed two consecutive menstrual periods, you may be pregnant. Check with your health-care provider immediately to determine whether you are pregnant. Stop taking oral contraceptives if you are pregnant.

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 should not be used during pregnancy. You should check with your health-care provider about risks to your unborn child of any medication taken during pregnancy.

2. While breast-feeding

If you are breast-feeding, consult your health-care provider 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), primidone (Mysoline®), topiramate (Topamax®), carbamazepine (Tegretol® is one brand of this drug), phenylbutazone (Butazolidin® is one brand), some drugs used for HIV or AIDS such as ritonavir (Norvir®), modafinil (Provigil®) and possibly certain antibiotics (such as ampicillin and other penicillins, and tetracyclines), and herbal products containing St. John's Wort (*Hypericum perforatum*). You may also need to use a nonhormonal method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective.

You may be at higher risk of a specific type of liver dysfunction if you take troleandomycin and oral contraceptives at the same time.

You should inform your health-care provider about all medicines you are taking, including nonprescription products.

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.

HOW TO TAKE AUBRA EQ

IMPORTANT POINTS TO REMEMBER

BEFORE YOU START TAKING AUBRA EQ:

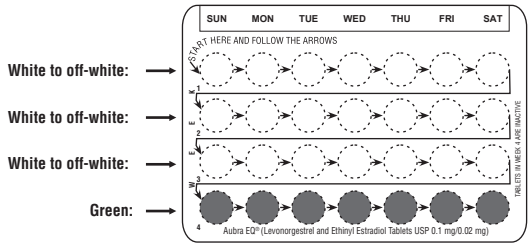
1. BE SURE TO READ THESE DIRECTIONS:
   Before you start taking Aubra EQ.
   And
   Anytime you are not sure what to do.
2. THE RIGHT WAY TO TAKE THE PILL IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant. See "WHAT TO DO IF YOU MISS PILLS" below.
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 feel sick to your stomach, do not stop taking Aubra EQ. The problem will usually go away. If it doesn't go away, check with your health-care provider.
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 (within 4 hours after you take your pill), you should follow the

instructions for WHAT TO DO IF YOU MISS PILLS. IF YOU HAVE DIARRHEA or IF YOU TAKE SOME MEDICINES, including some antibiotics, your pills may not work as well. Use a back-up nonhormonal method (such as condoms or spermicide) until you check with your health-care provider.

6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your health-care provider 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, contact your health-care provider.

BEFORE YOU START TAKING AUBRA EQ

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.
   The pill pack has 21 "active" white pills (with hormones) to take for 3 weeks followed by 1 week of reminder green pills (without hormones).
3. FIND:
   1. where on the pack to start taking pills, and
   2. in what order to take the pills (follow the arrow).



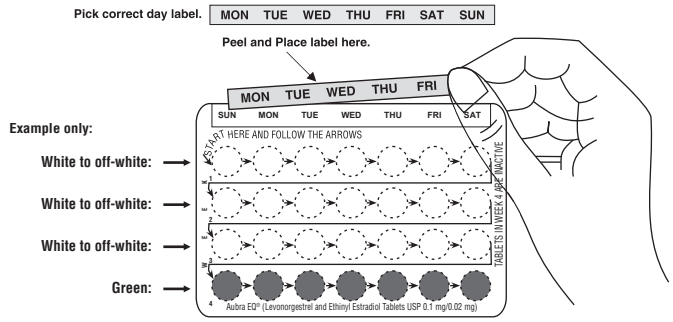
4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicide) to use as a back-up in case you miss pills.
   AN EXTRA, FULL PILL PACK.

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 health-care provider which is the best day for you. Pick a time of day which will be easy to remember.

DAY 1 START

1. Pick the day label strip that starts with the first day of your period. Place this day label strip over the area that has the days of the week (starting with Sunday) pre-printed on the tablet blister pack.



   Note: if the first day of your period is a Sunday, you can skip step#1.
2. Take the first "active" white pill of the first pack *during the first 24 hours of your period.*
3. You will not need to use a back-up nonhormonal method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START

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

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

IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS

If your previous brand had 21 pills: Wait 7 days to start taking Aubra EQ. You will probably have your period during that week. Be sure that no more than 7 days pass between the 21-day pack and taking the first white Aubra EQ pill ("active" with hormone).

If your previous brand had 28 pills: Start taking the first white Aubra EQ pill ("active" with hormone) on the day after your last reminder pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

Aubra EQ may not be as effective if you miss white "active" pills, and particularly if you miss the first few or the last few white "active" pills in a pack.

If you **MISS 1** white "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 COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a non-hormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.

If you **MISS 2** 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 COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a non-hormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.

If you **MISS 2** white "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 health-care provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.

If you **MISS 3 OR MORE** white "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 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 health-care provider because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills.
   You MUST use a nonhormonal birth-control method (such as condoms or spermicide) as a back-up for those 7 days.

If you forget any of the 7 green "reminder" pills in Week 4:

THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up nonhormonal birth-control method if you start your next pack on time.

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

Use a BACK-UP NONHORMONAL BIRTH-CONTROL METHOD anytime you have sex.
KEEP TAKING ONE PILL EACH DAY until you can reach your health-care provider.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately 1 per year (1 pregnancy per 100 women per year of use) if taken every day as directed, but the more typical failure rate is approximately 5% per year (5 pregnancies per 100 women per year of use) including women who do not always take the pill exactly as directed without missing any pills. If you do become pregnant, the risk to the fetus is minimal, but you should stop taking your pills and discuss the pregnancy with your health-care provider.

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.

BIRTH CONTROL AFTER STOPPING THE PILL

If you do not wish to become pregnant after stopping the pill, you should use another method of birth control immediately after stopping Aubra EQ. Speak to your health-care provider about another method of birth control.

OVERDOSAGE

Overdosage may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain and fatigue/drowsiness. Withdrawal bleeding may occur in females. In case of overdosage, contact your health-care provider or pharmacist.

OTHER INFORMATION

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

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

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

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

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES

In addition to preventing pregnancy, use of 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.
- Ovarian cysts may occur less frequently.
- Ectopic (tubal) pregnancy may occur less frequently.
- Noncancerous cysts or lumps in the breast may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.
- Oral-contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth-control pills, ask your health-care provider or pharmacist. They have a more technical leaflet called the Professional Labeling which you may wish to read.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 01/2021

afaxys®

Chateal EQ®
(Levonorgestrel and Ethinyl Estradiol Tablets USP 0.15 mg/0.03 mg)

Rx only

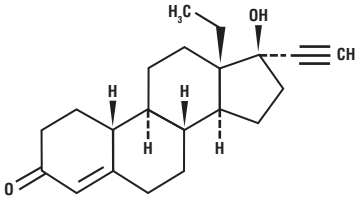
WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs, including Chateal EQ, are contraindicated in women who are over 35 years of age and smoke [see CONTRAINDICATIONS and WARNINGS (1)].

DESCRIPTION

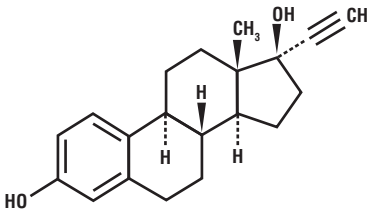
Chateal EQ (levonorgestrel and ethinyl estradiol tablets) is a combination oral contraceptive (COC) consisting of 21 orange active tablets, each containing 0.15 mg of levonorgestrel USP, a synthetic progestin and 0.03 mg of ethinyl estradiol USP, an estrogen, and 7 green inert tablets (without hormones).

The structural formulas for the active components are:



Levonorgestrel
$C_{21}H_{28}O_2$ MW: 312.4

Levonorgestrel is chemically 18,19-Dinorpregn-4-en-20-yn-3-one, 13-ethyl-17-hydroxy-,(17α)- (-)-.



Ethinyl Estradiol
$C_{20}H_{24}O_2$ MW: 296.4

Ethinyl Estradiol is 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3, 17-diol.

Each orange active tablet contains the following inactive ingredients: croscarmellose sodium, FD&C Yellow No. 6 Aluminum Lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and povidone.

Each green inert tablet contains the following inactive ingredients: anhydrous lactose, croscarmellose sodium, FD & C Blue No. 2 Aluminum Lake, ferric oxide (sicovit yellow 10), magnesium stearate, microcrystalline cellulose, and povidone.

CLINICAL PHARMACOLOGY

Combination oral contraceptives prevent pregnancy primarily by suppressing ovulation.

INDICATIONS AND USAGE

Chateal EQ is indicated for use by females of reproductive potential to prevent pregnancy.

CONTRAINDICATIONS

Chateal EQ is contraindicated in females who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 [see BOXED WARNING and WARNINGS (1)].
  - Have current or history of deep vein thrombosis or pulmonary embolism [see WARNINGS (1)].
  - Have cerebrovascular disease [see WARNINGS (1)].
  - Have coronary artery disease [see WARNINGS (1)].
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) [see WARNINGS (1)].
  - Have inherited or acquired hypercoagulopathies [see WARNINGS (1)].
  - Have uncontrolled hypertension or hypertension with vascular disease [see WARNINGS (3)].
  - Have diabetes mellitus and are over age 35, diabetes mellitus with hypertension or vascular disease or other end-organ damage, or diabetes mellitus of >20 years duration [see WARNINGS (7)].
  - Have headaches with focal neurological symptoms, migraine headaches with aura, or over age 35 with any migraine headaches [see WARNINGS (8)].
- Current or history of breast cancer or other estrogen- or progestin-sensitive cancer.
- Liver tumors, acute viral hepatitis, or severe (decompensated) cirrhosis [see WARNINGS (2)].
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations [see WARNINGS (5)].
- Undiagnosed abnormal uterine bleeding [see WARNINGS (9)].
- Pregnancy, because there is no reason to use COCs during pregnancy [see PRECAUTIONS (6)].

WARNINGS

1. Thromboembolic Disorders and Other Vascular Conditions

- Stop Chateal EQ if an arterial or venous thrombotic/thromboembolic event occurs.
- Stop Chateal EQ if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately.
- Discontinue Chateal EQ during prolonged immobilization. If feasible, stop Chateal EQ at least four weeks before and through two weeks after major surgery, or other surgeries known to have an elevated risk of thromboembolism.
- Start Chateal EQ no earlier than four weeks after delivery in females who are not breast-feeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the likelihood of ovulation increases after the third postpartum week.
- Before starting Chateal EQ evaluate any past medical history or family history of thrombotic or thromboembolic disorders and consider whether the history suggests an inherited or acquired hypercoagulopathy. Chateal EQ is contraindicated in females with a high risk of arterial or venous thrombotic/thromboembolic diseases (see CONTRAINDICATIONS).

Arterial Events

COCs increase the risk of cardiovascular events and cerebrovascular events, such as myocardial infarction and stroke. The risk is greater among older women (> 35 years of age), smokers, and females with hypertension, dyslipidemia, diabetes, or obesity.

Chateal EQ is contraindicated in women over 35 years of age who smoke (see CONTRAINDICATIONS). Cigarette smoking increases the risk of serious cardiovascular events from COC use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked.

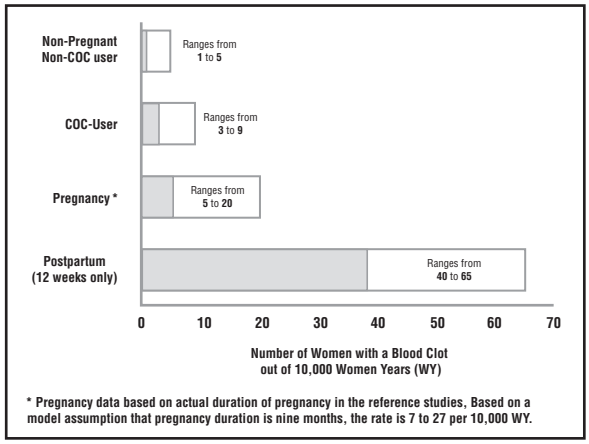
Venous Events

Use of COCs increases the risk of venous thromboembolic events (VTEs), such as deep vein thrombosis and pulmonary embolism. Risk factors for VTEs include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs (see CONTRAINDICATIONS). While the increased risk of VTE associated with use of COCs is well-established, the rates of VTE are even greater during pregnancy, and especially during the postpartum period (see Figure 1). The rate of VTE in females using COCs has been estimated to be 3 to 9 cases per 10,000 woman-years.

The risk of VTE is highest during the first year of use of a COC and when restarting hormonal contraception after a break of four weeks or longer. Based on results from a few studies, there is some evidence that this is true for non-oral products as well. The risk of thromboembolic disease due to COCs gradually disappears after COC use is discontinued.

Figure 1 shows the risk of developing a VTE for females who are not pregnant and do not use oral contraceptives, for females who use oral contraceptives, for pregnant females, and for females in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 females who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these females will develop a VTE.

Figure 1: Likelihood of Developing a VTE



*** Pregnancy data based on actual duration of pregnancy in the reference studies, Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.**

2. Liver Disease

Elevated Liver Enzymes

Chateal EQ is contraindicated in females with acute viral hepatitis or severe (decompensated) cirrhosis of liver (see CONTRAINDICATIONS). Discontinue Chateal EQ if jaundice develops. Acute liver test abnormalities may necessitate the discontinuation of COC use until the liver

tests return to normal and COC causation has been excluded.

Liver Tumors

Chateal EQ is contraindicated in females with benign or malignant liver tumors (see CONTRAINDICATIONS). COCs increase the risk of hepatic adenomas. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death from abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (> 8 years) COC users. The attributable risk of liver cancers in COC users is less than one case per million users.

3. Hypertension

Chateal EQ is contraindicated in females with uncontrolled hypertension or hypertension with vascular disease (see CONTRAINDICATIONS). For all females, including those with well-controlled hypertension, monitor blood pressure at routine visits and stop Chateal EQ if blood pressure rises significantly.

An increase in blood pressure has been reported in females using COCs, and this increase is more likely in older women with extended duration of use. The effect of COCs on blood pressure may vary according to the progestin in the COC.

4. Age-related Considerations

The risk for cardiovascular disease and prevalence of risk factors for cardiovascular disease increase with age. Certain conditions, such as smoking and migraine headache without aura, that do not contraindicate COC use in younger females, are contraindications to use in women over 35 years of age [see CONTRAINDICATIONS and WARNINGS (1)]. Consider the presence of underlying risk factors that may increase the risk of cardiovascular disease or VTE, particularly before initiating a COC for women over 35 years, such as:

- Hypertension
- Diabetes
- Dyslipidemia
- Obesity

5. Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications such as COCs. Discontinue Chateal EQ prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (see CONTRAINDICATIONS). Chateal EQ can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

6. Gallbladder Disease

Studies suggest an increased risk of developing gallbladder disease among COC users. Use of COCs may also worsen existing gallbladder disease.

A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Females with a history of pregnancy-related cholestasis may be at an increased risk for COC-related cholestasis.

7. Adverse Carbohydrate and Lipid Metabolic Effects

Hyperglycemia

Chateal EQ is contraindicated in diabetic women over age 35, or females who have diabetes with hypertension, nephropathy, retinopathy, neuropathy, other vascular disease, or females with diabetes of > 20 years duration (see CONTRAINDICATIONS). Chateal EQ may decrease glucose tolerance. Carefully monitor prediabetic and diabetic females who are using Chateal EQ.

Dyslipidemia

Consider alternative contraception for females with uncontrolled dyslipidemia. Chateal EQ may cause adverse lipid changes.

Females with hypertriglyceridemia, or a family history thereof, may have an increase in serum triglyceride concentrations when using Chateal EQ, which may increase the risk of pancreatitis.

8. Headache

Chateal EQ is contraindicated in females who have headaches with focal neurological symptoms or have migraine headaches with aura, and in women over age 35 years who have migraine headaches with or without aura (see CONTRAINDICATIONS).

If a woman using Chateal EQ develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Chateal EQ if indicated. Consider discontinuation of Chateal EQ if there is an increased frequency or severity of migraines during COC use (which may be prodromal of a cerebrovascular event).

9. Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Females using Chateal EQ may experience unscheduled (breakthrough or intracyclic) bleeding and spotting, especially during the first three months of use. Bleeding irregularities may resolve over time or by changing to a different contraceptive product. If bleeding persists or occurs after previously regular cycles, evaluate for causes such as pregnancy or malignancy.

In two clinical trials of Chateal EQ (1084 subjects reporting for a total of 8186 treatment cycles and 238 subjects reporting for a total of 1102 treatment cycles), breakthrough bleeding occurred in 6.9% and 8.1% of reported cycles, and spotting occurred in 8.6% and 7.9% of reported cycles over the total study duration, respectively. In the two trials, intermenstrual bleeding (i.e., breakthrough bleeding and/or spotting) occurred in 13.1% and 12.9% of reported cycles over the total study duration, respectively. In one trial, 33 subjects out of 1084 (3.0%) discontinued due to bleeding irregularities (i.e., breakthrough bleeding and spotting); in the other trial, 6 subjects out of 238 (2.5%) discontinued due to bleeding irregularities.

Amenorrhea and Oligomenorrhea

Females who use Chateal EQ may experience absence of scheduled (withdrawal) bleeding, even if they are not pregnant. In two clinical trials of Chateal EQ, one including 8186 reported treatment cycles, and the other including 1102 reported treatment cycles, amenorrhea occurred in 1.5% of treatment cycles in each trial.

If scheduled bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or two active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and perform appropriate diagnostic measures. If the patient has adhered to the prescribed dosing schedule and misses two consecutive periods, rule out pregnancy.

After discontinuation of a COC, amenorrhea or oligomenorrhea may occur, especially if these conditions were pre-existent.

10. Depression

Carefully observe females with a history of depression and discontinue Chateal EQ if depression recurs to a serious degree. Data on the association of COCs with onset of depression or exacerbation of existing depression are limited.

11. Cervical Cancer

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. There is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

12. Effect on Binding Globulins

The estrogen component of Chateal EQ may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

13. Hereditary Angioedema

In females with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

14. Chloasma

Chloasma may occur with Chateal EQ use, especially in females with a history of chloasma gravidarum. Advise females with a history of chloasma to avoid exposure to the sun or ultraviolet radiation while using Chateal EQ.

PRECAUTIONS

1. 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 [see WARNINGS (7)].

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been case reports of significant elevations of plasma triglycerides leading to pancreatitis.

2. 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.

3. Gastrointestinal Motility

Diarrhea and/or vomiting may reduce hormone absorption (see DOSAGE AND ADMINISTRATION).

4. Drug Interactions

The sections below provide information on substances for which data on drug interactions with COCs are available. There is little information available about the clinical effect of most drug interactions that may affect COCs. However, based on the known pharmacokinetic effects of these drugs, clinical strategies to minimize any potential adverse effect on contraceptive effectiveness or safety are suggested.

Consult the approved product labeling of all concurrently used drugs to obtain further information about interactions with COCs or the potential for metabolic enzyme or transporter system alterations.

No drug-drug interaction studies were conducted with Chateal EQ.

4.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances Decreasing the Plasma Concentrations of COCs and Potentially Diminishing the Efficacy of COCs:

Table 1 includes substances that demonstrated an important drug interaction with Chateal EQ.

Table 1: Significant Drug Interactions Involving Substances That Affect COCs

Metabolic Enzyme Inducers	
Clinical effect	• Concomitant use of COCs with metabolic enzyme inducers may decrease the plasma concentrations of the estrogen and/or progestin component of COCs. • Decreased exposure of the estrogen and/or progestin component of COCs may potentially diminish the effectiveness of COCs and may lead to contraceptive failure or an increase in breakthrough bleeding.
Prevention or management	• Counsel females to use an alternative method of contraception or a backup method when enzyme inducers are used with COCs. • Continue backup contraception for 28 days after discontinuing the enzyme inducer to maintain contraceptive reliability.
Examples	Aprepitant, barbiturates, bosentan, carbamazepine, efavirenz, felbamate, griseofulvin, oxcarbazepine, phenytoin, rifampin, rifabutin, rufinamide, topiramate, products containing St. John's wort[a], and certain protease inhibitors (see separate section on protease inhibitors below).
Colesevelam	
Clinical effect	• Concomitant use of COCs with colesevelam significantly decreases systemic exposure of ethinyl estradiol. • Decreased exposure of the estrogen component of COCs may potentially reduce contraceptive efficacy or result in an increase in breakthrough bleeding, depending on the strength of ethinyl estradiol in the COC.
Prevention or management	Administer 4 or more hours apart to attenuate this drug interaction.

[a] Induction potency of St. John's wort may vary widely based on preparation.

Substances increasing the systemic exposure of COCs:

Co-administration of atorvastatin or rosuvastatin and COCs containing ethinyl estradiol increase systemic exposure of ethinyl estradiol by approximately 20 to 25 percent. Ascorbic acid and acetaminophen may increase systemic exposure of ethinyl estradiol, possibly by inhibition of conjugation. CYP3A inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice,[7] or ketoconazole may increase systemic exposure of the estrogen and/or progestin component of COCs.

Human immunodeficiency virus (HIV)/hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:

Significant decreases in systemic exposure of the estrogen and/or progestin have been noted when COCs are co-administered with some HIV protease inhibitors (e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir), some HCV protease inhibitors (e.g., boceprevir and telaprevir), and some non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine).

In contrast, significant increases in systemic exposure of the estrogen and/or progestin have been noted when COCs are co-administered with certain other HIV protease inhibitors (e.g., indinavir and atazanavir/ritonavir) and with other non-nucleoside reverse transcriptase inhibitors (e.g., etravirine).

4.2 Effects of Combined Oral Contraceptives on Other Drugs

Table 2 provides significant drug interaction information for drugs co-administered with Chateal EQ.

Table 2: Significant Drug Interaction Information for Drugs Co-Administered With COCs

Lamotrigine	
Clinical effect	• Concomitant use of COCs with lamotrigine may significantly decrease systemic exposure of lamotrigine due to induction of lamotrigine glucuronidation. • Decreased systemic exposure of lamotrigine may reduce seizure control.
Prevention or management	Dose adjustment may be necessary. Consult the approved product labeling for lamotrigine.
Thyroid Hormone Replacement Therapy or Corticosteroid Replacement Therapy	
Clinical effect	Concomitant use of COCs with thyroid hormone replacement therapy or corticosteroid replacement therapy may increase systemic exposure of thyroid-binding and cortisol-binding globulin (see Warnings, EFFECT ON BINDING GLOBULINS).
Prevention or management	The dose of replacement thyroid hormone or cortisol therapy may need to be increased. Consult the approved product labeling for the therapy in use (see Warnings, EFFECT ON BINDING GLOBULINS).
Other Drugs	
Clinical effect	Concomitant use of COCs may decrease systemic exposure of acetaminophen, morphine, salicylic acid, and temazepam. Concomitant use with ethinyl estradiol-containing COCs may increase systemic exposure of other drugs (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole).
Lamotrigine	
Prevention or management	The dosage of drugs that can be affected by this interaction may need to be increased. Consult the approved product labeling for the concomitantly used drug.

4.3 Effect on Laboratory Tests

The use of COCs may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

5. Carcinogenesis

See WARNINGS (11).

6. Pregnancy

Risk Summary

Chateal EQ is contraindicated in pregnancy because there is no reason to use COCs in pregnancy. Discontinue Chateal EQ if pregnancy occurs. Epidemiologic studies and meta-analyses have not found an increased risk of genital or nongenital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to COCs before conception or during early pregnancy. Animal studies to evaluate embryo/fetal toxicity were not conducted.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4 percent and 15 to 20 percent, respectively.

7. Lactation

Risk Summary

Contraceptive hormones and/or metabolites are present in human milk. COCs can reduce milk production in breast-feeding females. This reduction can occur at any time but is less likely to occur once breast-feeding is well-established. When possible, advise the nursing female to use other methods of contraception until she discontinues breast-feeding. (see DOSAGE AND ADMINISTRATION). The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Chateal EQ and any potential adverse effects on the breast-fed child from Chateal EQ or from the underlying maternal condition.

8. Pediatric Use

Safety and efficacy of Chateal EQ have been established in females of reproductive potential. Use of Chateal EQ before menarche is not indicated.

9. Geriatric Use

Chateal EQ has not been studied in postmenopausal women and is not indicated in this population.

10. PATIENT COUNSELING INFORMATION

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that this product does not protect against HIV-infection (AIDS) and other sexually transmitted infections.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed.
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts Chateal EQ postpartum, and who has not yet had a period, to use an additional method of contraception until she has taken an orange tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Pregnancy should be considered in the event of amenorrhea, and should be ruled out if amenorrhea is associated with symptoms of pregnancy, such as morning sickness or unusual breast tenderness.

ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular adverse events [see BOXED WARNING and WARNINGS (1)]
- Vascular events [see WARNINGS (1)]
- Liver disease [see WARNINGS (2)]
- Hypertension [see WARNINGS (3)]
- Gallbladder disease [see WARNINGS (6)]
- Carbohydrate and lipid effects [see WARNINGS (7)]
- Headache [see WARNINGS (8)]
- Carcinoma of the cervix [see WARNINGS (11)]

Adverse reactions reported by COC users and described elsewhere in the labeling are:

- Bleeding irregularities and amenorrhea [see WARNINGS (9)]
- Mood changes, including depression [see WARNINGS (10)]
- Melasma/chloasma which may persist [see WARNINGS (14)]
- Edema/fluid retention [see PRECAUTIONS (2)]
- Diminution in lactation when given immediately postpartum [see PRECAUTIONS

(7)]

The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related: Breast tenderness, pain, enlargement, secretion; Nausea, vomiting and gastrointestinal symptoms (such as abdominal pain, cramps and bloating); Change in menstrual flow; Temporary infertility after discontinuation of treatment; Change in weight or appetite (increase or decrease); Change in cervical erosion and secretion; Cholestatic jaundice; Rash (allergic); Vaginitis, including candidiasis; Change in corneal curvature (steepening); Intolerance to contact lenses; Mesenteric thrombosis; Decrease in serum folate levels; Exacerbation of systemic lupus erythematosus; Exacerbation of porphyria; Exacerbation of chorea; Aggravation of varicose veins; Anaphylactic/ anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.

The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Congenital anomalies; Premenstrual syndrome; Cataracts; Optic neuritis, which may lead to partial or complete loss of vision; Cystitis-like syndrome; Nervousness; Dizziness; Hirsutism; Loss of scalp hair; Erythema multiforme; Erythema nodosum; Hemorrhagic eruption; Impaired renal function; Hemolytic uremic syndrome; Budd-Chiari syndrome; Acne; Changes in libido; Colitis; Sickle-cell disease; Cerebral-vascular disease with mitral valve prolapse; Lupus-like syndromes; Pancreatitis; Dysmenorrhea.

OVERDOSAGE

There have been no reports of serious adverse outcomes from overdose of COCs, including ingestion by children. Overdose may cause uterine bleeding in females and nausea.

DOSAGE AND ADMINISTRATION

1. How to Start and Take Chateal EQ

Chateal EQ is dispensed in a blister pack containing 28 tablets (see HOW SUPPLIED). Chateal EQ may be started using either a Day 1 start or a Sunday start (see Table 3). For the first cycle of a Sunday start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

Table 3: Instructions for Administration of Chateal EQ

Starting Chateal EQ in females with no current use of hormonal contraception	Day 1 start • Take first tablet without regard to meals on the first day of menses • Take subsequent tablets once daily at the same time each day • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet)
	Sunday start • Take first tablet without regard to meals on the first Sunday after the onset of menstrual period • Take subsequent tablets once daily at the same time each day • Use additional nonhormonal contraception for the first seven days of product use • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last tablet)
Switching from another contraceptive method • **A COC**	Start Chateal EQ: • On the day when the new pack of the previous COC would have been started
• **Transdermal patch**	• On the day when next application would have been scheduled
• **Vaginal ring**	• On the day when next insertion would have been scheduled
• **Injection**	• On the day when next injection would have been scheduled
• **Intrauterine contraceptive**	• On the day of removal
• **Implant**	• On the day of removal

Starting Chateal EQ after Abortion or Miscarriage

First-trimester

- After a first-trimester abortion or miscarriage, Chateal EQ may be started immediately. An additional method of contraception is not needed if Chateal EQ is started immediately.
- If Chateal EQ is not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms or spermicide) for the first seven days of her first cycle of Chateal EQ.

Second-trimester

- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start Chateal EQ following the instructions in Table 3 for Day 1 or Sunday start. Use additional non-hormonal contraception (such as condoms or spermicide) for the first seven days of the patient's first cycle of Chateal EQ (see CONTRAINDICATIONS, WARNINGS (1), PRECAUTIONS (10) and FDA-APPROVED PATIENT LABELING).

Starting Chateal EQ after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with Chateal EQ following the instructions in Table 3 for women not currently using hormonal contraception.
- Chateal EQ is not recommended for use in lactating women (see PRECAUTIONS (7) and FDA-APPROVED PATIENT LABELING).
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of Chateal EQ (see CONTRAINDICATIONS, WARNINGS (9), PRECAUTIONS (6) and FDA-APPROVED PATIENT LABELING).

2. Dosing Chateal EQ

Instruct patients to take one tablet by mouth at the same time every day. To achieve maximum contraceptive effectiveness, patients must take Chateal EQ as directed, in the order directed on the blister pack. The failure rate may increase when pills are missed or taken incorrectly.

3. Missed doses

Instruct patients about the handling of missed doses (e.g., to take single missed pills as soon as possible) and to follow the dosing instructions provided in the FDA-approved patient labeling.

Table 4: Instructions for Missed Chateal EQ

• If one active tablet is missed in Weeks 1, 2, or 3	Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.
• If two active tablets are missed in Week 1 or Week 2	Take the two missed tablets as soon as possible and the next two active tablets the next day. Continue taking one tablet a day until the pack is finished. **Additional nonhormonal contraception (such as condoms or spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**
• If two active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	Day 1 start: Throw out the rest of the pack and start a new pack that same day. Sunday start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. **Additional nonhormonal contraception (such as condoms or spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**

4. Advice in Case of Gastrointestinal Disturbances

If vomiting occurs within 3 to 4 hours after taking Chateal EQ, the patient should proceed as if she missed a tablet. In case of prolonged vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken.

HOW SUPPLIED/STORAGE AND HANDLING

Chateal EQ (Levonorgestrel and Ethinyl Estradiol Tablets USP, 0.15 mg/0.03 mg) are available in a carton of 3 pouches, each containing 28 tablets:

21 Active Tablets: Orange, round, biconvex, beveled-edge, unscored tablets, debossed with "S" on one side and "44" on other side.

7 Inert Tablets: Green, round, mottled biconvex, beveled-edge, unscored and uncoated tablets, debossed with "S" on one side and "61" on other side of the tablet.

1 Pouch of 28 tablets	NDC 50102-230-21
Carton of 3 Pouches	NDC 50102-230-23

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

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 01/2021

Patient Information
Chateal EQ®
[sha-teÉl]
(Levonorgestrel and Ethinyl Estradiol Tablets USP 0.15 mg/0.03 mg)

What is the most important information I should know about Chateal EQ?

Do not use Chateal EQ if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from hormonal birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

What is Chateal EQ?

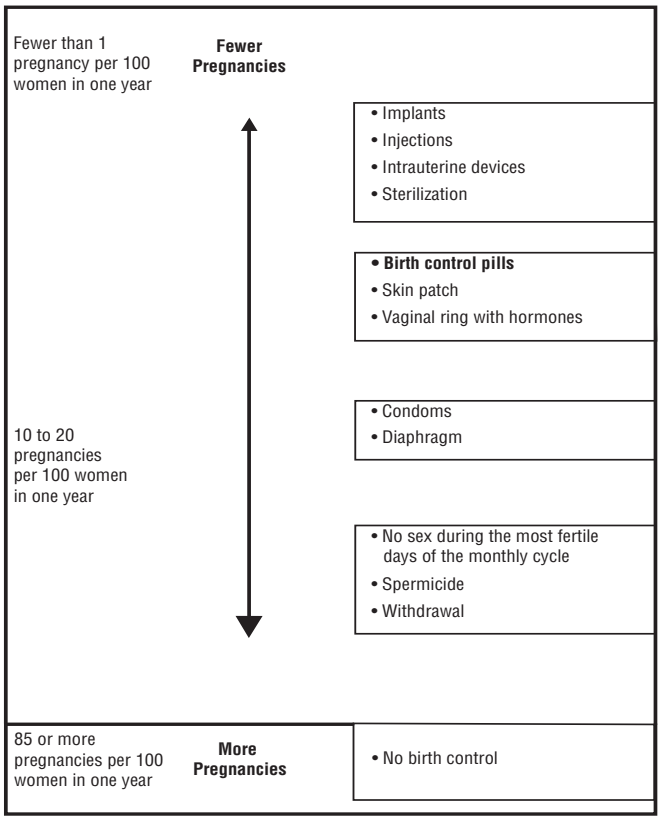
Chateal EQ is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

How does Chateal EQ work for contraception?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of clinical studies, about 1 to 5 out of 100 women may get pregnant during the first year they use Chateal EQ.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



Who should not take Chateal EQ?

Do not take Chateal EQ if you:

- smoke and are over 35 years of age
- had blood clots in your arms, legs, lungs, or eyes
- had a problem with your blood that makes it clot more than normal
- have certain heart valve problems or irregular heart beat
- had a stroke
- had a heart attack
- have high blood pressure that cannot be controlled by medicine
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or any migraine headaches if you are over 35 years of age
- had breast cancer or any cancer that is sensitive to female hormones
- have liver problems, including liver tumors
- have any unexplained vaginal bleeding
- are pregnant
- take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.

If any of these conditions happen while you are taking Chateal EQ, stop taking Chateal EQ right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking Chateal EQ.

What should I tell my healthcare provider before taking Chateal EQ?

Tell your healthcare provider if you:

- are pregnant or think you may be pregnant
- are depressed now or have been depressed in the past
- had yellowing of your skin or eyes (jaundice) caused by pregnancy (cholestasis of pregnancy)
- are breastfeeding or plan to breastfeed. Chateal EQ may decrease the amount of breast milk you make. A small amount of the hormones in Chateal EQ may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Chateal EQ may affect the way other medicines work, and other medicines may affect how well Chateal EQ works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Chateal EQ?

Read the Instructions for Use at the end of this Patient Information.

What are the possible serious side effects of Chateal EQ?

- Like pregnancy, Chateal EQ may cause serious side effects, including blood clots in your lungs, heart attack, or a stroke that may lead to death. Some other examples of serious blood clots include blood clots in the legs or eyes.

  Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age. Serious blood clots are more likely to happen when you:

  o first start taking birth control pills
  o restart the same or different birth control pills after not using them for a month or more

Call your healthcare provider or go to a hospital emergency room right away if you have:

- leg pain that will not go away
- sudden severe shortness of breath
- a sudden, severe headache unlike your usual headaches
- sudden change in vision or blindness
- chest pain
- weakness or numbness in your arm or leg
- trouble speaking

Other serious side effects include:

- **liver problems, including:**
  o rare liver tumors
  o jaundice (cholestasis), especially if you previously had cholestasis of pregnancy. Call your healthcare provider if you have yellowing of your skin or eyes.
- **high blood pressure.** You should see your healthcare provider for a yearly check of your blood pressure.
- **gallbladder problems**
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood**
- **new or worsening headaches, including migraine headaches**
- **irregular or unusual vaginal bleeding and spotting between your menstrual periods, especially during the first 3 months of taking Chateal EQ.**
- **depression**
- **possible cancer in your breast and cervix**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider if you have a swollen face, lips, mouth, tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher if you have a history of angioedema.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Women who tend to get chloasma should avoid spending a long time in sunlight, tanning booths, and under sun lamps while taking Chateal EQ. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of oral contraceptives?

- nausea
- vomiting
- bleeding between menstrual periods
- weight gain
- breast tenderness
- difficulty wearing contact lenses

These are not all the possible side effects of Chateal EQ. For more information, ask your healthcare provider or pharmacist.

You may report side effects to the FDA at 1-800-FDA-1088.

What else should I know about taking Chateal EQ?

- If you are scheduled for any lab tests, tell your healthcare provider you are taking Chateal EQ. Certain blood tests may be affected by Chateal EQ.
- Chateal EQ does not protect against HIV-infection (AIDS) and other sexually transmitted infections.

How should I store Chateal EQ?

- Store Chateal EQ at room temperature between 68° to 77°F (20° to 25°C).
- Protect from light.

General information about the safe and effective use of Chateal EQ.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Chateal EQ for a condition for which it was not prescribed. Do not give Chateal EQ to other people, even if they have the same symptoms that you have.

This Patient Information Leaflet summarizes the most important information about Chateal EQ. You can ask your pharmacist or healthcare provider for information about Chateal EQ that is written for health professionals.

For more information, call Afaxys Pharma, LLC at 1-855-888-2467

Do birth control pills cause cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What if I want to become pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

What should I know about my period when taking Chateal EQ?

Your periods may be lighter and shorter than usual. Some women may miss a period. Irregular vaginal bleeding or spotting may happen while you are taking Chateal EQ, especially during the first few months of use. This usually is not a serious problem. It is important to continue taking your pills on a regular schedule to prevent a pregnancy.

What are the ingredients in Chateal EQ?

Active ingredients: Each orange pill contains levonorgestrel and ethinyl estradiol.

Inactive ingredients:

Orange pills: croscarmellose sodium, FD&C Yellow No. 6 Aluminum Lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and povidone.

Green pills: anhydrous lactose, croscarmellose sodium, FD & C Blue No. 2 Aluminum Lake, ferric oxide (sicovit yellow 10), magnesium stearate, microcrystalline cellulose, and povidone.

Instructions For Use

Chateal EQ®

[sha-teÉl]

(Levonorgestrel and Ethinyl Estradiol Tablets USP 0.15 mg/0.03 mg)

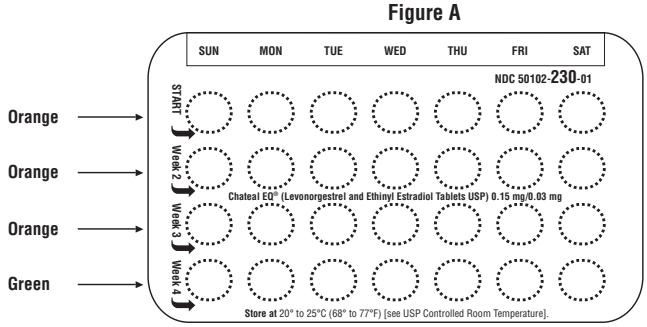
Important Information about taking Chateal EQ

- Take **1** pill every day at the same time. Take the pills in the order directed on your pill pack.
- Do not skip your pills, even if you do not have sex often. If you miss pills (including starting the pack late) **you could get pregnant**. The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take Chateal EQ, talk to your healthcare provider.
- When you first start taking Chateal EQ, spotting or light bleeding in between your periods may occur. Contact your healthcare provider if this does not go away after a few months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking Chateal EQ. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If your nausea does not go away, call your healthcare provider.
- Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills (see **What should I do if I miss any Chateal EQ pills?** below), you could also feel a little sick to your stomach.
- It is not uncommon to miss a period. However, if you miss a period and have not taken Chateal EQ according to directions, or feel like you may be pregnant, call your healthcare provider. If you have a positive pregnancy test, you should stop taking Chateal EQ.
- If you have vomiting or diarrhea within **3 to 4** hours of taking an orange pill, take another orange pill as soon as possible. Continue taking all your remaining pills in order. Start the first pill of your next pill pack the day after finishing your current pill pack. This will be 1 day earlier than originally scheduled. Continue on your new schedule.
- If you have vomiting or diarrhea for more than 1 day, your birth control pills may not work as well. Use an additional birth control method, like condoms or spermicide, until you check with your healthcare provider.
- Stop taking Chateal EQ at least **4** weeks before you have major surgery and do not restart after the surgery without asking your healthcare provider. Be sure to use other forms of contraception (like condoms or spermicide) during this time period.

Before you start taking Chateal EQ:

- Decide what time of day you want to take your pill. It is important to take it at the same time every day and in the order as directed on your pill pack.
- Look at your pill pack. Your pill pack consists of 1 blister pack that holds 28 individually sealed pills. The 28 pills consist of 21 orange pills (3 rows of 7 pills) and 7 green pills (1 row of 7 pills). **See Figure A**.

Figure A



- Also find:
  - Where on the blister pack to start taking pills (upper left corner) and
  - In what order to take the pills (follow the weeks)
- Be sure you have ready at all times another kind of birth control (such as condoms or spermicide), to use as a back-up in case you miss pills.

When should I start taking Chateal EQ?

If you start taking Chateal EQ and you have not used a hormonal birth control method before:

- There are 2 ways to start taking your birth control pills. You can either start on a Sunday (Sunday Start) or on the first day (Day 1) of your natural menstrual period (Day 1 Start). Your healthcare provider should tell you when to start taking your birth control pill.
- If you use the Sunday Start, use non-hormonal back-up contraception such as condoms or spermicide for the first 7 days that you take Chateal EQ. You do not need back-up contraception if you use the Day 1 Start.

If you start taking Chateal EQ and you are switching from another birth control pill:

- Start your new Chateal EQ pack on the same day that you would start the next pack of your previous birth control method.
- Do not continue taking the pills from your previous birth control pill pack.

If you start taking Chateal EQ and previously used a vaginal ring:

- Start using Chateal EQ on the day you would have started the next ring.

If you start taking Chateal EQ and previously used a transdermal patch:

- Start using Chateal EQ on the day you would have started a new cycle (first patch application).

If you start taking Chateal EQ and you are switching from a progestin-only method such as an implant or injection:

- Start taking Chateal EQ on the day of removal of your implant, or on the day when you would have had your next injection.

If you start taking Chateal EQ and you are switching from an intrauterine device or system (IUD or IUS):

- Start taking Chateal EQ on the day of removal of your IUD or IUS.
- You do not need back-up contraception if your IUD or IUS is removed on the first day (Day 1) of your period. If your IUD or IUS is removed on any other day, use non-hormonal back-up contraception such as condoms or spermicide for the first **7** days that you take Chateal EQ.

Keep a calendar to track your period: If this is the first time you are taking birth control pills, read, "**When should I start taking Chateal EQ?**" above. Follow these instructions for either a **Sunday Start** or a **Day 1 Start**.

Instructions for using your Chateal EQ Blister Pack:

Sunday Start:

You will use a **Sunday Start** if your healthcare provider told you to take your first pill on a Sunday.

- Take pill **1** on the Sunday **after your period starts.** To remove your tablet from the blister pack, push the tablet through foil.
- If your period starts on a Sunday, take pill "**1**" that day and refer to Day 1 Start instructions below.
- Take **1** pill every day in the order on the blister pack at the same time each day for **28** days.
- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack (Sunday). Take the first pill in the new pack whether or not you are having your period.
- Use non-hormonal back-up contraception such as condoms or spermicide for the first **7** days of the first cycle that you take Chateal EQ.

Day 1 Start:

You will use a **Day 1 Start** if your doctor told you to take your first pill (Day 1) on the **first day of your period**.

- Take **1** pill every day in the order of the blister pack, at the same time each day, for **28** days. To remove your tablet from the blister pack, push the tablet through foil.
- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack. Take the first pill in the new pack whether or not you are having your period.

What should I do if I miss any Chateal EQ pills?

If you miss 1 pill in Weeks 1, 2, or 3, follow these steps:

- 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.
- Then continue taking 1 pill every day until you finish the pack.
- You do not need to use a back-up birth control method if you have sex.

If you miss 2 pills in Week 1 or Week 2 of your pack, follow these steps:

- Take the 2 missed pills as soon as possible and the next 2 pills the next day.
- Then continue to take 1 pill every day until you finish the pack.
- Use a non-hormonal birth control method (such as a condom or spermicide) as a back-up if you have sex during the first 7 days after missing your pills.

If you miss 2 pills in a row in Week 3, or you miss 3 or more pills in a row during Weeks

1, 2, or 3 of the pack, follow these steps:

- **If you are a Day 1 Starter:**
  - Throw out the rest of the pill pack and start a new pack that same day.
  - 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 healthcare provider because you might be pregnant.
  - You could become pregnant if you have sex during the first 7 days after you restart your pills. You MUST use a non-hormonal birth control method (such as a condom or spermicide) as a back-up if you have sex during the first 7 days after you restart your pills.
- **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.
  - Use a non-hormonal birth control method (such as a condom or spermicide) as a back-up if you have sex during the first 7 days after you restart your pills.

If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

This Patient Information and Instructions for Use have been approved by the U.S. Food and Drug Administration.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 01/2021

afaxys®

Cyred EQ™
(Desogestrel and Ethinyl Estradiol Tablets USP 0.15 mg/0.03 mg)
Rx only

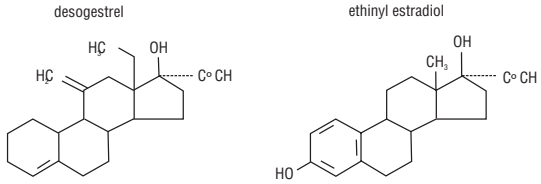
WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including Cyred EQ™, should not be used by women who are over 35 years of age and smoke.

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

DESCRIPTION

Cyred EQ™ tablets provide an oral contraceptive regimen of 21 white to off-white round tablets each containing 0.15 mg desogestrel (13-ethyl-11-methylene-18,19-dinor-17 alpha-pregn-4-en-20-yn-17-ol) and 0.03 mg ethinyl estradiol USP (19-nor-17 alpha-pregna-1,3,5 (10)-trien-20-yne-3,17,diol). Inactive ingredients include colloidal silicon dioxide, lactose monohydrate, potato starch, povidone, stearic acid, and vitamin E. Each green tablet contains the following inactive ingredients: anhydrous lactose, croscarmellose sodium, FD&C Blue No.2 Aluminum Lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, and povidone.



Cyred EQ meets USP Dissolution Test 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Combined 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 changes in the endometrium which reduce the likelihood of implantation.

Receptor binding studies, as well as studies in animals, have shown that 3-keto-desogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity.[91,92] The relevance of this latter finding in humans is unknown.

Pharmacokinetics

Desogestrel is rapidly and almost completely absorbed and converted into 3-keto-desogestrel, its biologically active metabolite. Following oral administration, the relative bioavailability of desogestrel, as measured by serum levels of 3-keto-desogestrel, is approximately 84%.

In the third cycle of use after a single dose of Cyred EQ™, maximum concentrations of 3-keto-desogestrel of 2,805 ± 1,203 pg/mL (mean ± SD) are reached at 1.4 ± 0.8 hours. The area under the curve ($AUC_{0-\infty}$) is 33,858 ± 11,043 pg/mL·hr after a single dose. At steady state, attained from at least day 19 onwards, maximum concentrations of 5,840 ± 1,667 pg/mL are reached at 1.4 ± 0.9 hours. The minimum plasma levels of 3-keto-desogestrel at steady state are 1,400 ± 560 pg/mL. The AUC_{0-24} at steady state is 52,299 ± 17,878 pg/mL·hr. The mean $AUC_{0-\infty}$ for 3-keto-desogestrel at single dose is significantly lower than the mean AUC_{0-24} at steady state. This indicates that the kinetics of 3-keto-desogestrel are non-linear due to an increase in binding of 3-keto-desogestrel to sex hormone-binding globulin in the cycle, attributed to increased sex hormone-binding globulin levels which are induced by the daily administration of ethinyl estradiol. Sex hormone-binding globulin levels increased significantly in the third treatment cycle from day 1 (150 ± 64 nmol/L) to day 21 (230 ± 59 nmol/L).

The elimination half-life for 3-keto-desogestrel is approximately 38 ± 20 hours at steady state. In addition to 3-keto-desogestrel, other phase I metabolites are 3α-OH-desogestrel, 3β-OH-desogestrel, and 3α-OH-5α-H-desogestrel. These other metabolites are not known to have any pharmacologic effects, and are further converted in part by conjugation (phase II metabolism) into polar metabolites, mainly sulfates and glucuronides.

Ethinyl estradiol is rapidly and almost completely absorbed. In the third cycle of use after a single dose of Cyred EQ™, the relative bioavailability is approximately 83%.

In the third cycle of use after a single dose of Cyred EQ™, maximum concentrations of ethinyl estradiol of 95 ± 34 pg/mL are reached at 1.5 ± 0.8 hours. The $AUC_{0-\infty}$ is 1,471 ± 268 pg/mL·hr after a single dose. At steady state, attained from at least day 19 onwards, maximum ethinyl estradiol concentrations of 141 ± 48 pg/mL are reached at about 1.4 ± 0.7 hours. The minimum serum levels of ethinyl estradiol at steady state are 24 ± 8.3 pg/mL. The AUC_{0-24} at steady state is 1,117 ± 302 pg/mL·hr. The mean $AUC_{0-\infty}$ for ethinyl estradiol following a single dose during treatment cycle 3 does not significantly differ from the mean AUC_{0-24} at steady state. This finding indicates linear kinetics for ethinyl estradiol.

The elimination half-life is 26 ± 6.8 hours at steady state. Ethinyl estradiol is subject to a significant degree of presystemic conjugation (phase II metabolism). Ethinyl estradiol escaping gut wall conjugation undergoes phase I metabolism and hepatic conjugation (phase II metabolism). Major phase I metabolites are 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol. Sulfate and glucuronide conjugates of both ethinyl estradiol and phase I metabolites, which are excreted in bile, can undergo enterohepatic circulation.

INDICATIONS AND USAGE

Cyred EQ™ tablets are indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

Oral contraceptives are highly effective. Table 1 lists the typical accidental pregnancy rates for users of combined oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, the IUD, and the Norplant System depends upon the reliability with which they are used. Correct and consistent use of these methods can result in lower failure rates.

In a clinical trial with Cyred EQ™, 1,195 subjects completed 11,656 cycles and a total of 10 pregnancies were reported. This represents an overall user-efficacy (typical user-efficacy) pregnancy rate of 1.12 per 100 women-years. This rate includes patients who did not take the drug correctly.

Table 1: PERCENTAGE OF WOMEN EXPERIENCING AN UNINTENDED PREGNANCY DURING THE FIRST YEAR OF TYPICAL USE AND THE FIRST YEAR OF PERFECT USE OF CONTRACEPTION AND THE PERCENTAGE CONTINUING USE AT THE END OF THE FIRST YEAR. UNITED STATES.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year*
Method (1)	**Typical Use † (2)**	**Perfect Use‡ (3)**	**(4)**
Chance#	85	85	
Spermicidesᵖ	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermalᵝ		2	
Post-Ovulation		1	
Withdrawal	19	4	
Capà			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragmà	20	6	56
Condomè			
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	0.1	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.§

Lactation Amenorrhea Method: LAM is a highly effective, temporary method of contraception.¶

Source: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowel D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York, NY; Irvington Publishers, 1998.

* 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 treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The FDA has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral® (1 dose is 2 white pills), Alesse® (1 dose is 5 pink pills), Nordette® or Levlen® (1 dose is

4 yellow pills).

¶ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency of duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

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.

Þ Foams, creams, gels, vaginal suppositories, and vaginal film.

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

à With spermicidal cream or jelly.

è Without spermicides.

Cyred EQ™ has not been studied for and is not indicated for use in emergency contraception.

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
- Known thrombophilic conditions
- Cerebral vascular or coronary artery disease (current or history)
- Valvular heart disease with complications
- Persistent blood pressure values of ≥ 160 mm Hg systolic or ≥ 100 mg Hg diastolic[102]
- Diabetes with vascular involvement
- Headaches with focal neurological symptoms
- Major surgery with prolonged immobilization
- Known or suspected carcinoma of the breast or personal history of breast cancer
- 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
- Acute or chronic hepatocellular disease with abnormal liver function
- Hepatic adenomas or carcinomas
- Known or suspected pregnancy
- Hypersensitivity to any component of this product
- Are receiving Hepatitis C drug combinations containing ombitasivir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations (see section 5 in WARNINGS, Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment).

WARNINGS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including Cyred EQ™, should not be used by women who are over 35 years of age and 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 formulations of higher doses of estrogens and progestogens than those in common use today. The effect of long-term use of the oral contraceptives with formulations of lower doses 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 Disorder and Other Vascular Problems

a. 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.[2,3,19 to 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 gradually disappears after combined oral contraceptive (COC) use is stopped.[2] VTE risk is highest in the first year of use and when restarting hormonal contraception after a break of four weeks or longer.

Several epidemiologic studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. In general, these studies indicate an approximate 2-fold increased risk, which corresponds to an additional 1 to 2 cases of venous thromboembolism per 10,000 women-years of use. However, data from additional studies have not shown this 2-fold increase in risk.

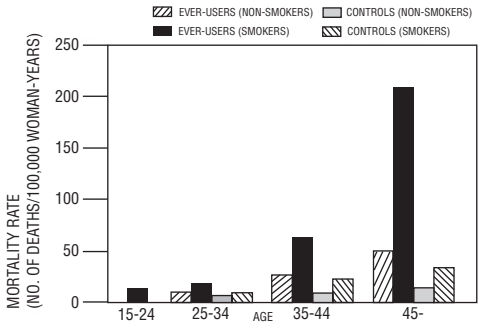
A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.[9] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[26] If feasible, 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 breastfeed.

b. 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 to 10] The risk is very low in women 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 and in nonsmokers over the age of 40 among women who use oral contraceptives. (See Figure 1.)

Figure 1: Circulatory Disease Mortality Rates per 100,000 Women-Years by Age, Smoking Status and Oral Contraceptive Use



(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 to 18] Oral contraceptives have been shown to increase blood pressure among users (see **section 10** 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.

There is some evidence that the risk of myocardial infarction associated with oral contraceptives is lower when the progestogen has minimal androgenic activity than when the activity is greater. Receptor binding and animal studies have shown that desogestrel or its active metabolite has minimal androgenic activity (see **CLINICAL PHARMACOLOGY**), although these findings have not been confirmed in adequate and well-controlled clinical trials.

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 to 29]

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

d. Dose-Related Risk of Vascular Disease from Oral Contraceptives

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease.[31 to 33] A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents.[14 to 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 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.

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 which is judged appropriate for the individual patient.

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 old 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 0.05 mg 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 2). 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 risk may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-dose formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means of contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks.

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

Table 2: 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 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44
No fertility-control methods*	7	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	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.

The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combined oral contraceptives (COC). However, this excess risk appears to decrease over time after COC discontinuation and by 10 years after cessation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use COCs before age 20. Most studies show a similar pattern of risk with COC use regardless of a woman's reproductive history or her family breast cancer history.

Breast cancers diagnosed in current or previous oral contraceptive users tend to be less clinically advanced than in nonusers.

Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormonally-sensitive tumor.

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 to 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.

In spite of many studies of the relationship between oral contraceptive use and breast and 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/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 from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

5. Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications such as COCs. Discontinue Cyred EQ™ prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (see **CONTRAINDICATIONS**). Cyred EQ™ can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

6. 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.

7. 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 to 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 oral contraceptives are 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. 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 if pregnancy is confirmed.

8. 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 to 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.

9. 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] In general, progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents.[17,66] 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 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** 1.a. and 1.d.), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

10. Elevated Blood Pressure

Women with significant hypertension should not be started on hormonal contraception.[98] An increase in blood pressure has been reported in women taking oral contraceptives[68] and this increase is more likely in older oral contraceptive users[69] and with extended duration of use.[61] Data from the Royal College of General Practitioners[12] and subsequent randomized trials have shown that the incidence of hypertension increases with increasing progestational activity and concentrations of progestogens.

Women with a history of hypertension or hypertension-related diseases, or renal disease[70] should be encouraged to use another method of contraception. If these women elect to use oral contraceptives, they should be monitored closely and if a clinically significant persistent elevation of blood pressure (BP) occurs (≥ 160 mm Hg systolic or ≥ 100 mm Hg diastolic) and cannot be adequately controlled, oral contraceptives should be discontinued. In general, women who develop hypertension during hormonal contraceptive therapy should be switched to a non-hormonal contraceptive. If other contraceptive methods are not suitable, hormonal contraceptive therapy may continue combined with antihypertensive therapy. Regular monitoring of BP throughout hormonal contraceptive therapy is recommended.[102] For most women, elevated blood pressure will return to normal after stopping oral contraceptives,[69] and there is no difference in the occurrence of hypertension among former and never users.[68,70,71]

11. 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.

12. 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 pre-existent.

13. Ectopic Pregnancy

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

PRECAUTIONS

1. General

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

2. 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.

3. 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.

4. 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.

5. 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.

6. Emotional Disorders

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

7. Contact Lenses

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

8. Drug Interactions

Consult the labeling of concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

Effects of Other Drugs on Combined Hormonal Contraceptives

Substances decreasing the plasma concentrations of COCs and potentially diminishing the efficacy of COCs:

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of COCs and potentially diminish the effectiveness of CHCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between hormonal contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with CHCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs:

Co-administration of atorvastatin or rosuvastatin and certain COCs containing EE increase AUC values for EE by approximately 20 to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir]) / HCV protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation:

Do not co-administer Cyred EQ™ with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations (see **section 5** in **WARNINGS, Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment**).

Colesevelam: Colesevelam, a bile acid sequestrant, given together with a combination oral hormonal contraceptive, has been shown to significantly decrease the AUC of EE. A drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Effects of Combined Hormonal Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. COCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increases with use of COCs.

9. 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. Triglycerides may be increased and levels of various other lipids and lipoproteins may be affected.
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.

10. Carcinogenesis

See **WARNINGS**.

11. Pregnancy

Pregnancy Category X.

See **CONTRAINDICATIONS** and **WARNINGS**.

12. 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 but to use other forms of contraception until she has completely weaned her child.

13. Pediatric Use

Safety and efficacy of Cyred EQ™ 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.

14. Geriatric Use

This product has not been studied in women over 65 years of age and is not indicated in this population.

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**).

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

There is evidence of an association between the following conditions and the use of oral contraceptives:

- 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
- Allergic reaction, including rash, urticaria, and angioedema
- 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 a causal association has been neither confirmed nor refuted:

- Pre-menstrual syndrome
- Cataracts
- Changes in appetite
- Cystitis-like syndrome
- Headache
- Nervousness
- Dizziness
- Hirsutism
- Loss of scalp hair
- Erythema multiforme
- Erythema nodosum
- Hemorrhagic eruption
- Vaginitis
- Porphyria
- Impaired renal function
- Hemolytic uremic syndrome
- Acne
- Changes in libido
- Colitis
- Budd-Chiari Syndrome

OVERDOSAGE

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

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of 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.[73 to 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

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, Cyred EQ™ must be taken exactly as directed and at intervals not exceeding 24 hours. Cyred EQ™ is available in the blister pack which is preset for a Sunday Start. Day 1 Start is also provided.

Day 1 Start

The dosage of Cyred EQ™ for the initial cycle of therapy is one white to off-white "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". Tablets are taken without interruption as follows: One white to off-white "active" tablet daily for 21 days, then one green "reminder" tablet daily for 7 days. After 28 tablets have been taken, a new course is started and a white to off-white "active" tablet is taken the next day.

The use of Cyred EQ™ 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: Nursing Mothers**.) If the patient starts on Cyred EQ™ postpartum, and has not yet had a period, she should be instructed to use another method of contraception until a white to off-white "active" tablet has been taken daily for 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses one (1) white to off-white "active" tablet in Weeks 1, 2, or 3, the white to off-white "active" tablet should be taken as soon as she remembers. If the patient misses two (2) white to off-white "active" tablets in Week 1 or Week 2, the patient should take two (2) white to off-white "active" tablets the day she remembers and two (2) white to off-white "active" tablets the next day; and then continue taking one (1) white to off-white "active" tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control such as a condom or spermicide if she has sex in the seven (7) days after missing pills. If the patient misses two (2) white to off-white "active" tablets in the third week or misses three (3) or more white to off-white "active" tablets in a row, the patient should throw out the rest of the pack and start a new pack that same day. The patient should be instructed to use a back-up method of birth control if she has sex in the seven (7) days after missing pills.

Sunday Start

When taking Cyred EQ™, the first white to off-white "active" tablet should be taken on the first Sunday after menstruation begins. If the period begins on Sunday, the first white to off-white "active" tablet is taken on that day. If switching directly from another oral contraceptive, the first white to off-white "active" tablet should be taken on the first Sunday after the last ACTIVE tablet of the previous product. Tablets are taken without interruption as follows: One white to off-white "active" tablet daily for 21 days, then one green "reminder" tablet daily for 7 days. After 28 tablets have been taken, a new course is started and a white to off-white "active" tablet is taken the next day (Sunday). When initiating a Sunday start regimen, another method of contraception should be used until after the first 7 consecutive days of administration.

The use of Cyred EQ™ for contraception may be initiated 4 weeks postpartum. 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**: **Nursing Mothers**.) If the patient starts on Cyred EQ™ postpartum, and has not yet had a period, she should be instructed to use another method of contraception until a white to off-white "active" tablet has been taken daily for 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered. If the patient misses one (1) white to off-white active tablet in Weeks 1, 2, or 3, the white to off-white "active" tablet should be taken as soon as she remembers. If the patient misses two (2) white to off-white "active" tablets in Week 1 or Week 2, the patient should take two (2) white to off-white "active" tablets the day she remembers and two (2) white to off-white "active" tablets the next day; and then continue taking one (1) white to off-white "active" tablet a day until she finishes the pack. The patient should be instructed to use a back-up method of birth control such as a condom or spermicide if she has sex in the seven (7) days after missing pills. If the patient misses two (2) white to off-white "active" tablets in the third week or misses three (3) or more white to off-white "active" tablets in a row, the patient should continue taking one white to off-white "active" 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.

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 if pregnancy is confirmed.
2. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out.

HOW SUPPLIED

Cyred EQ™ (Desogestrel and Ethinyl Estradiol Tablets USP 0.15 mg/0.03 mg) is available in a carton of 3 pouches, each containing 28 tablets:

21 active tablets: White to off-white, round, biconvex, beveled-edge tablets, debossed with "S" on one side and "25" on other side.

7 inert tablets: Green, round, mottled, biconvex, beveled-edge tablets, debossed with "S" on one side and "7" on other side.

1 Pouch of 28 tablets	NDC 50102-254-21
Carton of 3 Pouches	NDC 50102-254-23

STORAGE

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

REFERENCES

1. Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F. Contraceptive Technology: Seventeenth Revised Edition. New York, NY: Irvington Publishers, 1998.
2. Stadel BV. Oral contraceptives and cardiovascular disease. (Pt.1). N Engl J Med 1981;

305: 612-618.
3. Stadel BV. Oral contraceptives and cardiovascular disease. (Pt. 2). N Engl J Med 1981; 305: 672-677.
4. Adam SA, Thorogood M. Oral contraception and myocardial infarction revisited: the effects of new preparations and prescribing patterns. Br J Obstet and Gynecol 1981; 88:838-845.
5. Mann JI, Inman WH. Oral contraceptives and death from myocardial infarction. Br Med J 1975; 2(5965):245-248.
6. Mann JI, Vessey MP, Thorogood M, Doll R. Myocardial infarction in young women with special reference to oral contraceptive practice. Br Med J 1975;2(5956):241-245.
7. Royal College of General Practitioners' Oral Contraception Study: Further analyses of mortality in oral contraceptive users. Lancet 1981;1:541-546.
8. Slone D, Shapiro S, Kaufman DW, Rosenberg L, Miettinen OS, Stolley PD. Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. N Engl J Med 1981; 305:420-424.
9. Vessey MP. Female hormones and vascular disease-an epidemiological overview. Br J Fam Plann 1980; 6 (Supplement):1-12.
10. Russell Briefel RG, Ezzati TM, Fulwood R, Perlman JA, Murphy RS. Cardiovascular risk status and oral contraceptive use, United States, 1976-80. Prevent Med 1986; 15:352-362.
11. Goldbaum GM, Kendrick JS, Hogelin GC, Gentry EM. The relative impact of smoking and oral contraceptive use on women in the United States. JAMA 1987; 258:1339-1342.
12. Layde PM, Beral V. Further analyses of mortality in oral contraceptive users: Royal College of General Practitioners' Oral Contraception Study. (Table 5) Lancet 1981; 1:541-546.
13. Knopp RH. Arteriosclerosis risk: the roles of oral contraceptives and postmenopausal estrogens. J Reprod Med 1986; 31(9) (Supplement):913-921.
14. Krauss RM, Roy S, Mishell DR, Casagrande J, Pike MC. Effects of two low-dose oral contraceptives on serum lipids and lipoproteins: Differential changes in high density lipoproteins subclasses. Am J Obstet 1983; 145:446-452.
15. Wahl P, Walden C, Knopp R, Hoover J, Wallace R, Heiss G, Rifkind B. Effect of estrogen/progestin potency on lipid/lipoprotein cholesterol. N Engl J Med 1983; 308: 862-867.
16. Wynn V, Niththyananthan R. The effect of progestin in combined oral contraceptives on serum lipids with special reference to high-density lipoproteins. Am J Obstet Gynecol 1982; 142:766-771.
17. Wynn V, Godsland I. Effects of oral contraceptives and carbohydrate metabolism. J Reprod Med 1986; 31 (9) (Supplement):892-897.
18. LaRosa JC. Atherosclerotic risk factors in cardiovascular disease. J Reprod Med 1986;31 (9) (Supplement):906-912.
19. Inman WH, Vessey MP. Investigation of death from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. Br Med J 1968; 2 (5599):193-199.
20. Maguire MG, Tonascia J, Sartwell PE, Stolley PD, Tockman MS. Increased risk of thrombosis due to oral contraceptives: a further report. Am J Epidemiol 1979; 110 (2):188-195.
21. Pettiti DB, Wingerd J, Pellegrin F, Ramacharan S. Risk of vascular disease in women: smoking, oral contraceptives, noncontraceptive estrogens, and other factors. JAMA 1979; 242:1150-1154.
22. Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. Br Med J 1968; 2 (5599):199-205.
23. Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. Br Med J 1969; 2 (5658):651-657.
24. Porter JB, Hunter JR, Danielson DA, Jick H, Stergachis A. Oral contraceptives and non-fatal vascular disease-recent experience. Obstet Gynecol 1982; 59 (3):299-302.
25. Vessey M, Doll R, Peto R, Johnson B, Wiggins P. A long-term follow-up study of women using different methods of contraception: an interim report. J Biosocial Sci 1976; 8: 375-427.
26. Royal College of General Practitioners: Oral contraceptives, venous thrombosis, and varicose veins. J Royal Coll Gen Pract 1978; 28:393-399.
27. Collaborative Group for the Study of Stroke in Young Women: Oral contraception and increased risk of cerebral ischemia or thrombosis. N Engl J Med 1973; 288:871-878.
28. Petitti DB, Wingerd J. Use of oral contraceptives, cigarette smoking, and risk of subarachnoid hemorrhage. Lancet 1978; 2:234-236.
29. Inman WH. Oral contraceptives and fatal subarachnoid hemorrhage. Br Med J 1979; 2 (6203):1468-70.
30. Collaborative Group for the study of Stroke in Young Women: Oral contraceptives and stroke in young women: associated risk factors. JAMA 1975; 231:718-722.
31. Inman WH, Vessey MP, Westerholm B, Engelund A. Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. Br Med J 1970; 2:203-209.
32. Meade TW, Greenberg G, Thompson SG. Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50- and 35-mcg estrogen preparations. Br Med J 1980; 280 (6224):1157-1161.
33. Kay CR. Progestogens and arterial disease-evidence from the Royal College of General Practitioners' Study. Am J Obstet Gynecol 1982; 142:762-765.
34. Royal College of General Practitioners: Incidence of arterial disease among oral contraceptive users. J Royal Coll Gen Pract 1983; 33:75-82.
35. Ory HW. Mortality associated with fertility and fertility control: 1983. Family Planning Perspectives 1983; 15:50-56.
36. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Oral contraceptive use and the risk of breast cancer. N Engl J Med 1986; 315:405-411.
37. Pike MC, Henderson BE, Krailo MD, Duke A, Roy S. Breast cancer risk in young women and use of oral contraceptives: possible modifying effect of formulation and age at use. Lancet 1983; 2:926-929.
38. Paul C, Skegg DG, Spears GFS, Kaldor JM. Oral contraceptives and breast cancer: A national study. Br Med J 1986; 293: 723-725.
39. Miller DR, Rosenberg L, Kaufman DW, Schottenfeld D, Stolley PD, Shapiro S. Breast cancer risk in relation to early oral contraceptive use. Obstet Gynecol 1986; 68:863-868.
40. Olsson H, Olsson ML, Moller TR, Ranstam J, Holm P. Oral contraceptive use and breast cancer in young women in Sweden (letter). Lancet 1985; 1(8431):748-749.
41. McPherson K, Vessey M, Neil A, Doll R, Jones L, Roberts M. Early contraceptive use and breast cancer: Results of another case-control study. Br J Cancer 1987; 56:653-660.
42. Huggins GR, Zucker PF. Oral contraceptives and neoplasia: 1987 update. Fertil Steril 1987; 47:733-761.
43. McPherson K, Drife JO. The pill and breast cancer: why the uncertainty? Br Med J 1986; 293:709-710.
44. Shapiro S. Oral contraceptives - time to take stock. N Engl J Med 1987; 315:450-451.
45. Ory H, Naib Z, Conger SB, Hatcher RA, Tyler CW. Contraceptive choice and prevalence of cervical dysplasia and carcinoma in situ. Am J Obstet Gynecol 1976;124:573-577.
46. Vessey MP, Lawless M, McPherson K, Yeates D. Neoplasia of the cervix uteri and contraception: a possible adverse effect of the pill. Lancet 1983; 2:930.
47. Brinton LA, Huggins GR, Lehman HF, Malli K, Savitz DA, Trapido E, Rosenthal J, Hoover R. Long term use of oral contraceptives and risk of invasive cervical cancer. Int J Cancer 1986; 38:339-344.
48. WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Invasive cervical cancer and combined oral contraceptives. Br Med J 1985; 290:961-965.
49. Rooks JB, Ory HW, Ishak KG, Strauss LT, Greenspan JR, Hill AP, Tyler CW. Epidemiology of hepatocellular adenoma: the role of oral contraceptive use. JAMA 1979; 242:644-648.
50. Bein NN, Goldsmith HS. Recurrent massive hemorrhage from benign hepatic tumors secondary to oral contraceptives. Br J Surg 1977; 64:433-435.
51. Klatskin G. Hepatic tumors: possible relationship to use of oral contraceptives. Gastroenterology 1977; 73:386-394.
52. Henderson BE, Preston-Martin S, Edmondson HA, Peters RL, Pike MC. Hepatocellular carcinoma and oral contraceptives. Br J Cancer 1983; 48:437-440.
53. Neuberger J, Forman D, Doll R, Williams R. Oral contraceptives and hepatocellular carcinoma. Br Med J 1986; 292:1355-1357.
54. Forman D, Vincent TJ, Doll R. Cancer of the liver and oral contraceptives. Br Med J 1986; 292:1357-1361.
55. Harlap S, Eldor J. Births following oral contraceptive failures. Obstet Gynecol 1980; 55:447-452.
56. Savolainen E, Saksela E, Saxen L. Teratogenic hazards of oral contraceptives analyzed in a national malformation register. Am J Obstet Gynecol 1981; 140:521-524.
57. Janerich DT, Piper JM, Glebatis DM. Oral contraceptives and birth defects. Am J Epidemiol 1980; 112:73-79.
58. Ferencz C, Matanoski GM, Wilson PD, Rubin JD, Neill CA, Gutberlet R. Maternal hormone therapy and congenital heart disease. Teratology 1980; 21:225-239.
59. Rothman KJ, Fyler DC, Goldbatt A, Kreidberg MB. Exogenous hormones and other drug exposures of children with congenital heart disease. Am J Epidemiol 1979; 109:433-439.
60. Boston Collaborative Drug Surveillance Program: Oral contraceptives and venous thromboembolic disease, surgically confirmed gall-bladder disease, and breast tumors. Lancet 1973;1:1399-1404.
61. Royal College of General Practitioners: Oral contraceptives and health. New York, Pittman, 1974.
62. Layde PM, Vessey MP, Yeates D. Risk of gall bladder disease: a cohort study of young women attending family planning clinics. J Epidemiol Community Health 1982; 36:274-278.
63. Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO): Prevalence of gallstone disease in an Italian adult female population. Am J Epidemiol 1984; 119:796-805.
64. Strom BL, Tamragouri RT, Morse ML, Lazar EL, West SL, Stolley PD, Jones JK. Oral contraceptives and other risk factors for gall bladder disease. Clin Pharmacol Ther 1986; 39:335-341.
65. Wynn V, Adams PW, Godsland IF, Melrose J, Niththyananthan R, Oakley NW, Seedj A. Comparison of effects of different combined oral contraceptive formulations on carbohydrate and lipid metabolism. Lancet 1979; 1:1045-1049.
66. Wynn V. Effect of progesterone and progestins on carbohydrate metabolism. In Progesterone and Progestin. Edited by Bardin CW, Milgrom E, Mauvis-Jarvis P. New York, Raven Press, 1983; pp. 395-410.
67. Perlman JA, Roussell-Briefel RG, Ezzati TM, Lieberknecht G. Oral glucose tolerance and the potency of oral contraceptive progestogens. J Chronic Dis 1985; 38:857-864.
68. Royal College of General Practitioners' Oral Contraception Study: Effect on hypertension and benign breast disease of progestogen component in combined oral contraceptives. Lancet 1977; 1:624.
69. Fisch IR, Frank J. Oral contraceptives and blood pressure. JAMA 1977; 237:2499-2503.
70. Laragh AJ. Oral contraceptive induced hypertension - nine years later. Am J Obstet Gynecol 1976; 126:141-147.
71. Ramcharan S, Peritz E, Pellegrin FA, Williams WT. Incidence of hypertension in the Walnut Creek Contraceptive Drug Study cohort. In Pharmacology of Steroid Contraceptive Drugs. Garattini S, Berendes HW. Eds. New York, Raven Press, 1977; pp. 277-288. (Monographs of the Mario Negri Institute for Pharmacological Research, Milan).
72. Stockley I. Interactions with oral contraceptives. J Pharm 1976; 216:140-143.
73. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the

National Institute of Child Health and Human Development: Oral contraceptive use and the risk of ovarian cancer. JAMA 1983; 249:1596-1599.
74. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Combination oral contraceptive use and the risk of endometrial cancer. JAMA 1987; 257:796-800.
75. Ory HW. Functional ovarian cysts and oral contraceptives: negative association confirmed surgically. JAMA 1974; 228: 68-69.
76. Ory HW, Cole P, Macmahon B, Hoover R. Oral contraceptives and reduced risk of benign breast disease. N Engl J Med 1976; 294:419-422.
77. Ory HW. The noncontraceptive health benefits from oral contraceptive use. Fam Plann Perspect 1982; 14:182-184.
78. Ory HW, Forrest JD, Lincoln R. Making Choices: Evaluating the health risks and benefits of birth control methods. New York, The Alan Guttmacher Institute, 1983; p.1.
79. Schlesselman J, Stadel BV, Murray P, Lai S. Breast Cancer in relation to early use of oral contraceptives. JAMA 1988; 259:1828-1833.
80. Hennekens CH, Speizer FE, Lipnick RJ, Rosner B, Bain C, Belanger C, Stampfer MJ, Willett W, Peto R. A case-controlled study of oral contraceptive use and breast cancer. JNCI 1984;72:39-42.
81. LaVecchia C, Decarli A, Fasoli M, Franceschi S, Gentile A, Negri E, Parazzini F, Tognoni G. Oral contraceptives and cancers of the breast and of the female genital tract. Interim results from a case-control study. Br. J. Cancer 1986; 54:311-317.
82. Meirik O, Lund E, Adami H, Bergstrom R, Christoffersen T, Bergsjo P. Oral contraceptive use in breast cancer in young women. A Joint National Case-control study in Sweden and Norway. Lancet 1986; 11:650-654.
83. Kay CR, Hannaford PC. Breast cancer and the pill-A further report from the Royal College of General Practitioners' oral contraception study. Br. J. Cancer 1988; 58:675-680.
84. Stadel BV, Lai S, Schlesselman JJ, Murray P. Oral contraceptives and premenopausal breast cancer in nulliparous women. Contraception 1988; 38:287-299.
85. Miller DR, Rosenberg L, Kaufman DW, Stolley P, Warshauer ME, Shapiro S. Breast cancer before age 45 and oral contraceptive use: New Findings. Am. J. Epidemiol 1989; 129:269-280.
86. The UK National Case-Control Study Group, Oral contraceptive use and breast cancer risk in young women. Lancet 1989; 1:973-982.
87. Schlesselman JJ. Cancer of the breast and reproductive tract in relation to use of oral contraceptives. Contraception 1989; 40:1-38.
88. Vessey MP, McPherson K, Villard-Mackintosh L, Yeates D. Oral contraceptives and breast cancer: latest findings in a large cohort study. Br. J. Cancer 1989; 59:613-617.
89. Jick SS, Walker AM, Stergachis A, Jick H. Oral contraceptives and breast cancer. Br. J. Cancer 1989; 59:618-621.
90. Godsland, I et al. The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. N Engl J Med 1990; 323:1375-81.
91. Kloosterboer, HJ et al. Selectivity in progesterone and androgen receptor binding of progestogens used in oral contraception. Contraception 1988; 38:325-32.
92. Van der Vies, J and de Visser, J. Endocrinological studies with desogestrel. Arzneim Forsch/ Drug Res, 1983; 33(I),2:231-6.
93. Data on file, Organon Inc.
94. Fotherby, K. Oral contraceptives, lipids and cardiovascular diseases. Contraception 1985; Vol. 31; 4:367-94.
95. Lawrence, DM et al. Reduced sex hormone binding globulin and derived free testosterone levels in women with severe acne. Clinical Endocrinology 1981;15:87-91.
96. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet 1996; 347:1713-1727.
97. Palmer JR, Rosenberg L, Kaufman DW, Warshauer ME, Stolley P, Shapiro S. Oral Contraceptive Use and Liver Cancer. Am J Epidemiol 1989; 130:878-882.
98. Improving access to quality care in family planning: Medical eligibility criteria for contraceptive use. Geneva, WHO, Family and Reproductive Health, 1996.
99. Bork K, Fischer B, DeWald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. Am J Med 2003;114:294-298.
100. Van Giersbergen PLM, Halabi A, Dingemanse J. Pharmacokinetic interaction between bosentan and the oral contraceptives norethisterone and ethinyl estradiol. Int J Clin Pharmacol Ther 2006;44(3):113-118.
101. Christensen J, Petrenaite V, Atterman J, et al. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. Epilepsia 2007;48(3):484-489.
102. Chobanian et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003;42; 1206-1252.
103. Brown KS, Armstrong IC, Wang A, Walker JR, Noveck RJ, Swearingen D, Allison M, Kissling JC, Kisicki J, Salazar D. Effect of the bile acid sequestrant colesevelam on the pharmacokinetics of pioglitazone, repaglinide, estrogen estradiol, norethindrone, levothyroxine, and glyburide. J Clin Pharmacol 2010;50:554-565.

BRIEF SUMMARY PATIENT PACKAGE INSERT

Cyred EQ™ (Desogestrel and Ethinyl Estradiol Tablets USP)

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 without missing any pills, have a failure rate of approximately 1% per year. The typical failure rate is approximately 5% 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, high cholesterol
- have or have had clotting disorders, heart attack, stroke, angina pectoris, cancer of the breast or sex organs, jaundice or malignant or benign liver tumors

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

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

Do not use Cyred EQ™ if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from combination oral contraceptives, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you 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, headache, 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) 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) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes, and subsequent serious medical consequences.
2. In rare cases, oral contraceptives can cause benign but dangerous liver tumors. These benign liver tumors can rupture and cause fatal internal bleeding. In addition, some studies report an increased risk of developing liver cancer. However, liver cancers are rare.
3. High blood pressure, although blood pressure usually returns to normal when the pill is stopped.

The symptoms associated with these serious side effects are discussed in the detailed patient labeling given to you with your supply of pills. Notify your healthcare professional if you notice any unusual physical disturbances while taking the pill. In addition, drugs such as rifampin, bosentan, as well as some seizure medicines and herbal preparations containing St. John's wort (*Hypericum perforatum*) may decrease oral contraceptive effectiveness.

Oral contraceptives may interact with lamotrigine (LAMICTAL®), a seizure medicine used for epilepsy. This may increase the risk of seizures so your healthcare professional may need to adjust the dose of lamotrigine.

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go back down. You should have regular breast examinations by a healthcare professional and examine your own breasts monthly. Tell your healthcare professional if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone-sensitive tumor.

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 the pill may cause such cancers.

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

Be sure to discuss any medical condition you may have with your healthcare professional. Your healthcare professional 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 professional 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 labeling gives you further information which you should read and discuss with your healthcare professional.

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 to 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 healthcare professional.
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, or IF YOU TAKE SOME MEDICINES, your pills may not work as well.
   Use a back-up method (such as a condom or spermicide) until you check with your healthcare professional.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your healthcare professional 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 healthcare professional.

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:
   The pill pack has 21 white to off-white "active" pills (with hormones) to take for 3 weeks, followed by 1 week of green "reminder" pills (without hormones).
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills,
   3)check picture of pill pack and additional instructions for using this package below.
4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as a condom or spermicide) to use as a back-up method in case you miss pills.

   AN EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. Cyred EQ™ is available in the blister pack which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your healthcare professional which is the best day for you. Pick a time of day that will be easy to remember.

DAY 1 START:

1. Take the first white to off-white "active" 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 white to off-white "active" 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 such as a condom or spermicide as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

WHAT TO DO DURING THE MONTH

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

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

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

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
Start the next pack on the day after your last green "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** white to off-white "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** white to off-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 COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as a condom or spermicide) as a back-up method for those 7 days.

If you **MISS 2** white to off-white "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 healthcare professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as a condom or spermicide) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** white to off-white "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 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 healthcare professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as a condom or spermicide) as a back-up method for those 7 days.

A REMINDER:

If you forget any of the 7 green "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method.

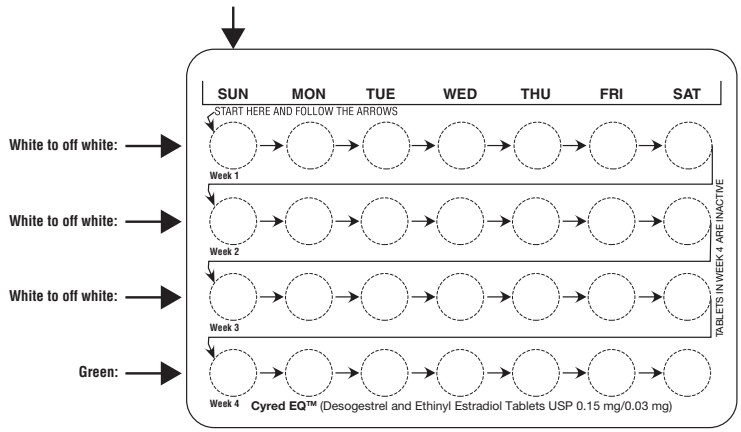
FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:

Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE WHITE TO OFF-WHITE "ACTIVE" PILL EACH DAY until you can reach your healthcare professional.

INSTRUCTIONS FOR USE

1. The blister pack comes to you set up for Sunday Start. If your healthcare professional has instructed you to start pill-taking on the first SUNDAY after your menstrual period has begun, or has instructed you to start pill-taking on the first day of your menstrual period and that day is SUNDAY, go to the directions in Number 3.
2. If you are to start pill-taking on a day other than SUNDAY, the enclosed calendar label has been provided and will be placed over the calendar printed on the blister pack. To put label in place, identify your correct starting day, locate that day label present in the calendar label and affix that day label over the printed calendar on the blister pack.
3. The first white to off-white "active" pill you will take is indicated by START and lines up with the black Day Arrow as indicated on the blister pack. For details, see the directions in the following picture.

DAY-1 STARTERS: If your period begins on a day other than Sunday, place the day label strip that starts with the first day of your period here.



Push down on the first white to off-white "active" pill with your thumb or forefinger. The pill will come out through a hole in the back of the package.

After you have taken all 21 white to off-white "active" pills, take one green "reminder" pill daily for 7 days. During this time your period should begin.

After you have taken all the pills, start a new pack of pills even if your period is not yet over.

STORAGE

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

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.

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

The following oral contraceptive product contains a combination of a progestogen and estrogen, the two kinds of female hormones:

Cyred EQ™ (Desogestrel and Ethinyl Estradiol Tablets USP)

Each white to off-white tablet contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. Each green 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

professional. 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 professional's advice with regard to regular check-ups while you are on the pill.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth control pills" or "the pill" are used to prevent pregnancy and are more effective than most other non-surgical methods of birth control. When they are taken correctly without missing any pills, the chance of becoming pregnant is approximately 1% (1 pregnancy per 100 women per year of use). Typical failure rates, including women who do not always take the pills exactly as directed, are approximately 5% per year. The chance of becoming pregnant increases with each missed pill during a menstrual cycle.

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

Implant: <1%	Male sterilization: <1%
Injection: <1%	Cervical Cap with spermicides: 20 to 40%
IUD: 1 to 2%	Condom alone (male): 14%
Diaphragm with spermicides: 20%	Condom alone (female): 21%
Spermicides alone: 26%	Periodic abstinence: 25%
Vaginal sponge: 20 to 40%	Withdrawal: 19%
Female sterilization: <1%	No methods: 85%

WHO SHOULD NOT TAKE ORAL CONTRACEPTIVES

Do not use Cyred EQ™ if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from combination oral contraceptives, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Some women should not use the pill. For example, you should not take 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
- An inherited problem that makes your blood clot more than normal
- 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 healthcare professional)
- 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)
- If you take any Hepatitis C drug combination containing ombitasvir/ paritaprevir/ ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.
- Known or suspected pregnancy
- If you plan to have surgery with prolonged bed rest

Tell your healthcare professional if you have ever had any of these conditions. Your healthcare professional can recommend another method of birth control.

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your healthcare professional if you have or have had:

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

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

Also, be sure to inform your healthcare professional 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. Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age. Serious blood clots are more likely to happen when you:

- First start taking birth control pills
- Restart the same or different birth control pills after not using them for a month or more

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. The risks of these side effects may be greater with desogestrel-containing oral contraceptives, such as Cyred EQ™, than with certain other low-dose pills. Rarely, clots occur in the blood vessels of the eye and may cause blindness, double vision, or impaired vision.

If you take oral contraceptives and need elective surgery, need to stay in bed for a prolonged illness or injury or have recently delivered a baby, you may be at risk of developing blood clots. You should consult your healthcare professional 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 breastfeeding. If you are breastfeeding, you should wait until you have weaned your child before using the pill. (See also the section on **Breastfeeding** in **GENERAL PRECAUTIONS**.)

The risk of circulatory disease in oral contraceptive users may be higher in users of high-dose pills. The risk of venous thromboembolic disease associated with oral contraceptives does not increase with length of use and disappears after pill use is stopped. 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

Various studies give conflicting reports on the relationship between breast cancer and oral contraceptive use. Oral contraceptive use may slightly increase your chance of having breast cancer diagnosed, particularly after using hormonal contraceptives at a younger age. After you stop using hormonal contraceptives, the chances of having breast cancer diagnosed begin to go back down. You should have regular breast examinations by a healthcare professional and examine your own breasts monthly. Tell your healthcare professional if you have a family history of breast cancer or if you have had breast nodules or an abnormal mammogram. Women who currently have or have had breast cancer should not use oral contraceptives because breast cancer is usually a hormone-sensitive tumor.

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 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44
No fertility-control methods*	7	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	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 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 four times higher (117/100,000

women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

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

WARNING SIGNALS

If any of these adverse effects occur while you are taking oral contraceptives, call your healthcare professional 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 healthcare professional 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 healthcare professional.

2. **Contact Lenses**

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

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 healthcare professional.

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, vaginal infections and allergic reactions.

   If any of these side effects bother you, call your healthcare professional.

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 professional 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 professional immediately to determine whether you are pregnant. Stop taking oral contraceptives if pregnancy is confirmed.

   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 should not be used during pregnancy. You should check with your healthcare professional about risks to your unborn child of any medication taken during pregnancy.

2. **While Breastfeeding**

   If you are breastfeeding, consult your healthcare professional 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 breastfeeding. You should use another method of contraception since breastfeeding provides only partial protection from becoming pregnant and this partial protection decreases significantly as you breastfeed 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 healthcare professional you are taking birth control pills. Certain blood tests may be affected by birth control pills.

4. **Drug Interactions**

   Tell your healthcare provider about all medicines and herbal products that you take.

   Some medicines and herbal products may make hormonal birth control less effective, including, but not limited to:

   - certain seizure medicines (carbamazepine, felbamate, oxcarbazepine, phenytoin, rufinamide, and topiramate)
   - aprepitant
   - barbiturates
   - bosentan
   - colesevelam
   - griseofulvin
   - certain combinations of HIV medicines (nelfinavir, ritonavir, ritonavir-boosted protease inhibitors)
   - certain non-nucleoside reverse transcriptase inhibitors (nevirapine)
   - rifampin and rifabutin
   - St. John's wort

Use another birth control method (such as a condom and spermicide or diaphragm and spermicide) when you take medicines that may make Cyred EQ™ less effective.

Some medicines and grapefruit juice may increase your level of the hormone ethinyl estradiol if used together, including:

- acetaminophen
- ascorbic acid
- medicines that affect how your liver breaks down other medicines (itraconazole, ketoconazole, voriconazole, and fluconazole)
- certain HIV medicines (atazanavir, indinavir)
- atorvastatin
- rosuvastatin
- etravirine

Hormonal birth control methods may interact with lamotrigine, a seizure medicine used for epilepsy. This may increase the risk of seizures, so your healthcare provider may need to adjust the dose of lamotrigine.

Women on thyroid replacement therapy may need increased doses of thyroid hormone.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

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.

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 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 healthcare professional.
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, or IF YOU TAKE SOME MEDICINES, your pills may not work as well.
   Use a back-up method (such as a condom or spermicide) until you check with your healthcare professional.
6. IF YOU HAVE TROUBLE REMEMBERING TO TAKE THE PILL, talk to your healthcare professional 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 healthcare professional.

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:
   The pill pack has 21 white to off-white "active" pills (with hormones) to take for 3 weeks, followed by 1 week of green "reminder" pills (without hormones).
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills.

CHECK PICTURE OF PILL PACK AND ADDITIONAL INSTRUCTIONS FOR USING THIS PACKAGE IN THE BRIEF SUMMARY PATIENT PACKAGE INSERT.

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

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. Cyred EQ™ is available in the blister pack which is preset for a Sunday Start. Day 1 Start is also provided. Decide with your healthcare professional which is the best day for you. Pick a time of day that will be easy to remember.

DAY 1 START:

1. Take the first white to off-white "active" 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 white to off-white "active" 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 such as a condom or spermicide as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

WHAT TO DO DURING THE MONTH

1. **TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**
   Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
   Do not skip pills even if you do not have sex very often.
2. **WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:**
   Start the next pack on the day after your last green "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** white to off-white "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** white to off-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 COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as a condom or spermicide) as a back-up method for those 7 days.

If you **MISS 2** white to off-white "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 healthcare professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as a condom or spermicide) as a back-up method for those 7 days.

If you **MISS 3 OR MORE** white to off-white "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 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 healthcare professional because you might be pregnant.
3. You COULD BECOME PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as a condom or spermicide) as a back-up method for those 7 days.

A REMINDER:

If you forget any of the 7 green "reminder" pills in Week 4:
THROW AWAY the pills you missed.
Keep taking 1 pill each day until the pack is empty.
You do not need a back-up method.

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

Use a BACK-UP METHOD anytime you have sex.

KEEP TAKING ONE WHITE TO OFF-WHITE "ACTIVE" PILL EACH DAY until you can reach your healthcare professional.

PREGNANCY DUE TO PILL FAILURE

When taken correctly without missing any pills, oral contraceptives are highly effective; however the typical failure rate of large numbers of pill users is 5% per year when women who miss pills are included. 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 professional.

OTHER INFORMATION

Your healthcare professional 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 professional 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 professional 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 professional 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 combined oral contraceptives may provide certain benefits. They are:

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

If you want more information about birth control pills, ask your healthcare professional or pharmacist. They have a more technical leaflet called the Professional Labeling, which you may wish to read.

STORAGE

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

Keep out of reach of children.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 01/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JASMIEL safely and effectively. See full prescribing information for JASMIEL.

JASMIEL® (drospirenone and ethinyl estradiol) tablets, for oral use
Initial U.S. Approval: 2001

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **Women over 35 years old who smoke should not use Jasmiel (4).**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. (4)**

----------RECENT MAJOR CHANGES----------

Contraindications (4)	08/2017
Warnings and Precautions (5.5)	08/2017

----------INDICATIONS AND USAGE----------

Jasmiel is an estrogen/progestin COC, indicated for use by women to:

- Prevent pregnancy. (1.1)
- Treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception. (1.2)
- Treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control. (1.3)

----------DOSAGE AND ADMINISTRATION----------

- Take one tablet daily by mouth at the same time every day. (2.1)
- Tablets must be taken in the order directed on the blister pack. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Jasmiel consists of 28 uncoated, flat faced, beveled-edge tablets in the following order (3):

- 24 light pink to pink tablets, each containing 3 mg drospirenone USP (DRSP) and 0.02 mg ethinyl estradiol USP (EE)
- 4 green inert tablets

----------CONTRAINDICATIONS----------

- Renal impairment (4)
- Adrenal insufficiency (4)
- A high risk of arterial or venous thrombotic diseases (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir, paritaprevir/ritonavir, with or without dasabuvir (4)

----------WARNINGS AND PRECAUTIONS----------

- Vascular risks: Stop Jasmiel if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1) COCs containing DRSP may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing levonorgestrel or some other progestins. Before initiating Jasmiel in a new COC user or a woman who is switching from a contraceptive that does not contain DRSP, consider the risks and benefits of a DRSP-containing COC in light of her risk of a VTE. (5.1)
- Hyperkalemia: DRSP has anti-mineralocorticoid activity. Do not use in patients predisposed to hyperkalemia. Check serum potassium concentration during the first treatment cycle in women on long-term treatment with medications that may increase serum potassium concentration. (5.2, 7.1, 7.2)
- Liver disease: Discontinue Jasmiel if jaundice occurs. (5.4)
- High blood pressure: Do not prescribe Jasmiel for women with uncontrolled hypertension or hypertension with vascular disease. (5.6)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Jasmiel. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.8)
- Headache: Evaluate significant change in headaches and discontinue Jasmiel if indicated. (5.9)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.10)

----------ADVERSE REACTIONS----------

- The most frequent adverse reactions (≥ 2%) in contraception and acne clinical trials were: headache/migraine (6.7%), menstrual irregularities (4.7%), nausea/vomiting (4.2%), breast pain/tenderness (4.0%) and mood changes (2.2%). (6.1)
- The most frequent adverse reactions (≥ 2%) in PMDD clinical trials were: menstrual irregularities (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Afaxys Pharma, LLC at 1-855-888-2467 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes (for example, CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Nursing Mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 03/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Jasmiel® is indicated for use by women to prevent pregnancy.

1.2 Premenstrual Dysphoric Disorder (PMDD)

Jasmiel is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of Jasmiel for PMDD when used for more than three menstrual cycles has not been evaluated.

The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

Jasmiel has not been evaluated for the treatment of premenstrual syndrome (PMS).

1.3 Acne

Jasmiel is indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. Jasmiel should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

2 DOSAGE AND ADMINISTRATION

2.1 How to Take Jasmiel

Take one tablet by mouth at the same time every day. The failure rate may increase when pills are missed or taken incorrectly.

To achieve maximum contraceptive and PMDD effectiveness, Jasmiel must be taken exactly as directed, in the order directed on the blister pack. Single missed pills should be taken as soon as remembered.

2.2 How to Start Jasmiel

Instruct the patient to begin taking Jasmiel either on the first day of her menstrual period (Day 1 Start) or on the first Sunday after the onset of her menstrual period (Sunday Start).

Day 1 Start

During the first cycle of Jasmiel use, instruct the patient to take one light pink to pink Jasmiel daily, beginning on Day 1 of her menstrual cycle. (The first day of menstruation is Day 1.) She should take one light pink to pink Jasmiel daily for 24 consecutive days, followed by one green inert tablet daily on Days 25 through 28. Jasmiel should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Jasmiel can be taken without regard to meals. If Jasmiel is first taken later than the first day of the menstrual cycle, Jasmiel should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

Sunday Start

During the first cycle of Jasmiel use, instruct the patient to take one light pink to pink Jasmiel daily, beginning on the first Sunday after the onset of her menstrual period. She should take one light pink to pink Jasmiel daily for 24 consecutive days, followed by one green inert tablet daily on Days 25 through 28. Jasmiel should be taken in the order directed on the package at the same time each day, preferably after the evening meal or at bedtime with some liquid, as needed. Jasmiel can be taken without regard to meals. Jasmiel should not be considered effective as a contraceptive until after the first 7 consecutive days of product administration. Instruct the patient to use a non-hormonal contraceptive as back-up during the first 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient should begin her next and all subsequent 28-day regimens of Jasmiel on the same day of the week that she began her first regimen, following the same schedule. She should begin taking her light pink to pink tablets on the next day after ingestion of the last green tablet, regardless of whether or not a menstrual period has occurred or is still in progress. Anytime a subsequent cycle of Jasmiel is started later than the day following administration of the last green tablet, the patient should use another method of contraception until she has taken a light pink to pink Jasmiel daily for seven consecutive days.

When switching from a different birth control pill

When switching from another birth control pill, Jasmiel should be started on the same day that a new pack of the previous oral contraceptive would have been started.

When switching from a method other than a birth control pill

When switching from a transdermal patch or vaginal ring, Jasmiel should be started when the next application would have been due. When switching from an injection, Jasmiel should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Jasmiel should be started on the day of removal.

Withdrawal bleeding usually occurs within 3 days following the last light pink to pink tablet. If spotting or breakthrough bleeding occurs while taking Jasmiel, instruct the patient to continue taking Jasmiel by the regimen described above. Counsel her that this type of bleeding is usually transient and without significance; however, advise her that if the bleeding is persistent or prolonged, she should consult her healthcare provider.

Although the occurrence of pregnancy is low if Jasmiel is taken according to directions, if withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy. Discontinue Jasmiel if pregnancy is confirmed.

The risk of pregnancy increases with each active light pink to pink tablet missed. For additional patient instructions regarding missed pills, see the "**WHAT TO DO IF YOU MISS PILLS"** section in the **FDA Approved Patient Labeling**. If breakthrough bleeding occurs following missed tablets, it will usually be transient and of no consequence. If the patient misses one or more green tablets, she should still be protected against pregnancy provided she begins taking a new cycle of light pink to pink tablets on the proper day.

For postpartum women who do not breastfeed or after a second trimester abortion, start Jasmiel no earlier than 4 weeks postpartum due to the increased risk of thromboembolism. If the patient starts on Jasmiel postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken Jasmiel for 7 consecutive days.

2.3 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3 to 4 hours after tablet-taking, this can be regarded as a missed tablet.

3 DOSAGE FORMS AND STRENGTHS

Jasmiel (drospirenone and ethinyl estradiol tablets, USP) are available in blister packs.

Each blister pack (28 tablets) contains in the following order:

- 24 light pink to pink tablets each containing 3 mg drospirenone USP (DRSP) and 0.02 mg ethinyl estradiol USP (EE)
- 4 green inert tablets

4 CONTRAINDICATIONS

Do not prescribe Jasmiel to women who are known to have the following:

- Renal impairment
- Adrenal insufficiency
- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
    - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
    - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
    - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
    - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
    - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
    - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
    - Have uncontrolled hypertension *[see Warnings and Precautions (5.6)]*
    - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.8)]*
    - Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35 *[see Warnings and Precautions (5.9)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.10)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.3)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.7)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)]*
- Use of Hepatitis C drug combinations containing ombitasvir, paritaprevir/ritonavir, with or without dasabuvir due to the potential for ALT elevations *[see Warnings and Precautions (5.5) and Drug Interactions (7.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

Stop Jasmiel if an arterial or venous thrombotic (VTE) event occurs.

Based on presently available information on DRSP-containing COCs with 0.03 mg ethinyl estradiol (that is, Yasmin), DRSP-containing COCs may be associated with a higher risk of venous thromboembolism (VTE) than COCs containing the progestin levonorgestrel or some other progestins. Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase. Before initiating use of Jasmiel in a new COC user or a woman who is switching from a contraceptive that does not contain DRSP, consider the risks and benefits of a DRSP-containing COC in light of her risk of a VTE. Known risk factors for VTE include smoking, obesity, and family history of VTE, in addition to other factors that contraindicate use of COCs *[see Contraindications (4)]*.

A number of studies have compared the risk of VTE for users of Yasmin (which contains 0.03 mg of EE and 3 mg of DRSP) to the risk for users of other COCs, including COCs containing levonorgestrel. Those that were required or sponsored by regulatory agencies are summarized in Table 1.

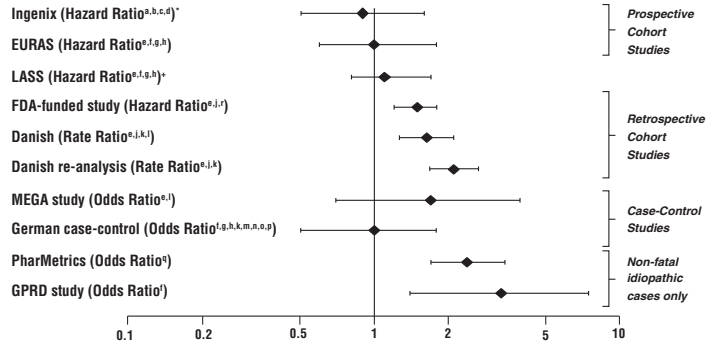
Table 1: Estimates (Hazard Ratios) of Venous Thromboembolism Risk in Current Users of Yasmin Compared to Users of Oral Contraceptives that Contain Other Progestins

Epidemiologic Study (Author, Year of Publication) Population Studied	Comparator Product (all are low-dose COCs; with ≤ 0.04 mg of EE)	Hazard Ratio (HR) (95% CI)
i3 Ingenix (Seeger 2007) Initiators, including new users[a]	All COCs available in the US during the conduct of the study[b]	HR: 0.9 (0.5 to 1.6)
EURAS (Dinger 2007) Initiators, including new users[a]	All COCs available in Europe during the conduct of the study[c] Levonorgestrel/EE	HR: 0.9 (0.6 to 1.4) HR: 1.0 (0.6 to 1.8)
"FDA-funded study" (2011) New users[a]	Other COCs available during the course of the study[d] Levonorgestrel/0.03 mg EE	HR: 1.8 (1.3 to 2.4) HR: 1.6 (1.1 to 2.2)
All users (i.e., initiation and continuing use of study combination hormonal contraception)	Other COCs available during the course of the study[d] Levonorgestrel/0.03 mg EE	HR: 1.7 (1.4 to 2.1) HR: 1.5 (1.2 to 1.8)

a) "New users" - no use of combination hormonal contraception for at least the prior 6 months
b) Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, levonorgestrel, desogestrel, norgestrel, medroxyprogesterone, or ethynodiol diacetate
c) Includes low-dose COCs containing the following progestins: levonorgestrel, desogestrel, dienogest, chlormadinone acetate, gestodene, cyproterone acetate, norgestimate, or norethindrone
d) Includes low-dose COCs containing the following progestins: norgestimate, norethindrone, or levonorgestrel

In addition to these "regulatory studies," other studies of various designs have been conducted. Overall, there are two prospective cohort studies (see Table 1): the US post-approval safety study Ingenix [Seeger 2007], the European post-approval safety study EURAS (European Active Surveillance Study) [Dinger 2007]. An extension of the EURAS study, the Long-Term Active Surveillance Study (LASS), did not enroll additional subjects, but continued to assess VTE risk. There are three retrospective cohort studies: one study in the US funded by the FDA (see Table 1), and two from Denmark [Lidegaard 2009, Lidegaard 2011]. There are two case-control studies: the Dutch MEGA study analysis [van Hylckama Vlieg 2009] and the German case-control study [Dinger 2010]. There are two nested case-control studies that evaluated the risk of non-fatal idiopathic VTE: the PharMetrics study [Jick 2011] and the GPRD study [Parkin 2011]. The results of all of these studies are presented in Figure 1.

Figure 1: VTE Risk with Yasmin Relative to LNG-Containing COCs (adjusted risk#)



Risk ratios displayed on logarithmic scale; risk ratio < 1 indicates a lower risk of VTE for DRSP, > 1 indicates an increased risk of VTE for DRSP.

*Comparator "Other COCs", including LNG- containing COCs

† LASS is an extension of the EURAS study

#Some adjustment factors are indicated by superscript letters: a) Current heavy smoking, b) hypertension, c) obesity, d) family history, e) age, f) BMI, g) duration of use, h) VTE history, i) period of inclusion, j) calendar year, k) education, l) length of use, m) parity, n) chronic disease, o) concomitant medication, p) smoking, q) duration of exposure, r) site

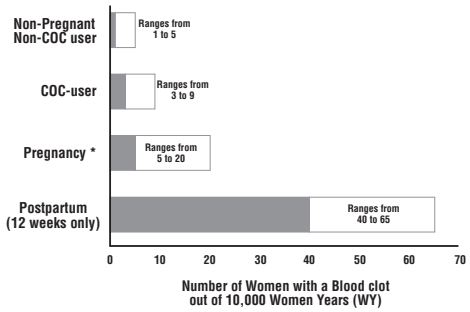
(References: Ingenix [Seeger 2007][1], EURAS (European Active Surveillance Study) [Dinger 2007][2], LASS (Long-Term Active Surveillance Study) [Dinger, unpublished document on file], FDA-funded study [Sidney 2011][3], Danish [Lidegaard 2009][4], Danish re-analysis [Lidegaard 2011][5], MEGA study [van Hylckama Vlieg 2009][6], German Case-Control study [Dinger 2010][7], PharMetrics [Jick 2011][8], GPRD study [Parkin 2011][9])

Although the absolute VTE rates are increased for users of hormonal contraceptives compared to non-users, the rates during pregnancy are even greater, especially during the post-partum period (see Figure 2). The risk of VTE in women using COCs has been estimated to be 3 to 9 per 10,000 woman-years. The risk of VTE is highest during the first year of use. Data from a large, prospective cohort safety study of various COCs suggest that this increased risk, as compared to that in non-COC users, is greatest during the first 6 months of COC use. Data from this safety study indicate that the greatest risk of VTE is present after initially starting a COC or restarting (following a 4 week or greater pill-free interval) the same or a different COC.

The risk of thromboembolic disease due to oral contraceptives gradually disappears after COC use is discontinued.

Figure 2 shows the risk of developing a VTE for women who are not pregnant and do not use oral contraceptives, for women who use oral contraceptives, for pregnant women, and for women in the postpartum period. To put the risk of developing a VTE into perspective: If 10,000 women who are not pregnant and do not use oral contraceptives are followed for one year, between 1 and 5 of these women will develop a VTE.

Figure 2: Likelihood of Developing a VTE



* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumpion that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.

If feasible, stop Jasmiel at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of thromboembolism.

Start Jasmiel no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum thromboembolism decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.

Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events.

COCs 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 of age), hypertensive women who also smoke. COCs also increase the risk for stroke in women with other underlying risk factors.

Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

Stop Jasmiel if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately. *[See Adverse Reactions (6).]*

5.2 Hyperkalemia

Jasmiel contains 3 mg of the progestin DRSP which has anti-mineralocorticoid activity, including the potential for hyperkalemia in high-risk patients, comparable to a 25 mg dose of spironolactone. Jasmiel is contraindicated in patients with conditions that predispose to hyperkalemia (that is, renal impairment, hepatic impairment, and adrenal insufficiency). Women receiving daily, long-term treatment for chronic conditions or diseases with medications that may increase serum potassium concentration should have their serum potassium concentration checked during the first treatment cycle. Medications that may increase serum potassium concentration include ACE inhibitors, angiotensin-II receptor antagonists, potassium-sparing diuretics, potassium supplementation, heparin, aldosterone antagonists, and NSAIDS. Consider monitoring serum potassium concentration in high-risk patients who take a strong CYP3A4 inhibitor long-term and concomitantly. Strong CYP3A4 inhibitors include azole antifungals (e.g. ketoconazole, itraconazole, voriconazole), HIV/HCV protease inhibitors (e.g., indinavir, boceprevir), and clarithromycin *[see Clinical Pharmacology (12.3)]*.

5.3 Carcinoma of the Breasts and Reproductive Organs

Women who currently have or have had breast cancer should not use Jasmiel because breast cancer is a hormonally-sensitive tumor.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.4 Liver Disease

Discontinue Jasmiel if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3

cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the attributable risk of liver cancers in COC users is less than one case per million users.

Oral contraceptive-related cholestasis may occur in women with a history of pregnancy-related cholestasis. Women with a history of COC-related cholestasis may have the condition recur with subsequent COC use.

5.5 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as COCs. Discontinue Jasmiel prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. Jasmiel can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.6 High Blood Pressure

For women with well-controlled hypertension, monitor blood pressure and stop Jasmiel if blood pressure rises significantly. Women with uncontrolled hypertension or hypertension with vascular disease should not use COCs.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use. The incidence of hypertension increases with increasing concentration of progestin.

5.7 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users.

5.8 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Jasmiel. COCs may decrease glucose intolerance in a dose-related fashion.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COC's.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.9 Headache

If a woman taking Jasmiel develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Jasmiel if indicated.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

5.10 Bleeding Irregularities

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

Based on patient diaries from two contraceptive clinical trials of Jasmiel, 8 to 25% of women experienced unscheduled bleeding per 28-day cycle. A total of 12 subjects out of 1,056 (1.1%) discontinued due to menstrual disorders including intermenstrual bleeding, menorrhagia, and metrorrhagia.

Women who use Jasmiel may experience absence of withdrawal bleeding, even if they are not pregnant. Based on subject diaries from contraception trials for up to 13 cycles, 6 to 10% of women experienced cycles with no withdrawal bleeding. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was pre-existent.

If withdrawal bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.11 COC 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. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy.

The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.12 Depression

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

5.13 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid-binding globulin increase with use of COCs *[see Drug Interactions (7.2)]*.

DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity.

5.14 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.15 Other Conditions

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema. Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.4)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Contraception and Acne Clinical Trials

The data provided reflect the experience with the use of Jasmiel in the adequate and well-controlled studies for contraception (N=1,056) and for moderate acne vulgaris (N=536).

For contraception, a Phase 3, multicenter, multinational, open-label study was conducted to evaluate safety and efficacy up to one year in 1,027 women aged 17 to 36 who took at least one dose of Jasmiel. A second Phase 3 study was a single center, open-label, active-controlled study to evaluate the effect of 7 28-day cycles of Jasmiel on carbohydrate metabolism, lipids and hemostasis in 29 women aged 18 to 35. For acne, two multicenter, double-blind, randomized, placebo-controlled studies, in 536 women aged 14 to 45 with moderate acne vulgaris who took at least one dose of Jasmiel, evaluated the safety and efficacy during up to 6 cycles.

The adverse reactions seen across the 2 indications overlapped, and are reported using the frequencies from the pooled dataset. The most common adverse reactions (≥ 2% of users) were: headache/migraine (6.7%), menstrual irregularities (including vaginal hemorrhage [primarily spotting] and metrorrhagia (4.7%), nausea/vomiting (4.2%), breast pain/tenderness (4%) and mood changes (mood swings, depression, depressed mood and affect lability) (2.2%).

PMDD Clinical Trials

Safety data from trials for the indication of PMDD are reported separately due to differences in study design and setting in the Contraception and Acne studies as compared to the PMDD clinical program.

Two (one parallel and one crossover designed) multicenter, double-blind, randomized, placebo-controlled trials for the secondary indication of treating the symptoms of PMDD evaluated safety and efficacy of Jasmiel during up to 3 cycles among 285 women aged 18 to 42, diagnosed with PMDD and who took at least one dose of Jasmiel.

Common adverse reactions (≥ 2% of users) were: menstrual irregularities (including vaginal hemorrhage [primarily spotting] and metrorrhagia) (24.9%), nausea (15.8%), headache (13.0%), breast tenderness (10.5%), fatigue (4.2%), irritability (2.8%), decreased libido (2.8%), increased weight (2.5%), and affect lability (2.1%).

Adverse Reactions (≥1%) Leading to Study Discontinuation:

Contraception Clinical Trials

Of 1,056 women, 6.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were headache/migraine (1.6%) and nausea/vomiting (1.0%).

Acne Clinical Trials

Of 536 women, 5.4% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reaction leading to discontinuation was menstrual irregularities (including menometrorrhagia, menorrhagia, metrorrhagia and vaginal hemorrhage) (2.2%).

PMDD Clinical Trials

Of 285 women, 11.6% discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were: nausea/vomiting (4.6%), menstrual irregularity (including vaginal hemorrhage, menorrhagia, menstrual disorder, menstruation irregular and metrorrhagia) (4.2%), fatigue (1.8%), breast tenderness (1.4%), depression (1.4%), headache (1.1%), and irritability (1.1%).

Serious Adverse Reactions

Contraception Clinical Trials: migraine and cervical dysplasia *Acne Clinical Trials:* none reported in the clinical trials *PMDD Clinical Trials*: cervical dysplasia

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Jasmiel.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions are grouped into System Organ Classes, and ordered by frequency.

Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, retinal thrombosis, myocardial infarction and stroke), hypertension (including hypertensive crisis)

Hepatobiliary disorders: Gallbladder disease, liver function disturbances, liver tumors Immune system disorders: Hypersensitivity (including anaphylactic reaction)

Metabolism and nutrition disorders: Hyperkalemia, hypertriglyceridemia, changes in glucose tolerance or effect on peripheral insulin resistance (including diabetes mellitus)

Skin and subcutaneous tissue disorders: Chloasma, angioedema, erythema nodosum, erythema multiforme Gastrointestinal disorders: Inflammatory bowel disease

Musculoskeletal and connective tissue disorders: Systemic lupus erythematosus

7 DRUG INTERACTIONS

Consult the labeling of all concurrently-used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampin, topiramate and products containing St. John's wort. Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation.

Concomitant administration of moderate or strong CYP3A4 inhibitors such as azole antifungals (e.g., ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g., clarithromycin, erythromycin), diltiazem, and grapefruit juice can increase the plasma concentrations of the estrogen or the progestin or both. In a clinical drug-drug interaction study conducted in premenopausal women, once daily co-administration of DRSP 3 mg/EE 0.02 mg containing tablets with strong CYP3A4 inhibitor, ketoconazole 200 mg twice daily for 10 days resulted in a moderate increase of DRSP systemic exposure. The exposure of EE was increased mildly *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

Human immunodeficiency virus (HIV)/ Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

COCs Increasing the Plasma Concentrations of CYP450 Enzymes*:* In clinical studies, administration of a hormonal contraceptive containing EE did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g., midazolam) while plasma concentrations of CYP2C19 substrates (e.g., omeprazole and voriconazole) and CYP1A2 substrates (e.g., theophylline and tizanidine) can have a weak or moderate increase.

Clinical studies did not indicate an inhibitory potential of DRSP towards human CYP enzymes at clinically relevant concentrations *[see Clinical Pharmacology (12.3)*].

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Jasmiel with other drugs that may increase serum potassium concentration *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*.

7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer Jasmiel with HCV drug combinations containing ombitasvir/ paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations *[see Warnings and Precautions (5.5)]*.

7.4 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. DRSP causes an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity. *[See Warnings and Precautions (5.12) and Drug Interactions (7.2).]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. COCs should not be used during pregnancy to treat threatened or habitual abortion. Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

After oral administration of 3 mg DRSP/0.03 mg EE (Yasmin) tablets, about 0.02% of the DRSP dose was excreted into the breast milk of postpartum women within 24 hours. This results in a maximal daily dose of about 0.003 mg DRSP in an infant.

8.4 Pediatric Use

Safety and efficacy of Jasmiel has been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Jasmiel has not been studied in postmenopausal women and is not indicated in this population.

8.6 Patients with Renal Impairment

Jasmiel is contraindicated in patients with renal impairment *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

In subjects with creatinine clearance (CLcr) of 50 to 79 mL/min, serum DRSP levels were comparable to those in a control group with CLcr ≥ 80 mL/min. In subjects with CLcr of 30 to 49 mL/min, serum DRSP concentrations were on average 37% higher than those in the control group. In addition, there is a potential to develop hyperkalemia in subjects with renal impairment whose serum potassium is in the upper reference range, and who are concomitantly using potassium sparing drugs *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Hepatic Impairment

Jasmiel is contraindicated in patients with hepatic disease *[see Contraindications (4) and Warnings and Precautions (5.4)]***.** The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Jasmiel has not been studied in women with severe hepatic impairment.

8.8 Race

No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

DRSP is a spironolactone analogue which has anti-mineralocorticoid properties. Serum concentration of potassium and sodium, and evidence of metabolic acidosis, should be monitored in cases of overdose.

11 DESCRIPTION

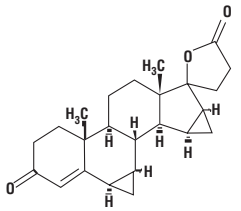
Jasmiel (drospirenone and ethinyl estradiol tablets, USP) provides an oral contraceptive regimen consisting of 24 light pink to pink active uncoated tablets each containing 3 mg of drospirenone USP and 0.02 mg of ethinyl estradiol USP and 4 green inert uncoated tablets.

The inactive ingredients in the light pink to pink tablets are corn starch, FD&C Red No. 40, lactose monohydrate, magnesium stearate, povidone, talc and vitamin-E. The green inert uncoated tablets contain anhydrous lactose, croscarmellose sodium, FD &C Blue No. 2 aluminum lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose and povidone.

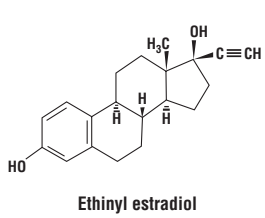
Drospirenone(6R,7R,8R,9S,10R,13S,14S,15S,16S,17S)-1,3',4',6,6a,7,8,9,10,11,12,13,14,15,15a,16-hexadecahydro10,13-dimethylspiro-[17H-dicyclopropa-[6,7:15,16] cyclopenta[a]phenanthrene-17,2'(5H)-furan]-3,5'(2H)-dione) is a synthetic progestational compound and has a molecular weight of 366.5 and a molecular formula of $C_{24}H_{30}O_3$.

Ethinyl estradiol (19-nor-17α-pregna 1,3,5(10)-triene-20-yne-3, 17-diol) is a synthetic estrogenic compound and has a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

The structural formulas are as follows:



Drospirenone



Ethinyl estradiol

USP Dissolution Test is pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and the endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

Drospirenone is a spironolactone analogue with anti-mineralocorticoid and antiandrogenic activity. The estrogen in Jasmiel is ethinyl estradiol.

Contraception

Two studies evaluated the effect of 3 mg DRSP/0.02 mg EE combinations on the suppression of ovarian activity as assessed by measurement of follicle size via transvaginal ultrasound and serum hormone (progesterone and estradiol) analyses during two treatment cycles (21-day active tablet period plus 7-day pill-free period). More than 90% of subjects in these studies demonstrated ovulation inhibition. One study compared the effect of 3 mg DRSP/0.02 mg EE combinations with two different regimens (24-day active tablet period plus 4-day pill-free period vs. 21-day active tablet period plus 7-day pill-free period) on the suppression of ovarian activity during two treatment cycles. During the first treatment cycle, there were no subjects (0/49, 0%) taking the 24-day regimen who ovulated compared to 1 subject (1/50, 2%) using the 21-day regimen. After intentionally introduced dosing errors (3 missed active tablets on Days 1 to 3) during the second treatment cycle, there was 1 subject (1/49, 2%) taking the 24-day regimen who ovulated compared to 4 subjects (4/50, 8%) using the 21-day regimen.

Acne

Acne vulgaris is a skin condition with a multifactorial etiology including androgen stimulation of sebum production. While the combination of EE and DRSP increases sex hormone binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established. The impact of the antiandrogenic activity of DRSP on acne is not known.

12.3 Pharmacokinetics

Absorption

The absolute bioavailability of DRSP from a single entity tablet is about 76%. The absolute bioavailability of EE is approximately 40% as a result of presystemic conjugation and first-pass metabolism. The absolute bioavailability of Jasmiel, which is a combination tablet of DRSP and EE, has not been evaluated. Serum concentrations of DRSP and EE reached peak levels within 1 to 2 hours after administration of Jasmiel.

The pharmacokinetics of DRSP are dose proportional following single doses ranging from 1 to 10 mg. Following daily dosing of Jasmiel, steady state DRSP concentrations were observed after 8 days. There was about 2 to 3 fold accumulation in serum C_{max} and $AUC_{(0\ to\ 24h)}$ values of DRSP following multiple dose administration of Jasmiel (see Table 2).

For EE, steady-state conditions are reported during the second half of a treatment cycle. Following daily administration of Jasmiel, serum C_{max} and $AUC_{(0\ to\ 24h)}$ values of EE accumulate by a factor of about 1.5 to 2 (see Table 2).

Table 2: Pharmacokinetic Parameters Of Jasmiel (DRSP 3 mg and EE 0.02 mg)

DRSP					
Cycle / Day	**No. of Subjects**	**C_{max}[a] (ng/mL)**	**T_{max}[b] (h)**	**$AUC_{(0\ to\ 24h)}$[a] (ng•h/mL)**	**$t_{1/2}$[a] (h)**
1/1	23	38.4 (25)	1.5 (1 to 2)	268 (19)	NA[c]
1/21	23	70.3 (15)	1.5 (1 to 2)	763 (17)	30.8 (22)
EE					
Cycle / Day	**No. of Subjects**	**C_{max}[a] (pg/mL)**	**T_{max}[b] (h)**	**$AUC_{(0\ to\ 24h)}$[a] (pg•h/mL)**	**$t_{1/2}$[a] (h)**
1/1	23	32.8 (45)	1.5 (1 to 2)	108 (52)	NA[c]
1/21	23	45.1 (35)	1.5 (1 to 2)	220 (57)	NA[c]

a) geometric mean (geometric coefficient of variation)
b) median (range)
c) NA = Not available

Food Effect

The rate of absorption of DRSP and EE following single administration of a formulation similar to Jasmiel was slower under fed (high fat meal) conditions with the serum C_{max} being reduced about 40% for both components. The extent of absorption of DRSP, however, remained unchanged. In contrast, the extent of absorption of EE was reduced by about 20% under fed conditions.

Distribution

DRSP and EE serum concentrations decline in two phases. The apparent volume of distribution of DRSP is approximately 4 L/kg and that of EE is reported to be approximately 4 to 5 L/kg.

DRSP does not bind to SHBG or corticosteroid binding globulin (CBG) but binds about 97% to other serum proteins. Multiple dosing over 3 cycles resulted in no change in the free fraction (as measured at trough concentrations). EE is reported to be highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of both SHBG and CBG. EE induced effects on SHBG and CBG were not affected by variation of the DRSP dosage in the range of 2 to 3 mg.

Metabolism

The two main metabolites of DRSP found in human plasma were identified to be the acid form of DRSP generated by opening of the lactone ring and the 4,5-dihydrodrospirenone-3-sulfate, formed by reduction and subsequent sulfation. These metabolites were shown not to be pharmacologically active. Drospirenone is also subject to oxidative metabolism catalyzed by CYP3A4.

EE has been reported to be subject to significant gut and hepatic first-pass metabolism. Metabolism of EE and its oxidative metabolites occur primarily by conjugation with glucuronide or sulfate. CYP3A4 in the liver is responsible for the 2-hydroxylation which is the major oxidative reaction. The 2-hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion

DRSP serum concentrations are characterized by a terminal disposition phase half-life of approximately 30 hours after both single and multiple dose regimens. Excretion of DRSP was nearly complete after ten days and amounts excreted were slightly higher in feces compared to urine. DRSP was extensively metabolized and only trace amounts of unchanged DRSP were excreted in urine and feces. At least 20 different metabolites were observed in urine and feces. About 38 to 47% of the metabolites in urine were glucuronide and sulfate conjugates. In feces, about 17 to 20% of the metabolites were excreted as glucuronides and sulfates.

For EE the terminal disposition phase half-life has been reported to be approximately 24 hours. EE is not excreted unchanged. EE is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic circulation.

Use in Specific Populations

Pediatric Use: Safety and efficacy of Jasmiel has been established in women of reproductive age. Efficacy is expected to be the same for postpubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

Geriatric Use: Jasmiel has not been studied in postmenopausal women and is not indicated in this population.

Race: No clinically significant difference was observed between the pharmacokinetics of DRSP or EE in Japanese versus Caucasian women (age 25 to 35) when 3 mg DRSP/0.02 mg EE was administered daily for 21 days. Other ethnic groups have not been specifically studied.

Renal Impairment: Jasmiel is contraindicated in patients with renal impairment.

The effect of renal impairment on the pharmacokinetics of DRSP (3 mg daily for 14 days) and the effect of DRSP on serum potassium concentrations were investigated in three separate groups of female subjects (n=28, age 30 to 65). All subjects were on a low potassium diet. During the study, 7 subjects continued the use of potassium-sparing drugs for the treatment of their underlying illness. On the 14th day (steady-state) of DRSP treatment, the serum DRSP concentrations in the group with CLcr of 50 to 79 mL/min were comparable to those in the control group with CLcr ≥ 80 mL/min. The serum DRSP concentrations were on average 37% higher in the group with CLcr of 30 to 49 mL/min compared to those in the control group. DRSP treatment did not show any clinically significant effect on serum potassium concentration. Although hyperkalemia was not observed in the study, in five of the seven subjects who continued use of potassium-sparing drugs during the study, mean serum potassium concentrations increased by up to 0.33 mEq/L. *[See Contraindications (4) and Warnings and Precautions (5.2).]*

Hepatic Impairment: Jasmiel is contraindicated in patients with hepatic disease.

The mean exposure to DRSP in women with moderate liver impairment is approximately three times higher than the exposure in women with normal liver function. Jasmiel has not been studied in women with severe hepatic impairment. *[See Contraindications (4) and Warnings and Precautions (5.4).]*

Drug Interactions

Consult the labeling of all concurrently used drugs to obtain further information about interactions with oral contraceptives or the potential for enzyme alterations.

Effects of Other Drugs on Combined Oral Contraceptives

Substances diminishing the efficacy of COCs: Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding.

Substances increasing the plasma concentrations of COCs: Co-administration of atorvastatin and certain COCs containing EE increase AUC values for EE by approximately 20%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. In a clinical drug-drug interaction study conducted in 20 premenopausal women, co-administration of a DRSP (3 mg)/EE (0.02 mg) COC with the strong CYP3A4 inhibitor ketoconazole (200 mg twice daily) for 10 days increased the $AUC_{(0\ to\ 24h)}$ of DRSP and EE by 2.68-fold (90% CI: 2.44, 2.95) and 1.40-fold (90% CI: 1.31, 1.49), respectively. The increases in C_{max} were 1.97-fold (90% CI: 1.79, 2.17) and 1.39-fold (90% CI: 1.28, 1.52) for DRSP and EE, respectively. Although no clinically relevant effects on safety or laboratory parameters including serum potassium were observed, this study only assessed subjects for 10 days. The clinical impact for a patient taking a DRSP-containing COC concomitantly with chronic use of a CYP3A4/5 inhibitor is unknown *[see Warnings and Precautions (5.2)]*.

HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma concentrations of estrogen and progestin have been noted in some cases of co-administration with HIV/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds. COCs have been shown to significantly decrease plasma concentrations of lamotrigine, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary. Consult the labeling of the concurrently-used drug to obtain further information about interactions with COCs or the potential for enzyme alterations.

In vitro, EE is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism-based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. Metabolism of DRSP and potential effects of DRSP on hepatic CYP enzymes have been investigated in *in vitro* and *in vivo* studies. In *in vitro* studies DRSP did not affect turnover of model substrates of CYP1A2 and CYP2D6, but had an inhibitory influence on the turnover of model substrates of CYP1A1, CYP2C9, CYP2C19, and CYP3A4, with CYP2C19 being the most sensitive enzyme. The potential effect of DRSP on CYP2C19 activity was investigated in a clinical pharmacokinetic study using omeprazole as a marker substrate. In the study with 24 postmenopausal women [including 12 women with homozygous (wild type) CYP2C19 genotype and 12 women with heterozygous CYP2C19 genotype] the daily oral administration of 3 mg DRSP for 14 days did not affect the oral clearance of omeprazole (40 mg, single oral dose) and the CYP2C19 product 5-hydroxy omeprazole. Furthermore, no significant effect of DRSP on the systemic clearance of the CYP3A4 product omeprazole sulfone was found. These results demonstrate that DRSP did not inhibit CYP2C19 and CYP3A4 *in vivo*.

Two additional clinical drug-drug interaction studies using simvastatin and midazolam as marker substrates for CYP3A4 were each performed in 24 healthy postmenopausal women. The results of these studies demonstrated that pharmacokinetics of the CYP3A4 substrates were not influenced by steady state DRSP concentrations achieved after administration of 3 mg DRSP/day.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentration of thyroid-binding globulin increases with use of COCs.

Interactions With Drugs That Have the Potential to Increase Serum Potassium Concentration: There is a potential for an increase in serum potassium concentration in women taking Jasmiel with other drugs that may increase serum potassium concentration *[see Warnings and Precautions (5.2)]*.

A drug-drug interaction study of DRSP 3 mg/estradiol (E2) 1 mg versus placebo was performed in 24 mildly hypertensive postmenopausal women taking enalapril maleate 10 mg twice daily. Potassium concentrations were obtained every other day for a total of 2 weeks in all subjects. Mean serum potassium concentrations in the DRSP/E2 treatment group relative to baseline were 0.22 mEq/L higher than those in the placebo group. Serum potassium concentrations also were measured at multiple time points over 24 hours at baseline and on Day 14. On Day 14, the ratios for serum potassium C_{max} and AUC in the DRSP/E2 group to those in the placebo group were 0.955 (90% CI: 0.914, 0.999) and 1.010 (90% CI: 0.944, 1.08), respectively. No patient in either treatment group developed hyperkalemia (serum potassium concentrations > 5.5 mEq/L).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24 month oral carcinogenicity study in mice dosed with 10 mg/kg/day DRSP alone or 1 + 0.01, 3 + 0.03 and 10 + 0.1 mg/kg/day of DRSP and EE, 0.1 to 2 times the exposure (AUC of DRSP) of women taking a contraceptive dose, there was an increase in carcinomas of the harderian gland in the group that received the high dose of DRSP alone. In a similar study in rats given 10 mg/kg/day DRSP alone or 0.3 + 0.003, 3 + 0.03 and 10 + 0.1 mg/kg/day DRSP and EE, 0.8 to 10 times the exposure of women taking a contraceptive dose, there was an increased incidence of benign and total (benign and malignant) adrenal gland pheochromocytomas in the group receiving the high dose of DRSP. Mutagenesis studies for DRSP were conducted *in vivo* and *in vitro* and no evidence of mutagenic activity was observed.

14 CLINICAL STUDIES

14.1 Oral Contraceptive Clinical Trial

In the primary contraceptive efficacy study of Jasmiel (3 mg DRSP/0.02 mg EE) of up to 1 year duration, 1,027 subjects were enrolled and completed 11,480 28-day cycles of use. The age range was 17 to 36 years. The racial demographic was: 87.8% Caucasian, 4.6% Hispanic, 4.3% Black, 1.2% Asian, and 2.1% other. Women with a BMI greater than 35 were excluded from the trial. The pregnancy rate (Pearl Index) was 1.41 (95% CI [0.73, 2.47]) per 100 woman-years of use based on 12 pregnancies that occurred after the onset of treatment and within 14 days after the last dose of Jasmiel in women 35 years of age or younger during cycles in which no other form of contraception was used.

14.2 Premenstrual Dysphoric Disorder Clinical Trials

Two multicenter, double-blind, randomized, placebo-controlled studies were conducted to evaluate the effectiveness of Jasmiel in treating the symptoms of PMDD. Women aged 18 to 42 who met DSM-IV criteria for PMDD, confirmed by prospective daily ratings of their symptoms, were enrolled. Both studies measured the treatment effect of Jasmiel using the Daily Record of Severity of Problems scale, a patient-rated instrument that assesses the symptoms that constitute the DSM-IV diagnostic criteria. The primary study was a parallel group design that included 384 evaluable reproductive-aged women with PMDD who were randomly assigned to receive Jasmiel or placebo treatment for 3 menstrual cycles. The supportive study, a crossover design, was terminated prematurely prior to achieving recruitment goals due to enrollment difficulties. A total of 64 women of reproductive age with PMDD were treated initially with Jasmiel or placebo for up to 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.

Efficacy was assessed in both studies by the change from baseline during treatment using a scoring system based on the first 21 items of the Daily Record of Severity of Problems. Each of the 21 items was rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum score of 126 was possible. In both trials, women who received Jasmiel had statistically significantly greater improvement in their Daily Record of Severity of Problems scores. In the primary study, the average decrease (improvement) from baseline was 37.5 points in women taking Jasmiel, compared to 30.0 points in women taking placebo.

14.3 Acne Clinical Trials

In two multicenter, double-blind, randomized, placebo-controlled studies, 889 subjects, ages 14 to 45 years, with moderate acne received Jasmiel or placebo for six 28-day cycles. The primary efficacy endpoints were the percent change in inflammatory lesions, non-inflammatory lesions, total lesions, and the percentage of subjects with a "clear" or "almost clear" rating on the Investigator's Static Global Assessment (ISGA) scale on day 15 of cycle 6, as presented in Table 3:

Table 3: Efficacy Results for Acne Trials*

	Study 1		Study 2	
	Jasmiel N=228	Placebo N=230	Jasmiel N=218	Placebo N=213
ISGA Success Rate	35 (15%)	10 (4%)	46 (21%)	19 (9%)
Inflammatory Lesions				
Mean Baseline Count	33	33	32	32
Mean Absolute (%) Reduction	15 (48%)	11 (32%)	16 (51%)	11 (34%)
Non-inflammatory Lesions				
Mean Baseline Count	47	47	44	44
Mean Absolute (%) Reduction	18 (39%)	10 (18%)	17 (42%)	11 (26%)
Total Lesions				
Mean Baseline Count	80	80	76	76
Mean Absolute (%) Reduction	33 (42%)	21 (25%)	33 (46%)	22 (31%)

* Evaluated at day 15 of cycle 6, last observation carried forward for the Intent to treat population

15 REFERENCES

1. Seeger, J.D., Loughlin, J., Eng, P.M., Clifford, C.R., Cutone, J., and Walker, A.M. (2007). Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. Obstet Gynecol *110*, 587-593.
2. Dinger, J.C., Heinemann, L.A., and Kuhl-Habich, D. (2007). The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception *75*, 344-354.
3. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular endpoints. Sidney, S. (primary author), http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf, accessed Oct 27, 2011.
4. Lidegaard, O., Lokkegaard, E., Svendsen, A.L., and Agger, C. (2009). Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ *339*, b2890.
5. Lidegaard, O., Nielsen, L.H., Skovlund, C.W., Skjeldestad, F.E., and Lokkegaard, E. (2011). Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ *343*, d6423.
6. van Hylckama Vlieg, A., Helmerhorst, F.M., Vandenbroucke, J.P., Doggen, C.J., and Rosendaal, F.R. (2009). The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case- control study. BMJ *339*, b2921.
7. Dinger, J., Assmann, A., Mohner, S., and Minh, T.D. (2010). Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. J Fam Plann Reprod Health Care *36*, 123-129.
8. Jick, S.S., and Hernandez, R.K. (2011). Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ *342*, d2151.
9. Parkin, L., Sharples, K., Hernandez, R.K., and Jick, S.S. (2011). Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ *342*, d2139.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Jasmiel (drospirenone and ethinyl estradiol tablets, USP) are available in Blister Pack Containing 28 tablets in the following order.

Each blister pack (28 tablets) contains in the following order:

- 24 active light pink to pink, round, flat faced, beveled-edge tablets, debossed with "S" on one side and "77" on other side
- 4 inert green, round, mottled, flat faced beveled-edge, uncoated tablets, debossed with "S" on one side and "37" on other side.

The blister packs are available in the following packages:

- The Blister Packs are packed in Pouches and the pouches are packaged in cartons

1 Pouch containing one Blister Pack	NDC 50102-240-21
Carton of 3 Pouches	NDC 50102-240-23

16.2 Storage

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Counsel patients that cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs.
- Counsel patients that the increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC.
- Counsel patients about the information regarding the risk of VTE with DRSP-containing COCs compared to COCs that contain levonorgestrel or some other progestins.
- Counsel patients that Jasmiel does not protect against HIV-infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with COCs.
- Counsel patients that Jasmiel contains DRSP. Drospirenone may increase potassium. Patients should be advised to inform their healthcare provider if they have kidney, liver or adrenal disease because the use of Jasmiel in the presence of these conditions could cause serious heart and health problems. They should also inform their healthcare provider if they are currently on daily, long-term treatment (NSAIDs, potassium-sparing diuretics, potassium supplementation, ACE inhibitors, angiotensin-II receptor antagonists, heparin or aldosterone antagonists) for a chronic condition or taking strong CYP3A4 inhibitors.
- Inform patients that Jasmiel is not indicated during pregnancy. If pregnancy occurs during treatment with Jasmiel, instruct the patient to stop further intake.
- Counsel patients to take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed. *See **"What to Do if You Miss Pills"** section in **FDA-Approved Patient Labeling**.*
- Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs.
- Counsel patients who are breastfeeding or who desire to breastfeed that COCs may reduce breast milk production. This is less likely to occur if breastfeeding is well established.
- Counsel any patient who starts COCs postpartum, and who has not yet had a period, to use an additional method of contraception until she has taken a light pink to pink tablet for 7 consecutive days.
- Counsel patients that amenorrhea may occur. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles.

Manufactured For:
Afaxys Pharma LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahabubnagar (Dt)-509302, India

Revised: 03/2021

FDA Approved Patient Labeling

Guide for Using Jasmiel

WARNING TO WOMEN WHO SMOKE

Do not use Jasmiel if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

Birth control pills help to lower the chances of becoming pregnant when taken as directed. They do not protect against HIV infection (AIDS) and other sexually transmitted diseases.

What is Jasmiel?

Jasmiel is a birth control pill. It contains two female hormones, a synthetic estrogen called ethinyl estradiol and a progestin called drospirenone.

The progestin drospirenone may increase potassium. Therefore, you should not take Jasmiel if you have kidney, liver or adrenal disease because this could cause serious heart and health problems. Other drugs may also increase potassium. If you are currently on daily, long-term treatment for a chronic condition with any of the medications below, you should consult your healthcare provider about whether Jasmiel is right for you, and during the first month that you take Jasmiel, you should have a blood test to check your potassium level.

- NSAIDs (ibuprofen [Motrin, Advil], naproxen [Aleve and others] when taken long-term and daily for treatment of arthritis or other problems)
- Potassium-sparing diuretics (spironolactone and others)
- Potassium supplementation
- ACE inhibitors (Capoten, Vasotec, Zestril and others)
- Angiotensin-II receptor antagonists (Cozaar, Diovan, Avapro and others)
- Heparin
- Aldosterone antagonists

Jasmiel may also be taken to treat premenstrual dysphoric disorder (PMDD) if you choose to use the Pill for birth control. Unless you have already decided to use the Pill for birth control, you should not start Jasmiel to treat your PMDD because there are other medical therapies for PMDD that do not have the same risks as the Pill. PMDD is a mood disorder related to the menstrual cycle. PMDD significantly interferes with work or school, or with usual social activities and relationships with others. Symptoms include markedly depressed mood, anxiety or tension, mood swings, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD may include breast tenderness, headache, joint and muscle pain, bloating and weight gain.

These symptoms occur regularly before menstruation starts and go away within a few days following the start of the period. Diagnosis of PMDD should be made by healthcare providers.

You should only use Jasmiel for treatment of PMDD if you:

- Have already decided to use oral contraceptives for birth control, and
- Have been diagnosed with PMDD by your healthcare provider.

Jasmiel has not been shown to be effective for the treatment of premenstrual syndrome (PMS), a less serious set of symptoms occurring before menstruation. If you or your healthcare provider believe you have PMS, you should take Jasmiel only if you want to prevent pregnancy; and not for the treatment of PMS.

Jasmiel may also be taken to treat moderate acne if all of the following are true:

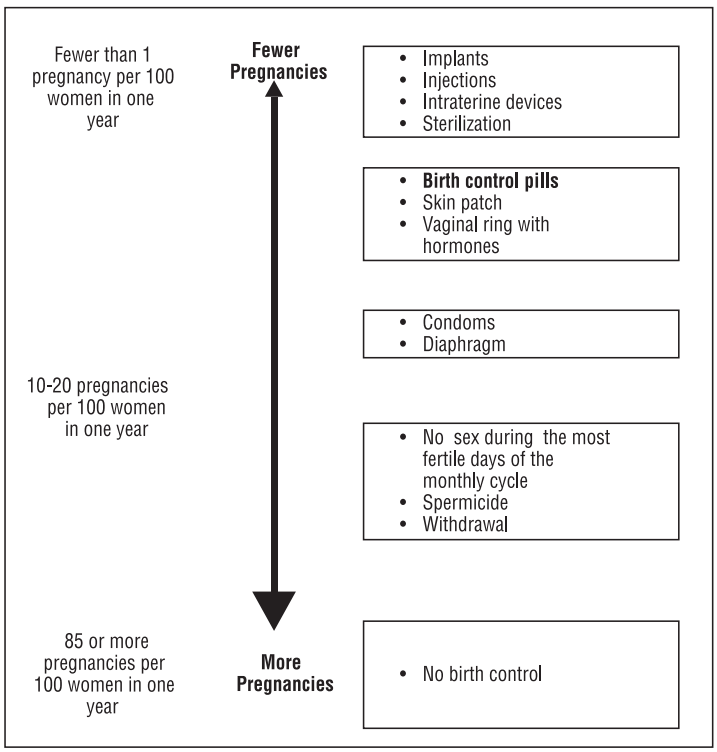
- Your healthcare provider says it is safe for you to use Jasmiel.
- You are at least 14 years old.
- You have started having menstrual periods.
- You want to use a birth control pill to prevent pregnancy.

How Well Does Jasmiel Work?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of one clinical study, 1 to 2 women out of 100 women, may get pregnant during the first year they use Jasmiel.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How Do I Take Jasmiel?

1. **Be sure to read these directions** before you start taking your pills or 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 in the order directed on the package. Preferably, take the pill after the evening meal or at bedtime, with some liquid, as needed. Jasmiel can be taken without regard to meals.

   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. See "WHAT TO DO IF YOU MISS PILLS" below.
3. Many women have spotting or light bleeding at unexpected times, or may feel sick to their stomach during the first 1 to 3 packs of pills.

   If you do have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your healthcare provider.
4. Missing pills can also cause spotting or light bleeding, even when you make up these

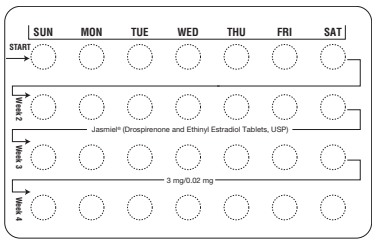
missed pills. On the days you take two pills, to make up for missed pills, you could also feel a little sick to your stomach.

5. If you have vomiting (within 3 to 4 hours after you take your pill), you should follow the instructions for "WHAT TO DO IF YOU MISS PILLS." If you have diarrhea or if you take certain medicines, including some antibiotics and some herbal products such as St. John's Wort, your pills may not work as well.

   Use a back-up method (such as condoms and spermicides) until you check with your healthcare provider.
6. If you have trouble remembering to take the pill, talk to your healthcare provider 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 healthcare provider.**

Before You Start Taking Your Pills

1. Decide What Time of Day You Want to Take Your Pill
It is important to take Jasmiel in the order directed on the package at the same time every day, preferably after the evening meal or at bedtime, with some liquid, as needed. Jasmiel can be taken without regard to meals.
2. Look at Your Pill Pack – It has 28 Pills
The Jasmiel-pill pack has 24 light pink to pink pills (with hormones) to be taken for 24 days, followed by 4 green pills (without hormones) to be taken for the next four days.
3. Also look for:
a) Where on the pack to start taking pills,
b) In what order to take the pills (follow the arrows)



4. Be sure you have ready at all times (a) another kind of birth control (such as condoms and spermicides) to use as a back-up in case you miss pills, and (b) 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. Decide with your healthcare provider 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 light pink to pink pill of the 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. However, if you start Jasmiel later than the first day of your period, you should use another method of birth control (such as a condom and spermicide) as a back-up method until you have taken 7 light pink to pink pills.

Sunday Start:

1. Take the first light pink to pink pill of the 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 (such as a condom and spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). This also applies if you start Jasmiel after having been pregnant, and you have not had a period since your pregnancy.

When You Switch From a Different Birth Control Pill

When switching from another birth control pill, Jasmiel should be started on the same day that a new pack of the previous birth control pill would have been started.

When You Switch From Another Type of Birth Control Method

When switching from a transdermal patch or vaginal ring, Jasmiel should be started when the next application would have been due. When switching from an injection, Jasmiel should be started when the next dose would have been due. When switching from an intrauterine contraceptive or an implant, Jasmiel should be started on the day of removal.

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 of pills, start the next pack on the day after your last green pill. Do not wait any days between packs.

What to Do if You Miss Pills

If you miss 1 light pink to pink pill of your pack:

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

If you miss 2 light pink to pink pills in a row in Week 1 or Week 2 of your pack:

1. Take two pills on the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. You could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.

If you miss 2 light pink to pink pills in a row in Week 3 or Week 4 of your pack:

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 one 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 could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as a condom and spermicide) as a back-up for those 7 days.
3. You may not have your period this month but this is expected. However, if you miss your period two months in a row, call your healthcare provider because you might be pregnant.

If you miss 3 or more light pink to pink pills in a row during any 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 could become pregnant if you have sex in the 7 days after you restart your pills. You must use another birth control method (such as condoms and spermicides) as a back-up for those 7 days.
3. Call your healthcare provider if you miss your period, because you might be pregnant.

If you miss any of the 4 green 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 (such as condoms and spermicides) anytime you have sex.

Contact your healthcare provider and continue taking one active light pink to pink pill each day until otherwise directed.

WHO SHOULD NOT TAKE JASMIEL?

Your healthcare provider will not give you Jasmiel if you:

- Ever had blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
- Ever had a stroke
- Ever had a heart attack
- Have certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- Have an inherited problem with your blood that makes it clot more than normal
- Have high blood pressure that medicine can't control
- Have diabetes with kidney, eye, nerve, or blood vessel damage
- Ever had certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision
- Ever had breast cancer or any cancer that is sensitive to female hormones
- Have liver disease, including liver tumors
- Take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.
- Have kidney disease
- Have adrenal disease

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are or suspect you are pregnant

Birth control pills may not be a good choice for you if you have ever had jaundice (yellowing of the skin or eyes) caused by pregnancy (also called cholestasis of pregnancy).

Tell your healthcare provider if you have ever had any of the above conditions (your healthcare provider can recommend another method of birth control).

What Else Should I Know about Taking Jasmiel?

Birth control pills do not protect you against any sexually transmitted disease, including HIV, the virus that causes AIDS.

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

If you miss a period, you could be pregnant. However, some women miss periods or have light periods on birth control pills, even when they are not pregnant. Contact your healthcare provider for advice if you:

- Think you are pregnant
- Miss one period and have not taken your birth control pills every day
- Miss two periods in a row

Birth control pills should not be taken during pregnancy. However, birth control pills taken by accident during pregnancy are not known to cause birth defects.

You should stop Jasmiel at least four weeks before you have major surgery and not restart it until at least two weeks after the surgery due to an increased risk of blood clots.

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like Jasmiel, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like condoms and a spermicide, until you check with your healthcare provider.

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.

Tell your healthcare provider about all the medicines you take, including prescription and overthe-counter medicines, vitamins and herbal supplements.

Jasmiel may affect the way other medicines work, and other medicines may affect how well Jasmiel works. Know the medicines you take.

Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

What are the Most Serious Risks of Taking Birth Control Pills?

Like pregnancy, birth control pills increase the risk of serious blood clots (see following graph), especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. This increased risk is highest when you first start taking birth control pills and when you restart the same or different birth control pills after not using them for a month or more. Women who use birth control pills with drospirenone (like Jasmiel) may have a higher risk of getting a blood clot. Some studies reported that the risk of blood clots was higher for women who use birth control pills that contain drospirenone than for women who use birth control pills that do not contain drospirenone.

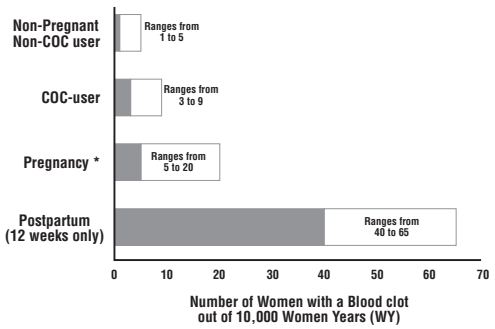
Talk with your healthcare provider about your risk of getting a blood clot before deciding which birth control pill is right for you.

It is possible to die or be permanently disabled from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious clots are blood clots in the:

- Legs (deep vein thrombosis or DVT)
- Lungs (pulmonary embolus or PE)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

To put the risk of developing a blood clot into perspective: If 10,000 women who are not pregnant and do not use birth control pills are followed for one year, between 1 and 5 of these women will develop a blood clot. The figure below shows the likelihood of developing a serious blood clot for women who are not pregnant and do not use birth control pills, for women who use birth control pills, for pregnant women, and for women in the first 12 weeks after delivering a baby.

Likelihood of Developing a Serious Blood Clot



*** Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY.**

A few women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumors

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the Common Side Effects of Birth Control Pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat (cholesterol; triglyceride) levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your healthcare provider if you develop any side effects that concern you. You may report side effects to the FDA at 1-800-FDA-1088.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

Do Birth Control Pills Cause Cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What Should I Know about My Period when Taking Jasmiel?

Irregular vaginal bleeding or spotting may occur while you are taking Jasmiel. 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, is unusually heavy, or lasts for more than a few days, call your healthcare provider.

Some women may not have a menstrual period but this should not be cause for alarm as long has you have taken the pills according to direction.

What if I Miss My Scheduled Period when Taking Jasmiel?

It is not uncommon to miss your period. However, if you miss two periods in a row or miss one period when you have not taken your birth control pills according to directions, call your healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking Jasmiel if you are pregnant.

What If I Want to Become Pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

General Advice about Jasmiel

Your healthcare provider prescribed Jasmiel for you. Please do not share Jasmiel with anyone else. Keep Jasmiel out of the reach of children.

If you have concerns or questions, ask your healthcare provider. You may also ask your healthcare provider for a more detailed label written for medical professionals.

Manufactured For:
Afaxys Pharma LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahabubnagar (Dt)-509302, India

Revised: 03/2021

afaxys®

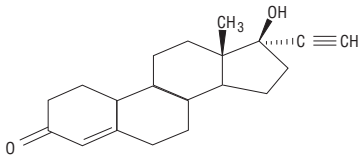
Lyleq™
(Norethindrone Tablets USP, 0.35 mg)
Rx only

Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually Transmitted diseases (STDs) such as Chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DESCRIPTION

Each light yellow to yellow Lyleq™ tablet provides a continuous oral contraceptive regimen of 0.35 mg norethindrone USP daily, and the inactive ingredients include corn starch, D&C Yellow No. 10 aluminum lake, FD&C Yellow # 6 aluminum lake, lactose monohydrate, magnesium stearate, povidone and talc.

The chemical name for norethindrone is 17-Hydroxy-19-Nor-17α-pregn-4-en-20-yn-3-one. The structural formula follows:



norethindrone

Therapeutic class = oral contraceptive.

CLINICAL PHARMACOLOGY

1. Mode of Action

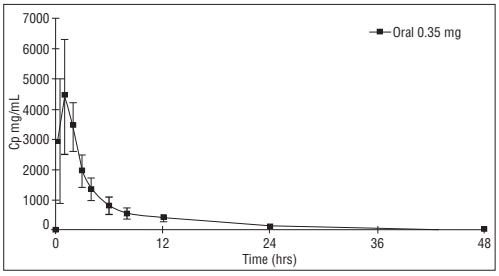
Lyleq progestin-only oral contraceptives prevent conception by suppressing ovulation in approximately half of users, thickening the cervical mucus to inhibit sperm penetration, lowering the mid-cycle LH and FSH peaks, slowing the movement of the ovum through the fallopian tubes, and altering the endometrium.

2. Pharmacokinetics

Absorption

Norethindrone is rapidly absorbed with maximum plasma concentrations occurring within 1 to 2 hours after Lyleq administration (see Table 1). Norethindrone appears to be completely absorbed following oral administration; however, it is subject to first pass metabolism resulting in an absolute bioavailability of approximately 65%.

Figure 1: Mean ± SD Norethindrone Plasma Concentrations Following Lyleq Administration



Peak plasma concentrations occur approximately 1 hour after administration (mean T_{max} 1.2 hours). The mean (SD) C_{max} was 4816.8 (1532.6) pg/mL and generally occurred within 1 hour (mean) of tablet administration, ranging from 0.5 to 2 hours. The mean (SD) C_{avg} was 885 (250) pg/mL, however, the mean concentration at 24 hrs was 130 (47) pg/mL.

Table 1 provides summary statistics of the pharmacokinetic parameters associated with single dose Lyleq administration.

Table 1: Mean ± SD Pharmacokinetic Parameters Following Single Dose Administration of Lyleq in 12 Healthy Female Subjects Under Fasting Conditions

Pharmacokinetic Parameter	Norethindrone 0.35 mg
T_{max} (hr)	1.2 ± 0.5
C_{max} (pg/mL)	4817 ± 1533
$AUC_{(0-48)}$ (pg·h/mL)	21233 ± 6002
t½ (h)	7.7 ± 0.5

The food effect on the rate and extent of norethindrone absorption after Lyleq administration has not been evaluated.

Distribution

Following oral administration, norethindrone is 36% bound to sex hormone-binding globulin (SHBG) and 61% bound to albumin. Volume of distribution of norethindrone is approximately 4 L/kg.

Metabolism

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation; less than 5% of a norethindrone dose is excreted unchanged; greater than 50% and 20 to 40% of a dose is excreted in urine and feces, respectively. The majority of metabolites in the circulation are sulfate, with glucuronides accounting for most of the urinary metabolites.

Excretion

Plasma clearance rate for norethindrone has been estimated to be approximately 600 L/day. Norethindrone is excreted in both urine and feces, primarily as metabolites. The mean terminal elimination half-life of norethindrone following single dose administration of Lyleq is approximately 8 hours.

INDICATIONS AND USAGE

1. Indications

Progestin-only oral contraceptives are indicated for the prevention of pregnancy.

2. Efficacy

If used perfectly, the first-year failure rate for progestin-only oral contraceptives is 0.5%. However, the typical failure rate is estimated to be closer to 5%, due to late or omitted pills. The following table lists the pregnancy rates for users of all major methods of contraception.

Table 2: Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception and the Percentage Continuing Use at the End of the First Year. United States.

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[3]
Method (1)	Typical Use[1] (2)	Perfect Use[2] (3)	(4)
Chance[4]	85	85	
Spermicides[5]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal[6]		2	
Post-Ovulation		1	
Cap[7]			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm[7]	20	6	56
Withdrawal	19	4	
Condom[8]			
Female (Reality)	21	5	56
Male	14	3	61
Pill	5		71
Progestin only		0.5	
Combined		0.1	
IUDs			
Progesterone T	2	1.5	81
Copper T380A	0.8	0.6	78
LNg20	0.1	0.1	81
Depo-Provera®	0.3	0.3	70
Levonorgestrel Implants (Norplant®)	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.1	100

Emergency Contraceptive Pills

Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.[9]

Lactational Amenorrhea Method

LAM is a highly effective, *temporary* method of contraception.[10]

Source: Trussell, J, Contraceptive Efficacy. In: Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Kowal D, Guest F, Contraceptive Technology: Seventeenth Revised Edition. New York NY: Irvington Publishers, 1998.

1. Among *typical* couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any reason.
2. Among couples who initiate use of a method (not necessarily for the first time), and who use it *perfectly* (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
3. Among couples attempting to avoid pregnancy, the percentage who continue to use a method for one year.
4. The percentage of women becoming pregnant noted 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 percentage that would become pregnant within one year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

5. Foams, creams, gels, vaginal suppositories, and vaginal film.
6. Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phases.
7. With spermicidal cream or jelly.
8. Without spermicides.
9. The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral® (1 dose is 2 white pills), Alesse® (1 dose is 5 pink pills), Nordette® or Levlen® (1 dose is 4 yellow pills).
10. However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

CONTRAINDICATIONS

Progestin-only oral contraceptives (POPs) should not be used by women who currently have the following conditions:

- Known or suspected pregnancy
- Known or suspected carcinoma of the breast
- Undiagnosed abnormal genital bleeding
- Hypersensitivity to any component of this product
- Benign or malignant liver tumors
- Acute liver disease

WARNINGS

Cigarette smoking greatly increases the possibility of suffering heart attacks and strokes. Women who use oral contraceptives are strongly advised not to smoke.

Lyleq does not contain estrogen and, therefore, this insert does not discuss the serious health risks that have been associated with the estrogen component of combined oral contraceptives. The health care provider is referred to the prescribing information of combined oral contraceptives for a discussion of those risks, including, but not limited to, an increased risk of serious cardiovascular disease in women who smoke, carcinoma of the breast and reproductive organs, hepatic neoplasia, and changes in carbohydrate and lipid metabolism. The relationship between progestin-only oral contraceptives and these risks have not been established and there are no studies definitely linking progestin-only pill (POP) use to an increased risk of heart attack or stroke.

The physician should remain alert to the earliest manifestation of symptoms of any serious disease and discontinue oral contraceptive therapy when appropriate.

1. Ectopic Pregnancy

The incidence of ectopic pregnancies for progestin-only oral contraceptive users is 5 per 1000 woman-years. Up to 10% of pregnancies reported in clinical studies of progestin-only oral contraceptive users are extrauterine. Although symptoms of ectopic pregnancy should be watched for, a history of ectopic pregnancy need not be considered a contraindication to use of this contraceptive method. Health providers should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain while on progestin-only oral contraceptives.

2. Delayed Follicular Atresia/Ovarian Cysts

If follicular development occurs, atresia of the follicle is sometimes delayed, and the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally these enlarged follicles disappear spontaneously. Often they are asymptomatic; in some cases they are associated with mild abdominal pain. Rarely they may twist or rupture, requiring surgical intervention.

3. Irregular Genital Bleeding

Irregular menstrual patterns are common among women using progestin-only oral contraceptives. If genital bleeding is suggestive of infection, malignancy or other abnormal conditions, such nonpharmacologic causes should be ruled out. If prolonged amenorrhea occurs, the possibility of pregnancy should be evaluated.

4. Carcinoma of the Breast and Reproductive Organs

Some epidemiologic studies of oral contraceptive users have reported an increased relative risk of developing breast cancer, particularly at a younger age and apparently related to duration of use. These studies have predominantly involved combined oral contraceptives and there is insufficient data to determine whether the use of POPs similarly increase the risk. Women with breast cancer should not use oral contraceptives because the role of female hormone in breast cancer has not been fully determined.

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. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. There is insufficient data to determine whether the use of POPs increases the risk of developing cervical intraepithelial neoplasia.

5. Hepatic Neoplasia

Benign hepatic adenomas are associated with combined oral contraceptive use, although the incidence of benign tumors is rare in the United States. Rupture of benign, hepatic adenomas may cause death through intraabdominal hemorrhage.

Studies from Britain and the U.S. have shown an increased risk of developing hepatocellular carcinoma in combined oral contraceptive users. However, these cancers are rare. There is insufficient data to determine whether POPs increase the risk of developing hepatic neoplasia.

PRECAUTIONS

1. General

Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as Chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

2. Physical Examination and Followup

It is considered good medical practice for sexually active women using oral contraceptives to have annual history and physical examinations. The physical examination may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician.

3. Carbohydrate and Lipid Metabolism

Some users may experience slight deterioration in glucose tolerance, with increases in plasma insulin, but women with diabetes mellitus who use progestin-only oral contraceptives do not generally experience changes in their insulin requirements. Nonetheless, prediabetic and diabetic women in particular should be carefully monitored while taking POPs.

Lipid metabolism is occasionally affected in that HDL, HDL_2, and apolipoprotein A-I and A-II may be decreased; hepatic lipase may be increased. There is no effect on total cholesterol, HDL_3, LDL, or VLDL.

4. Drug Interactions

Change in contraceptive effectiveness associated with co-administration of other products:

a. *Anti-Infective Agents and Anticonvulsants.*

Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnancy or breakthrough bleeding. Examples include rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, felbamate, oxcarbazepine, topiramate, and griseofulvin.

b. *Anti-HIV Protease Inhibitors.*

Several of the anti-HIV protease inhibitors have been studied with co-administration of oral contraceptives; significant changes (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of OC products may be affected with the co-administration of anti-HIV protease inhibitors. Health care providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

c. *Herbal Products.*

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

5. Interactions with Laboratory Tests

The following endocrine tests may be affected by progestin-only oral contraceptive use:

- Sex hormone-binding globulin (SHBG) concentrations may be decreased.
- Thyroxine concentrations may be decreased, due to a decrease in thyroid binding globulin (TBG).

6. Carcinogenesis

See **WARNINGS** section.

7. Pregnancy

Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins. The few studies of infant growth and development that have been conducted have not demonstrated significant adverse effects. It is nonetheless prudent to rule out suspected pregnancy before initiating any hormonal contraceptive use.

8. Nursing Mothers

Small amounts of progestin pass into the breast milk, resulting in steroid levels in infant plasma of 1 to 6% of the levels of maternal plasma.[6] However, isolated post-market cases of decreased milk production have been reported in POPs. Very rarely, adverse effects in the infant/child have been reported, including jaundice.

9. Fertility Following Discontinuation

The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only oral contraceptives.

10. Headache/Migraine

If you have a headache or a worsening migraine headache with a new pattern that is recurrent, persistent, or severe, this requires discontinuation of oral contraceptives and evaluation of the cause.

11. Gastrointestinal

Diarrhea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations.

12. Pediatric Use

Safety and efficacy of Lyleq 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.

Lyleq (norethindrone tablets) contains FD&C Yellow No. 6 as a color additive.

INFORMATION FOR THE PATIENT

1. See **PATIENT LABELING** for detailed information.

2. Counseling Issues

The following points should be discussed with prospective users before prescribing progestin-only oral contraceptives:

- The necessity of taking pills at the same time every day, including throughout all bleeding episodes.
- The need to use a backup method such as condoms and spermicides for the next 48 hours whenever a progestin-only oral contraceptive is taken 3 or more hours late.
- The potential side effects of progestin-only oral contraceptives, particularly menstrual irregularities.
- The need to inform the clinician of prolonged episodes of bleeding, amenorrhea or severe abdominal pain.
- The importance of using a barrier method in addition to progestin-only oral contraceptives if a woman is at risk of contracting or transmitting STDs/HIV.

ADVERSE REACTIONS

- Menstrual irregularity is the most frequently reported side effect.
- Frequent and irregular bleeding are common, while long duration of bleeding episodes and amenorrhea are less likely.
- Headache, breast tenderness, nausea, and dizziness are increased among progestin-only oral contraceptive users in some studies.
- Androgenic side effects such as acne, hirsutism, and weight gain occur rarely.

OVERDOSAGE

There have been no reports of serious ill effects from overdosage, including ingestion by children.

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, Lyleq tablets must be taken exactly as directed. One tablet is taken every day, at the same time. Administration is continuous, with no interruption between pill packs. See **PATIENT LABELING** for detailed instructions.

HOW SUPPLIED

Lyleq (**Norethindrone Tablets USP, 0.35 mg)** are light yellow to yellow, round, flat faced beveled edge tablets, debossed with 'S' on one side and '14' on other side of the tablet and are available in Blister Pack Containing 28 tablets.

The blister packs are available in the following packages:

- The Blister Packs are packed in cartons

Carton of 1 Blister Pack	NDC 50102-300-11
Carton of 3 Blister Packs	NDC 50102-300-13

STORAGE

Store at controlled room temperature 20° to 25°C (68° to 77° F) [see USP Controlled Room Temperature].

DETAILED INFORMATION FOR THE PATIENT

Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as Chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

INTRODUCTION

This leaflet is about birth control pills that contain one hormone, a progestin. Please read this leaflet before you begin to take your pills. It is meant to be used along with talking with your doctor or clinic.

Progestin-only pills are often called "POPs" or "the minipill." POPs have less progestin than the combined birth control pill (or "the pill") which contains both an estrogen and a progestin.

HOW EFFECTIVE ARE POPS?

About 1 in 200 (0.5%) POPs users will get pregnant in the first year if they all take POPs perfectly (that is, on time, every day). About 1 in 20 (5%) "typical" POPs users (including women who are late taking pills or miss pills) gets pregnant in the first year of use. The following table will help you compare the efficacy of different methods.

IUD: 1 to 2%
Depo-Provera® (injectable progesterone): 0.3%
Norplant® System (levonorgestrel implants): 0.1%
Diaphragm with spermicides: 18%
Spermicides alone: 21%
Male condom alone: 12%
Female condom alone: 21%
Cervical cap:
Women who have never given birth: 18%
Women who have given birth: 36%
Periodic abstinence: 20%
No methods: 85%

HOW DO POPS WORK?

- They make the cervical mucus at the entrance to the womb (the uterus) too thick for the sperm to get through to the egg.
- They prevent ovulation (release of the egg from the ovary) in about half the time.
- They also affect other hormones, the fallopian tubes and the lining of the uterus.

YOU SHOULD NOT TAKE POPS

- If there is any chance you may be pregnant.
- If you have breast cancer.
- If you have bleeding between your periods which has not been diagnosed.
- If you are taking certain drugs for epilepsy (seizures) or for TB. (See **USING POPS WITH OTHER MEDICINES** below.)
- If you are hypersensitive or allergic to any component of this product.
- If you have liver tumors, either benign or cancerous.
- If you have acute liver disease.

RISKS OF TAKING POPS

WARNING

If you have sudden or severe pain in your lower abdomen or stomach area, you may have an ectopic pregnancy or an ovarian cyst. If this happens, you should contact your doctor or clinic immediately.

1. Ectopic Pregnancy

An ectopic pregnancy is a pregnancy outside the womb. Because POPs protect against pregnancy, the chance of having pregnancy outside the womb is very low. If you do get pregnant while taking POPs, you have a slightly higher chance that the pregnancy will be ectopic than do users of some other birth control methods.

2. Ovarian Cysts

These cysts are small sacs of fluid in the ovary. They are more common among POP users than among users of most other birth control methods. They usually disappear without treatment and rarely cause problems.

3. Cancer of the Reproductive Organs and Breasts

Some studies in women who use combined oral contraceptives that contain both estrogen and a progestin have reported an increase in the risk of developing breast cancer, particularly at a younger age and apparently related to duration of use. There is insufficient data to determine whether the use of POPs similarly increases this risk.

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 and there is insufficient data to determine whether the use of POPs increases the risk of developing cancer of the cervix.

4. Liver Tumors

In rare cases, combined 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 combined oral contraceptives and liver cancers in studies in which a few women who developed these very rare cancers were found to have used combined oral contraceptives for long periods of time. There is insufficient data to determine whether POPs increase the risk of liver tumors.

SEXUALLY TRANSMITTED DISEASES (STDS)

WARNING: POPs do not protect against getting or giving someone HIV (AIDS) or any other STD, such as Chlamydia, gonorrhea, genital warts or herpes.

SIDE EFFECTS

1. Irregular Bleeding

The most common side effect of POPs is a change in menstrual bleeding. Your periods may be either early or late, and you may have some spotting between periods. Taking pills late or missing pills can also result in some spotting or bleeding.

2. Other Side Effects

Less common side effects include headaches, tender breasts, nausea and dizziness. Weight gain, acne and extra hair on your face and body have been reported, but are rare.

If you are concerned about any of these side effects, check with your doctor or clinic.

USING POPS WITH OTHER MEDICINES

Before taking a POP, inform your health care provider of any other medication, including over-the-counter medicine, that you may be taking.

If you are taking medicines for seizures (epilepsy) or tuberculosis (TB), tell your doctor or clinic. These medicines can make POPs less effective:

Medicines for seizures:

- Phenytoin (Dilantin®)
- Carbamazepine (Tegretol®)
- Phenobarbital

Medicine for TB:

- Rifampin (Rifampicin)

Before you begin taking any new medicines be sure your doctor or clinic knows you are taking birth control pills that contain a progestin.

HOW TO TAKE POPS

IMPORTANT POINTS TO REMEMBER

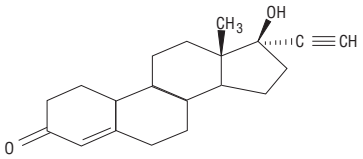
- POPs must be taken at the same time every day, so choose a time and then take the pill at the same time every day. Every time you take a pill late, and especially if you miss a pill, you are more likely to get pregnant.
- Start the next pack the day after the last pack is finished. There is no break between packs. Always have your next pack of pills ready.
- You may have some menstrual spotting between periods. Do not stop taking your pills if this happens.

- If you vomit soon after taking a pill, use a backup method (such as condom and/or spermicide) for 48 hours.
- If you want to stop taking POPs, you can do so at any time, but, if you remain sexually active and don't wish to become pregnant, be certain to use another birth control method.
- If you are not sure about how to take POPs, ask your doctor or clinic.

STARTING POPS

- It's best to take your first POP on the first day of your menstrual period.

1. Pick the day label strip that starts with the first day of your period
2. Place this day label strip on the tablet blister pack over the area that has the days of the week (starting with Sunday) pre-printed on the tablet blister pack.
   Note: If the first day of your period is a Sunday, you can skip steps # 1 and #2



- If you decide to take your first POP on another day, use a backup method (such as condom and/or spermicide) every time you have sex during the next 48 hours.
- If you have had a miscarriage or an abortion, you can start POPs the next day.

IF YOU ARE LATE OR MISS TAKING YOUR POPS

- If you are more than 3 hours late or you miss one or more POPs:

1. TAKE a missed pill as soon as you remember that you missed it,
2. THEN go back to taking POPs at your regular time,
3. BUT be sure to use a backup method (such as condom and/or spermicide) every time you have sex for the next 48 hours.

- If you are not sure what to do about the pills you have missed, keep taking POPs and use a backup method until you can talk to your doctor or clinic.

IF YOU ARE BREASTFEEDING

- If you are fully breastfeeding (not giving your baby any food or formula), you may start your pills 6 weeks after delivery.
- If you are partially breastfeeding (giving your baby some food or formula), you should start taking pills by 3 weeks after delivery.

IF YOU ARE SWITCHING PILLS

- If you are switching from the combined pills to POPs, take the first POP the day after you finish the last active combined pill. Do not take any of the 7 inactive pills from the combined pill pack. You should know that many women have irregular periods after switching to POPs, but this is normal and to be expected.
- If you are switching from POPs to the combined pills, take the first active combined pill on the first day of your period, even if your POPs pack is not finished.
- If you switch to another brand of POPs, start the new brand anytime.
- If you are breastfeeding, you can switch to another method of birth control at any time, except do not switch to the combined pills until you stop breastfeeding or at least until 6 months after delivery.

PREGNANCY WHILE ON THE PILL

If you become pregnant, or think you might be, stop taking POPs and contact your physician. Even though research has shown that POPs do not cause harm to the unborn baby, it is always best not to take any drugs or medicines that you don't need when you are pregnant.

You should get a pregnancy test:

- If your period is late and you took one or more pills late or missed taking them and had sex without a backup method.
- Anytime you miss 2 periods in a row.

WILL POPS AFFECT YOUR ABILITY TO GET PREGNANT LATER?

If you want to become pregnant, simply stop taking POPs. POPs will not delay your ability to get pregnant.

BREASTFEEDING

If you are breastfeeding, POPs will not affect the quality or amount of your breast milk or the health of your nursing baby. However, isolated cases of decreased milk production have been reported. If you suspect that you are not producing enough milk for your baby, contact your doctor or clinic.

OVERDOSE

No serious problems have been reported when many pills were taken by accident, even by a small child, so there is usually no reason to treat an overdose.

OTHER QUESTIONS OR CONCERNS

WARNING: Cigarette smoking greatly increases the possibility of suffering heart attacks and strokes. Women who use oral contraceptives are strongly advised not to smoke.

Diabetic women taking POPs do not generally require changes in the amount of insulin they are taking. However, your physician may monitor you more closely under these conditions.

If you have any questions or concerns, check with your doctor or clinic. You can also ask for the more detailed "professional package labeling" written for doctors and other health care providers.

HOW TO STORE YOUR POPS

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

Keep out of reach of children

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India
Revised: 01/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TARINA 24 Fe safely and effectively. See Full Prescribing Information for TARINA 24 Fe.

Tarina® 24 Fe (norethindrone acetate and ethinyl estradiol tablets and ferrous fumarate tablets) for Oral Use
Initial U.S. Approval: 1968

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See Full Prescribing Information for complete boxed warning.

- **Tarina 24 Fe is contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. (4)**

----------RECENT MAJOR CHANGES----------

Contraindications (4)
08/2017
Warnings (5.3)
08/2017

----------INDICATIONS AND USAGE----------

Tarina 24 Fe is a progestin/estrogen COC indicated for use by women to prevent pregnancy. (1) The efficacy of Tarina 24 Fe in women with a body mass index (BMI) of greater than 35 kg/m^2 has not been evaluated. (1, 8.8)

----------DOSAGE AND ADMINISTRATION----------

- Take one tablet by mouth at the same time every day for 28 days (2.1)
- Take tablets in the order directed on the blister pack (2.1)
- Tarina 24 Fe may be administered without regard to meals (12.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tarina 24 Fe consists of 28 tablets in the following order (3):

- 24 light yellow to yellow tablets (active), each containing 1 mg norethindrone acetate USP and 20 mcg ethinyl estradiol USP.
- 4 brown tablets (non-hormonal placebo), each containing 75 mg ferrous fumarate. The ferrous fumarate tablets do not serve any therapeutic purpose.

----------CONTRAINDICATIONS----------

- A high risk of arterial or venous thrombotic diseases (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Pregnancy (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

----------WARNINGS AND PRECAUTIONS----------

- Thrombotic Disorders and Other Vascular Problems: Stop Tarina 24 Fe if a thrombotic event occurs. Stop at least 4 weeks before through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue Tarina 24 Fe if jaundice occurs. (5.2)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop Tarina 24 Fe if blood pressure rises significantly. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Tarina 24 Fe. Consider an alternative contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue Tarina 24 Fe if indicated. (5.7)
- Bleeding Irregularities and Amenorrhea: Evaluate irregular bleeding or amenorrhea. (5.8)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (greater than or equal to 2%) were: headache, vaginal candidiasis, nausea, menstrual cramps, breast tenderness, mood changes, bacterial vaginitis, acne, and weight gain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Afaxys Pharma, LLC at 1-855-888-2467 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Drugs or herbal products that induce certain enzymes (for example CYP3A4) may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: Advise use of another contraceptive method. Tarina 24 Fe can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed

---

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

Tarina 24 Fe is indicated for use by women to prevent pregnancy *[see Clinical Studies (14)]*.

The efficacy of Tarina 24 Fe in women with a body mass index (BMI) of greater than 35 kg/m^2 has not been evaluated.

2 DOSAGE AND ADMINISTRATION

2.1 How to Start Tarina 24 Fe

Tarina 24 Fe is available in a blister pack *[see How Supplied/Storage and Handling (16)]*.

Tarina 24 Fe may be started using either a Day 1 start or a Sunday start (see Table 1). For the first cycle of a Sunday Start regimen, an additional method of contraception must be used until after the first 7 consecutive days of administration.

2.2 How to Take Tarina 24 Fe

Table 1: Instructions for Administration of Tarina 24 Fe

Starting COCs in women not currently using hormonal contraception (Day 1 Start or Sunday Start) **Important:** Consider the possibility of ovulation and conception prior to initiation of this product. **Tablet Color:** • Tarina 24 Fe active tablets are light yellow to yellow (Day 1 to Day 24). • Tarina 24 Fe inactive tablets are brown (Day 25 to Day 28).	**Day 1 Start:** • Take first **light yellow to yellow** active tablet without regard to meals on the first day of menses. • Take subsequent active tablets once daily at the same time each day for a total of 24 days. • Take one **brown** inactive tablet daily for 4 days and at the same time of day that active tablets were taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last inactive tablet).
	Sunday Start: For each 28-day course, take in the following order: • Take the **light yellow to yellow** active tablet without regard to meals on the first Sunday after the onset of menses. **Due to the potential risk of becoming pregnant, use additional non-hormonal contraception (such as condoms and spermicide) for the first 7 days of the patient's first cycle pack of Tarina 24 Fe**. • Take subsequent active tablets once daily at the same time each day for a total of 24 days. • Take one **brown** tablet (ferrous fumarate) daily for the following 4 days and at the same time of day that active tablets were taken. A scheduled period should occur during the 4 days that the brown tablets are taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the Sunday after taking the last inactive tablet) and additional non-hormonal contraceptive is not needed.
Switching to Tarina 24 Fe from another oral contraceptive	Start on the same day that a new pack of the previous oral contraceptive would have started.
Switching from another contraceptive method to Tarina 24 Fe	**Start Tarina 24 Fe:**
• **Transdermal patch**	• On the day when next application would have been scheduled.
• **Vaginal ring**	• On the day when next insertion would have been scheduled.
• **Injection**	• On the day when next injection would have been scheduled.
• **Intrauterine contraceptive**	• On the day of removal • If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraceptive (such as condoms and spermicide) is needed for the first seven days of the first cycle pack.
• **Implant**	• On the day of removal
Complete instructions on proper tablet usage are located in the FDA-approved patient labeling.	

Starting Tarina 24 Fe after Abortion or Miscarriage

First-trimester

- After a first-trimester abortion or miscarriage, Tarina 24 Fe may be started immediately. An additional method of contraception is not needed if Tarina 24 Fe is started immediately.
- If Tarina 24 Fe is not started within 5 days after termination of the pregnancy, the patient must use additional non-hormonal contraception (such as condoms and spermicide) for the first 7 days of her first 28-day course of Tarina 24 Fe.

Second-trimester

- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start Tarina 24 Fe following the instructions in Table 1 for Sunday start. Use additional non-hormonal contraception (such as condoms and spermicide) for the first 7 days of the patient's first 28-day course of Tarina 24 Fe *[see Contraindications (4), Warnings and Precautions (5.1), and FDA-approved Patient Labeling]*.

Starting Tarina 24 Fe after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with Tarina 24 Fe following the instructions in Table 1 for women not currently using hormonal contraception.
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of Tarina 24 Fe *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1 and 8.3)]*.

2.3 Missed Tablets

Table 2: Instructions for Missed Tarina 24 Fe Tablets

• If one active tablet is missed in Weeks 1, 2 or 3	Take the tablet as soon as possible. Take the next pill at the regular time, and continue taking one tablet a day until the pack is finished. Back-up contraception is not needed
• If two consecutive active tablets are missed in Week 1 or Week 2	Take the two missed tablets as soon as possible and the next two active tablets the next day. Continue taking one tablet a day until the pack is finished. **Additional non-hormonal contraception (such as condoms and spermicide) must be used as back-up if the patient has sex within 7 days after missing tablets.**
• If two consecutive active tablets are missed in Week 3 or Week 4 or three or more consecutive active tablets are missed at any time	Day 1 Start: Throw out the rest of the pack and start a new pack that same day. Sunday Start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. **Additional non-hormonal contraception (such as condoms and spermicide) must be used as back-up if the patient has sex within 7 days after missing tablets.**

2.4 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures must be taken. If vomiting or diarrhea occurs within 3 to 4 hours after taking a light yellow to yellow tablet, handle this as a missed tablet *[see FDA-Approved Patient Labeling]*.

3 DOSAGE FORMS AND STRENGTHS

Tarina 24 Fe (norethindrone acetate and ethinyl estradiol tablets USP and ferrous fumarate tablets) is available in blister packs.

Each blister pack (28 tablets) contains in the following order:

- 24 light yellow to yellow, round, flat-faced, beveled-edge, uncoated (active) tablets debossed with 'S' on one side and '64' on other side and each containing 1 mg of norethindrone acetate USP and 20 mcg of ethinyl estradiol USP.
- 4 brown, mottled, round, flat-faced, beveled-edge (non-hormonal placebo) tablets debossed with 'S' on one side and '57' on other side and each containing 75 mg ferrous fumarate USP. The ferrous fumarate tablets do not serve any therapeutic purpose.

4 CONTRAINDICATIONS

Do not prescribe Tarina 24 Fe to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or have migraine headaches with aura *[see Warnings and Precautions (5.7)]*
    - Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.7)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.2)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.11)]*
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thrombotic Disorders and Other Vascular Problems

- Stop Tarina 24 Fe if an arterial thrombotic event or venous thromboembolic (VTE) event occurs.
- Stop Tarina 24 Fe if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately *[see Adverse Reactions (6.2)]*.
- If feasible, stop Tarina 24 Fe at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during the following prolonged immobilization.
- Start Tarina 24 Fe no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of a COCs and when restarting oral contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after COC use is discontinued.
- Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.
- Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function

Do not use Tarina 24 Fe in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver *[see Contraindications (4)]*. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Tarina 24 Fe if jaundice develops.

Liver Tumors

Tarina 24 Fe is contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)]*. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases per 100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (greater than 8 years) COC users. However, the risk of liver cancers in COC users is less than one case per million users.

5.3 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as COCs. Discontinue Tarina 24 Fe prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. Tarina 24 Fe can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.4 High Blood Pressure

Tarina 24 Fe is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop Tarina 24 Fe if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may worsen existing gallbladder disease. A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC related cholestasis.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who are taking Tarina 24 Fe. COCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemias. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache

If a woman taking Tarina 24 Fe develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Tarina 24 Fe if indicated.

Consider discontinuation of Tarina 24 Fe in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event).

5.8 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different contraceptive product.

In a clinical trial of Tarina 24 Fe, the frequency and duration of unscheduled bleeding and/or spotting was assessed in 743 women (3,823 28-day cycles). A total of 10 subjects (1.3%) discontinued Tarina 24 Fe, at least in part, due to bleeding or spotting. Based on data from the clinical trial, [24 to 38%] of women using Tarina 24 Fe experienced unscheduled bleeding per cycle in the six months of the trial. The percent of women who experienced unscheduled bleeding tended to decrease over time.

Amenorrhea and Oligomenorrhea

Women who use Tarina 24 Fe may experience absence of withdrawal bleeding, even if they are not pregnant. In the clinical trial with Tarina 24 Fe, 31 to 41% of the women using Tarina 24 Fe did not have a withdrawal menses in at least one of 6 cycles of use.

Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was preexistent.

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.9 COC Use Before or During Early Pregnancy

Extensive epidemiologic studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue Tarina 24 Fe use if pregnancy is confirmed.

Administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Carefully observe women with a history of depression and discontinue Tarina 24 Fe if depression recurs to a serious degree.

5.11 Carcinoma of the Breast and Cervix

Tarina 24 Fe is contraindicated in women who currently have or have had breast cancer because breast cancer is a hormonally-sensitive *[see Contraindications (4)]*.

There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.

Some studies suggest that COCs are associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings may be due to differences in sexual behavior and other factors.

5.12 Effect on Binding Globulins

The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.15 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Tarina 24 Fe.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in the labeling:

- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Tarina 24 Fe was evaluated in 743 subjects who participated in an open-label, randomized, active-controlled, multicenter clinical trial of Tarina 24 Fe for contraception. This trial examined healthy, non-pregnant volunteers aged 18 to 45 years, who were sexually active and had a body mass index of less than or equal to 35 kg/m^2. Subjects were followed for up to six 28-day cycles providing a total of 3,823 treatment-cycles of exposure.

Common Adverse Reactions (greater than or equal to 2% of all subjects): The most common adverse reactions reported by at least 2% of the 743 women using Tarina 24 Fe were the following, in order of decreasing incidence: headache (6.3%), vaginal candidiasis (6.1%), nausea (4.6%), menstrual cramps (4.4%), breast tenderness (3.4%), mood changes (including mood swings (2.2%) and depression (1.1%), bacterial vaginitis (3.1%), acne (2.7%), and weight gain (2.0%).

Adverse Reactions Leading to Study Discontinuation: Among the 743 women using Tarina 24 Fe, 46 women (6.2%) withdrew because of an adverse event. Adverse events occurring in 3 or more subjects leading to discontinuation of treatment were, in decreasing order: abnormal bleeding (0.9%), nausea (0.8%), mood changes (0.8%), menstrual cramps (0.4%), increased blood pressure (0.4%), and irregular bleeding (0.4%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Tarina 24 Fe. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Cardiovascular: chest pain, palpitations, tachycardia, angina pectoris, myocardial infarction.

Endocrine disorders: hypothyroidism, hyperthyroidism.

Eye disorders: blurred vision, visual impairment, transient blindness, corneal thinning, change in corneal curvature (steepening).

GI disorders: nausea, vomiting, abdominal pain, constipation, pancreatitis.

Hepatobiliary disorders: cholelithiasis, cholecystitis, hepatic adenoma, hemangioma of liver.

Immune system disorders: anaphylactic reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms.

Infections: vaginal infection.

Metabolism and nutrition disorders: change in weight or appetite (increase or decrease).

hypoglycemia, diabetes mellitus, anemia.

Musculoskeletal and connective tissue disorders: myalgia.

Skin and subcutaneous disorders: alopecia, rash (generalized and allergic), pruritus, skin discoloration, night sweats, swelling face or lips, hirsutism, skin burning sensation, erythema multiforme, erythema nodosum, hemorrhagic eruption.

Nervous system disorders: headache, dizziness, migraine, hyperesthesia, paraesthesia, hypoaesthesia, somnolence, loss of consciousness, sensory disturbance.

Psychiatric disorders: mood swings, depression, insomnia, anxiety, suicidal ideation, panic attack, changes in libido, bipolar disorder, dissociation, homicidal ideation.

Renal and urinary disorders: pollakiuria, dysuria, cystitis-like syndrome.

Reproductive system and breast disorders: breast changes (tenderness, pain, enlargement, and secretion), premenstrual syndrome, ovarian cyst, pelvic pain, ovarian cyst ruptured, pelvic fluid collection.

Vascular disorders: hot flush, thrombosis/embolism (coronary artery, pulmonary, cerebral, deep vein), migraine, transient ischemic attack, ischemic stroke.

7 DRUG INTERACTIONS

Consult the labeling of concurrently used drugs to obtain further information about interactions with oral contraceptives or the potential for enzyme alterations.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances decreasing the plasma concentrations of COCs and potentially diminishing the efficacy of COCs:

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of COCs and potentially diminish the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of oral contraceptives including phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between COCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Substances increasing the plasma concentrations of COCs:

Co-administration of atorvastatin or rosuvastatin and certain COCs containing ethinyl estradiol (EE) increase AUC values for EE by approximately 20 to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

7.2 Effects of Combined Oral Contraceptives on Other Drugs

COCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations. COCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, and temazepam. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs *[see Warnings and Precautions (5.12)]*.

7.3 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer Tarina 24 Fe with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations *[see Warnings and Precautions (5.3)]*.

7.4 Interactions with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

Do not administer COCs to induce withdrawal bleeding as a test for pregnancy. Do not use COCs during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed should not start COCs earlier than 4 weeks postpartum.

8.3 Nursing Mothers

Advise the nursing mother to use another contraceptive method, when possible, until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of Tarina 24 Fe have been established in women of reproductive age. Efficacy is expected to be the same in postpubertal adolescents under the age of 18 years as for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Tarina 24 Fe has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

The pharmacokinetics of Tarina 24 Fe has not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

8.7 Renal Impairment

The pharmacokinetics of Tarina 24 Fe has not been studied in women with renal impairment.

8.8 Body Mass Index

The safety and efficacy of Tarina 24 Fe in women with a body mass index (BMI) greater than 35 kg/m^2 has not been evaluated *[see Clinical Studies (14)]*.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdose of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

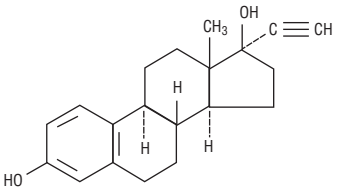
11 DESCRIPTION

Tarina 24 Fe is a combination oral contraceptive for oral administration consisting of active tablets containing norethindrone acetate, a progestin, and ethinyl estradiol, an estrogen, and placebo tablets containing ferrous fumarate, which serve no therapeutic purpose.

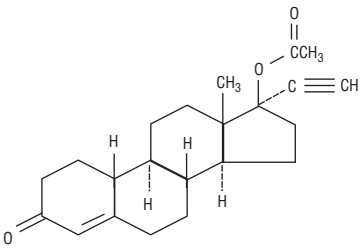
- Each active light yellow to yellow tablet contains 1 mg norethindrone acetate USP and 20 mcg ethinyl estradiol USP. Inactive ingredients include compressible sugar, croscarmellose sodium, D & C Yellow No. 10 Aluminum Lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and vitamin E.

- Each placebo brown tablet contains 75 mg ferrous fumarate, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, Nat spearmint FL SD #11475, povidone and sucralose. The ferrous fumarate tablets do not serve any therapeutic purpose. Ferrous fumarate tablets are not USP for dissolution and assay.

The chemical name of ethinyl estradiol is 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol. The molecular formula of ethinyl estradiol is $C_{20}H_{24}O_2$ and the structural formula is:



The chemical name of norethindrone acetate is 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate. The molecular formula of norethindrone acetate is $C_{22}H_{28}O_3$ and the structural formula is:



USP Dissolution Test Pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Tarina 24 Fe.

12.3 Pharmacokinetics

Absorption

Norethindrone acetate appears to be completely and rapidly deacetylated to norethindrone after oral administration, because the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol are rapidly absorbed from Tarina 24 Fe tablets, with maximum plasma concentrations of norethindrone and ethinyl estradiol occurring 1 to 4 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 43% for ethinyl estradiol.

The plasma norethindrone and ethinyl estradiol pharmacokinetics following single- and multiple-dose administrations of Tarina 24 Fe tablets in 17 healthy female volunteers are provided in Figures 1 and 2, and Table 3.

Following multiple-dose administration of Tarina 24 Fe tablets, mean maximum concentrations of norethindrone and ethinyl estradiol were increased by 95% and 27%, respectively, as compared to single-dose administration. Mean norethindrone and ethinyl estradiol exposures (AUC values) were increased by 164% and 51% respectively, as compared to single-dose administration of Tarina 24 Fe tablets.

Steady-state with respect to norethindrone was reached by Day 17 and steady-state with respect to ethinyl estradiol was reached by Day 13.

Mean SHBG concentrations were increased by 150% from baseline (57.5 nmol/L) to 144 nmol/L at steady-state.

Figure 1. Mean Plasma Norethindrone Concentration-Time Profiles Following Single- and Multiple-Dose Oral Administration of Tarina 24 Fe Tablets to Healthy Female Volunteers Under Fasting Condition (n = 17)

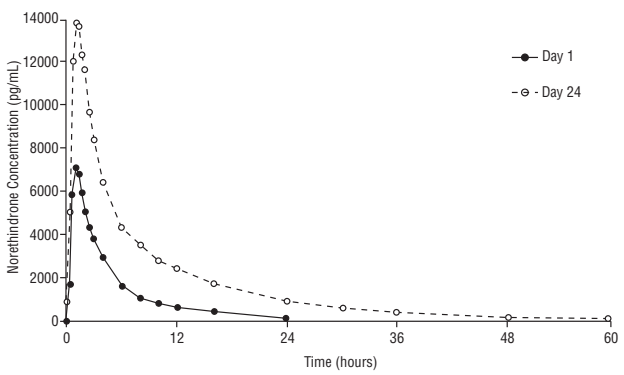


Figure 2. Mean Plasma Ethinyl Estradiol Concentration-Time Profiles Following Single- and Multiple-Dose Oral Administration of Tarina 24 Fe Tablets to Healthy Female Volunteers Under Fasting Condition (n = 17)

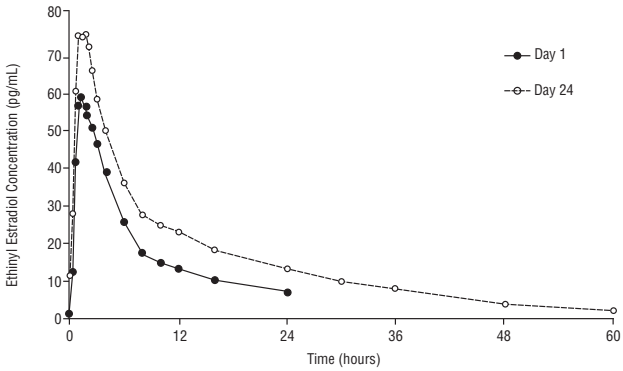


Table 3. Summary of Norethindrone (NE) and Ethinyl Estradiol (EE) Pharmacokinetics Following Single- and Multiple-Dose Oral Administration of Tarina 24 Fe Tablets to Healthy Female Volunteers Under Fasting Condition (n = 17)

Regimen	Analyte	Arithmetic Mean[a] (% CV) by Pharmacokinetic Parameter					
		C_{max} (pg/mL)	t_{max} (hr)	$AUC_{(0-24)}$ (pg/mL•h)	C_{min} (pg/mL)	$t_{½}$ (hr)	C_{avg} (pg/mL)
Day 1 (Single Dose)	NE	8420 (31)	1.0 (0.7 to 4.0)	33390 (40)	--	--	--
	EE	64.5 (27)	1.3 (0.7 to 4.0)	465.4 (26)	--	--	--
	SHBG	--	--	--	57.5 (37)[b]	--	--
Day 24 (Multiple Dose)	NE	16400 (26)	1.3 (0.7 to 4.0)	88160 (30)	880 (51)	8.4	3670 (30)
	EE	81.9 (24)	1.7 (1.0 to 2.0)	701.3 (28)	11.4 (43)	14.5	29.2 (28)
	SHBG	--	--	--	144 (24)	--	--

C_{max} = Maximum plasma concentration
t_{max} = Time of C_{max}
C_{min} = minimum plasma concentration at steady-state
$AUC_{(0-24)}$ = Area under plasma concentration versus time curve from 0 to 24 hours
$t_{½}$ = Apparent first-order terminal elimination half-life
C_{avg} = Average plasma concentration = $AUC_{(0-24)/24}$
% CV = Coefficient of Variation (%)
SHBG = Sex Hormone Binding Globulin (nmol/L)
[a] The harmonic mean (0.693/mean apparent elimination rate constant) is reported for $t_{½}$, and the median (range) is reported for t_{max}.
[b] The SHBG concentration reported here is the pre-dose concentration.

Food Effect

A single-dose administration of Tarina 24 Fe tablet with food decreased the maximum concentration of norethindrone by 11% and increased the extent of absorption by 27% and decreased the maximum concentration of ethinyl estradiol by 30% but not the extent of absorption.

Distribution

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (greater than 95%); norethindrone binds to both albumin and SHBG, whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

Metabolism

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

Excretion

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar

(approximately 0.4 L/hr/kg). Steady-state elimination half-lives of norethindrone and ethinyl estradiol following administration of Tarina 24 Fe tablets are approximately 8 hours and 14 hours, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.2, 5.11) and Use in Specific Populations (8.1).]

14 CLINICAL STUDIES

In an active-controlled clinical trial, 743 women 18 to 45 years of age were studied to assess the efficacy of Tarina 24 Fe, for up to six 28-day cycles. The racial demographic of women randomized to Tarina 24 Fe was: 69.5% Caucasian, 15.5% African-American, 10.4% Hispanic, 2.3% Asian and 2.3% Native American/Other. Women with body mass index (BMI) greater than 35 mg/m^2 were excluded from the study. The weight range for those women treated was 90 to 260 pounds, with a mean weight of 147 pounds. Among the women in the study randomized to Tarina 24 Fe, 38.9% had not used hormonal contraception immediately prior to enrolling in this study.

A total of 583 women completed 6 cycles of treatment. There were a total of 5 on-treatment pregnancies among women aged 18 to 45 years in 3,565 treatment cycles during which no back-up contraception was used. The Pearl Index for Tarina 24 Fe was 1.82 (95% confidence interval 0.59 to 4.25).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Tarina® 24 Fe is available in blister packs containing 28 tablets. The Blister Packs are packed in pouches (NDC 50102-224-21) and the pouches are packaged in cartons:

pouch containing one Blister pack	NDC 50102-224-21
Carton of 3 Pouches	NDC 50102-224-23

Each blister pack (28 tablets) contains in the following order:

- 24 light yellow to yellow, round, flat-faced, beveled-edge, uncoated (active) tablets debossed with 'S' on one side and '64' on other side and each containing 1 mg of norethindrone acetate USP and 20 mcg of ethinyl estradiol USP.
- 4 brown, mottled, round, flat-faced, beveled-edge (non-hormonal placebo) tablets debossed with 'S' on one side and '57' on other side and each containing 75 mg ferrous fumarate USP. The ferrous fumarate tablets do not serve any therapeutic purpose.

16.2 Storage Conditions

- **Store at** 20º to 25ºC (68º to 77ºF) [see USP Controlled Room Temperature].
- Protect from light.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (Patient Information and Instructions for Use).

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs *[see Boxed Warning]*.
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC *[see Warnings and Precautions (5.1)]*.
- Tarina 24 Fe does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
- Tarina 24 Fe is not to be used during pregnancy; if pregnancy occurs during use of Tarina 24 Fe instruct the patient to stop further use *[see Warnings and Precautions (5.9)]*.
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event pills are missed *[see Dosage and Administration (2.2)]*.
- Use a back-up or alternative method of contraception when enzyme inducers are used with Tarina 24 Fe *[see Drug Interactions (7.1)]*.
- COCs may reduce breast milk production; this is less likely to occur if breastfeeding is well established *[see Use in Specific Populations (8.3)]*.
- Women who start COCs postpartum, and who has not yet had a period, must use an additional method of contraception until she has taken a light yellow to yellow tablet for 7 consecutive days *[see Dosage and Administration (2.2)]*.
- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea at the time of the first missed period. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles *[see Warnings and Precautions (5.8)]*.

PATIENT INFORMATION

Tarina® 24 Fe

(norethindrone acetate and ethinyl estradiol tablets USP and ferrous fumarate tablets)

What is the most important information I should know about Tarina 24 Fe?

Do not use Tarina 24 Fe if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from hormonal birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

What is Tarina 24 Fe?

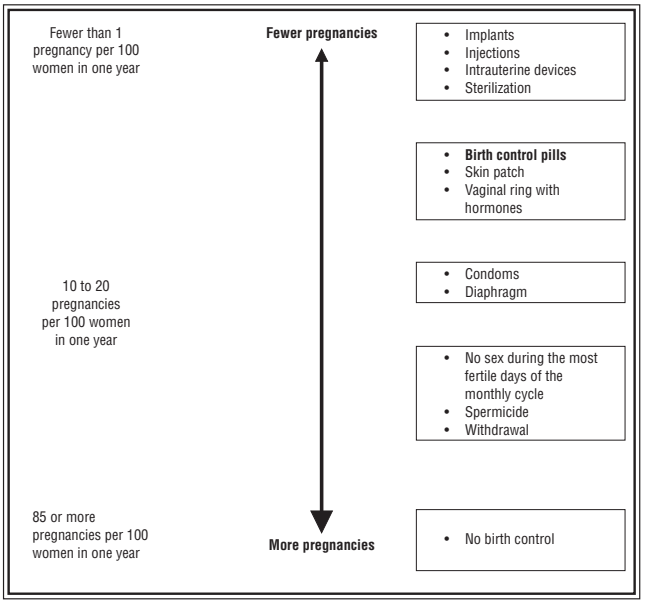
Tarina 24 Fe is a birth control pill (hormonal contraceptive) used by women to prevent pregnancy.

How does Tarina 24 Fe work for contraception?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results from the clinical study, about 1 to 4 out of 100 women may get pregnant during the first year they use Tarina 24 Fe.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



Who should not take Tarina 24 Fe?

Do not take Tarina 24 Fe if you:

- smoke and are over 35 years of age
- had blood clots in your arms, legs, lungs, or eyes
- had a problem with your blood that makes it clot more than normal
- have certain heart valve problems or irregular heart beat that increases your risk of having blood clots
- had a stroke
- had a heart attack
- have high blood pressure that cannot be controlled by medicine
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or any migraine headaches if you are over 35 years of age
- have liver problems, including liver tumors
- have any unexplained vaginal bleeding
- are pregnant
- had breast cancer or any cancer that is sensitive to female hormones
- take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.

If any of these conditions happen while you are taking Tarina 24 Fe, stop taking Tarina 24 Fe right away and talk to your healthcare provider. Use non-hormonal contraception (such as condoms and spermicide) when you stop taking Tarina 24 Fe.

What should I tell my healthcare provider before taking Tarina 24 Fe?

Tell your healthcare provider if you:

- are pregnant or think you may be pregnant
- are depressed now or have been depressed in the past
- had yellowing of your skin or eyes (jaundice) caused by pregnancy (cholestasis of pregnancy)
- are breastfeeding or plan to breastfeed. Tarina 24 Fe may decrease the amount of breast milk you make. A small amount of the hormones in Tarina 24 Fe may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Tarina 24 Fe may affect the way other medicines work, and other medicines may affect how well Tarina 24 Fe works.

Know the medicines you take. Keep a list of them to show your healthcare provider and

pharmacist when you get a new medicine.

How should I take Tarina 24 Fe?

Read the **Instructions for Use** at the end of this Patient Information.

What are the possible serious side effects of Tarina 24 Fe?

- **Like pregnancy, Tarina 24 Fe may cause serious side effects, including blood clots in your lungs, heart attack, or a stroke that may lead to death.** Some other examples of serious blood clots include blood clots in the legs or eyes.

Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age. Serious blood clots are more likely to happen when you:

- first start taking birth control pills
- restart the same or different birth control pills after not using them for a month or more

Call your healthcare provider or go to a hospital emergency room right away if you have:

- o leg pain that will not go away
- o sudden severe shortness of breath
- o sudden change in vision or blindness
- o chest pain
- o a sudden, severe headache unlike your usual headaches
- o weakness or numbness in your arm or leg
- o trouble speaking

Other serious side effects include:

- **liver problems, including:**
  - o rare liver tumors
  - o jaundice (cholestasis), especially if you previously had cholestasis of pregnancy. Call your healthcare provider if you have yellowing of your skin or eyes.
- **high blood pressure.** You should see your healthcare provider for a yearly check of your blood pressure.
- **gallbladder problems**
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood**
- **new or worsening headaches including migraine headaches**
- **depression**
- **possible cancer in your breast and cervix**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider if you have a swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher is you have a history of angioedema.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Women who tend to get chloasma should avoid spending a long time in sunlight, tanning booths, and under sun lamps while taking Tarina 24 Fe. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of Tarina 24 Fe?

- headache
- vaginal infections
- nausea
- menstrual cramps
- breast tenderness
- mood changes
- acne
- weight gain

These are not all the possible side effects of Tarina 24 Fe. For more information, ask your healthcare provider or pharmacist.

You may report side effects to the FDA at 1-800-FDA-1088.

What else should I know about taking Tarina 24 Fe?

- If you are scheduled for any lab tests, tell your healthcare provider you are taking Tarina 24 Fe. Certain blood tests may be affected by Tarina 24 Fe.
- Tarina 24 Fe does not protect against HIV infection (AIDS) and other sexually transmitted infections.

How should I store Tarina 24 Fe?

- Store Tarina 24 Fe at room temperature between 20° to 25°C (68° to 77°F).
- Store away from light.
- Keep Tarina 24 Fe and all medicines out of the reach of children.

General information about the safe and effective use of Tarina 24 Fe.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Tarina 24 Fe for a condition for which it was not prescribed. Do not give Tarina 24 Fe to other people.

This Patient Information summarizes the most important information about Tarina 24 Fe. You can ask your pharmacist or healthcare provider for information about Tarina 24 Fe that is written for health professionals.

For more information, call Afaxys Pharma, LLC at 1-855-888-2467.

Do birth control pills cause cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What if I want to become pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

What should I know about my period when taking Tarina 24 Fe?

Your periods may be lighter and shorter than usual. Some women may miss a period. Irregular vaginal bleeding or spotting may happen while you are taking Tarina 24 Fe, especially during the first few months of use. This usually is not a serious problem. It is important to continue taking your pills on a regular schedule to prevent a pregnancy.

What are the ingredients in Tarina 24 Fe?

Active ingredients:

Light yellow to yellow pills: norethindrone acetate and ethinyl estradiol

Inactive ingredients:

Light yellow to yellow pills: compressible sugar, croscarmellose sodium, D & C Yellow No. 10 Aluminum Lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and vitamin E.

Brown pills: ferrous fumarate, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, Nat spearmint FL SD #11475, povidone and sucralose.

INSTRUCTIONS FOR USE

Tarina 24 Fe

(norethindrone acetate and ethinyl estradiol tablets USP and ferrous fumarate tablets)

Important Information about taking Tarina 24 Fe

- Take **1** pill every day at the same time. Take the pills in the order directed on your blister pack.
- Do not skip your pills, even if you do not have sex often. If you miss pills (including starting the pack late), **you could get pregnant**. The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take Tarina 24 Fe, talk to your healthcare provider.
- When you first start taking Tarina 24 Fe, spotting or light bleeding in between your periods may occur. Contact your healthcare provider if this does not go away after a few months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking Tarina 24 Fe. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If your nausea does not go away, call your healthcare provider.
- Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills (see **What should I do if I miss any Tarina 24 Fe pills?** below), you could also feel a little sick to your stomach.
- It is not uncommon to miss a period. However, if you miss a period and have not taken Tarina 24 Fe according to directions, or miss **2** periods in a row, or feel like you may be pregnant, call your healthcare provider. If you have a positive pregnancy test, you should stop taking Tarina 24 Fe.
- If you have vomiting or diarrhea within **3 to 4** hours of taking a light yellow to yellow active pill, take another light yellow to yellow pill from your extra blister pack. If you do not have an extra blister pack, take the next light yellow to yellow pill in your blister pack. Continue taking all your remaining pills in order. Start the first pill of your next blister pack the day after finishing your current blister pack. This will be 1 day earlier than originally scheduled. Continue on your new schedule.
- If you have vomiting or diarrhea for more than 1 day, your birth control pills may not work as well. Use an additional birth control method, like condoms and a spermicide, until you check with your healthcare provider.
- Stop taking Tarina 24 Fe at least **4** weeks before you have major surgery and do not restart after the surgery without asking your healthcare provider. Be sure to use other forms of contraception (like condoms and spermicide) during this time period.

Before you start taking Tarina 24 Fe:

- Decide what time of day you want to take your pill. It is important to take it at the same time every day and in the order as directed on your blister pack.
- Have backup contraception (condoms and spermicide) available and if possible, an extra full pack of pills as needed.

When should I start taking Tarina 24 Fe?

If you start taking Tarina 24 Fe and you have not used a hormonal birth control method before:

- There are 2 ways to start taking your birth control pills. You can either start on a Sunday (Sunday Start) or on the first day (Day 1) of your natural menstrual period (Day 1 Start). Your healthcare provider should tell you when to start taking your birth control pill.
- If you use the Sunday Start, use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days that you take Tarina 24 Fe. You do not need back-up contraception if you use the Day 1 Start.

If you start taking Tarina 24 Fe and you are switching from another birth control pill:

- Start your new Tarina 24 Fe pack on the same day that you would start the next pack of your previous birth control method.
- Do not continue taking the pills from your previous birth control pack.

If you start taking Tarina 24 Fe and previously used a vaginal ring or transdermal patch:

- Start using Tarina 24 Fe on the day you would have reapplied the next ring or patch.

If you start taking Tarina 24 Fe and you are switching from a progestin-only method such as an implant or injection:

- Start taking Tarina 24 Fe on the day of removal of your implant or on the day when you would have had your next injection.

If you start taking Tarina 24 Fe and you are switching from an intrauterine device or system (IUD or IUS):

- Start taking Tarina 24 Fe on the day of removal of your IUD or IUS.
- You do not need back-up contraception if your IUD or IUS is removed on the first day (Day 1) of your period. If your IUD or IUS is removed on any other day, use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days that you take Tarina 24 Fe.

Keep a calendar to track your period:

If this is the first time you are taking birth control pills, read, "**When should I start taking Tarina 24 Fe?**" above. Follow these instructions for either a **Sunday Start** or a **Day 1 Start**.

Sunday Start:

You will use a **Sunday Start** if your healthcare provider told you to take your first pill on a Sunday.

- Take pill **1** on the Sunday **after your period starts.**
- If your period starts on a Sunday, take pill "**1**" that day and refer to Day 1 Start instructions below.
- Take **1** pill every day in the order on the blister pack at the same time each day for **28** days.
- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack (Sunday). Take the first pill in the new pack whether or not you are having your period.
- Use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days of the first cycle that you take Tarina 24 Fe.

Day 1 Start:

You will use a **Day 1 Start** if your doctor told you to take your first pill (Day 1) on the **first day of your period**.

- Take **1** pill every day in the order of the blister pack, at the same time each day, for **28** days.
- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack. Take the first pill in the new pack whether or not you are having your period.

Instructions for using your blister pack:

The Tarina 24 Fe blister pack has 24 "active" light yellow to yellow pills (with hormones) to be taken for **24** days, followed by 4 "reminder" brown pills (without hormones) to be taken for the next **4** days.

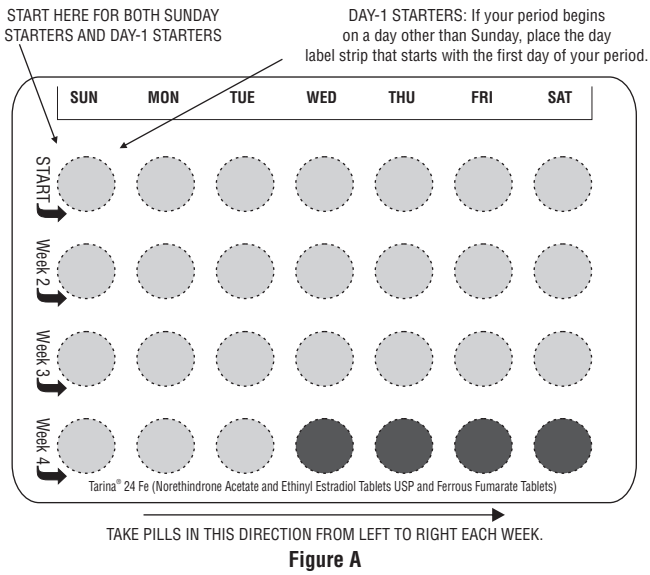


Figure A

Look for:

- Where on the pack to start taking pills
- In what order to take the pills. Follow the arrows shown in **Figure A**.
- The week numbers as shown in **Figure A.**

What if should I do if I miss any Tarina 24 Fe light yellow to yellow pills?

If you miss 1 light yellow to yellow pill in Weeks 1, 2, or 3, follow these steps:

- 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.
- Then continue taking **1** pill every day until you finish the pack.
- You do not need to use a back-up birth control method if you have sex.

If you miss 2 light yellow to yellow pills in a row in Week 1 or Week 2 of your pack, follow these steps:

- Take the 2 missed pills as soon as possible and the next 2 pills the next day.
- Then continue to take 1 pill every day until you finish the pack.
- Use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first 7 days after missing your pills.

If you miss 2 light yellow to yellow pills in a row in Week 3 or Week 4, or you miss 3 or more light yellow to yellow pills in a row at any time, follow these steps:

- **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.
- 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 healthcare provider because you might be pregnant.
- You could become pregnant if you have sex during the first 7 days after you restart your pills. You MUST use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first 7 days after you restart your pills.

If you miss any of the 4 brown "reminder" pills in Week 4, throw away the pills you missed and keep taking 1 pill each day until the pack is empty. You do not need to use a back-up method of birth control.

If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured for:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 02/2021

Tarina Fe 1/20 EQ®

(norethindrone acetate and ethinyl estradiol tablets USP and ferrous fumarate tablets)

Rx only

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

DESCRIPTION

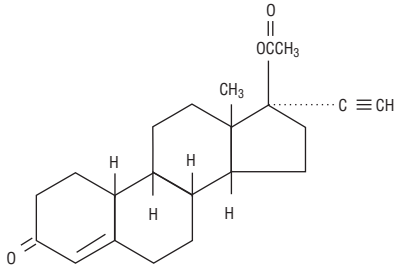
Tarina Fe 1/20 EQ is progestogen-estrogen combination.

Tarina Fe 1/20 EQ: Each provides a continuous dosage regimen consisting of 21 oral contraceptive tablets and seven ferrous fumarate tablets. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose.

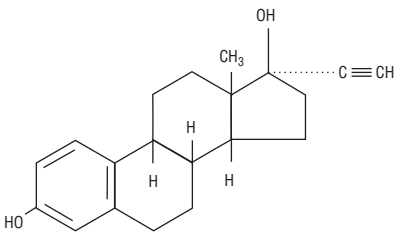
Each light yellow to yellow tablet contains norethindrone acetate USP (17 alpha-ethinyl-19-nortestosterone acetate), 1 mg; ethinyl estradiol USP (17 alpha-ethinyl-1,3,5(10)-estratriene-3, 17 beta-diol), 20 mcg. Each light yellow to yellow tablet contains the following inactive ingredients: compressible sugar, croscarmellose sodium, D&C yellow No.10 aluminum lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and vitamin E.

Each brown placebo tablet contains the following ingredients: croscarmellose sodium, ferrous fumarate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, Nat spearmint FL, povidone and sucralose. The ferrous fumarate tablets do not serve any therapeutic purpose.

The structural formulas are as follows:



Norethindrone Acetate



Ethinyl Estradiol

USP Dissolution test is pending

CLINICAL PHARMACOLOGY

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).

Pharmacokinetics

The pharmacokinetics of Tarina Fe 1/20 EQ has not been characterized; however, the following pharmacokinetic information regarding norethindrone acetate and ethinyl estradiol is taken from the literature.

Absorption

Norethindrone acetate appears to be completely and rapidly deacetylated to norethindrone after oral administration, since the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone (1). Norethindrone acetate and ethinyl estradiol are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 43% for ethinyl estradiol (1 to 3).

Distribution

Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg (1 to 3). Plasma protein binding of both steroids is extensive (greater than 95%); norethindrone binds to both albumin and sex hormone binding globulin, whereas ethinyl estradiol binds only to albumin (4).

Metabolism

Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites (5). A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol. Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine.

The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation (6).

Excretion

Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites (5,6). Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg) (1 to 3).

Special Population

Race

The effect of race on the disposition of Tarina Fe 1/20 EQ has not been evaluated.

Renal Insufficiency

The effect of renal disease on the disposition of Tarina Fe 1/20 EQ has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

Hepatic Insufficiency

The effect of hepatic disease on the disposition of Tarina Fe 1/20 EQ has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function.

Drug-Drug Interactions

Numerous drug-drug interactions have been reported for oral contraceptives. A summary of these is found under **PRECAUTIONS**, **Drug Interactions**.

INDICATIONS AND USAGE

Tarina Fe 1/20 EQ is indicated for the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception.

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

TABLE I
LOWEST EXPECTED AND TYPICAL FAILURE RATES DURING THE FIRST YEAR OF CONTINUOUS USE OF A METHOD

% of Women Experiencing an Unintended Pregnancy in the First Year of Continuous Use		
Method	Lowest Expected*	Typical**
(No contraception)	(85)	(85)
Oral contraceptives		3
combined	0.1	N/A***
progestin only	0.5	N/A***
Diaphragm with spermicidal cream or jelly	6	20
Spermicides alone (foam, creams, gels, vaginal suppositories, and vaginal film)	6	26
Vaginal Sponge		
nulliparous	9	20
parous	20	40
Implant	0.05	0.05
Injection: depot medroxyprogesterone acetate	0.3	0.3
IUD		
progesterone T	1.5	2
copper T 380A	0.6	0.8
LNg 20	0.1	0.1
Condom without spermicides		
female	5	21
male	3	14
Cervical Cap with spermicidal cream or jelly		
nulliparous	9	20
parous	26	40
Periodic abstinence (all methods)	1 to 9	25
Withdrawal	4	19
Female sterilization	0.5	0.5
Male sterilization	0.1	0.15

Adapted from RA Hatcher et al, Reference 7.
* The authors' best guess of the percentage of women expected to experience an accidental pregnancy among couples who initiate a method (not necessarily for the first time) and who use it consistently and correctly during the first year if they do not stop for any other reason.
** This term represents "typical" couples who initiate use of a method (not necessarily for the first time), who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
*** N/A--Data not available.

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
- Are receiving Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations (see **WARNINGS, Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment)**.

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 References 8 and 9 with the author's permission). For further information, the reader is referred to a text on epidemiological methods.

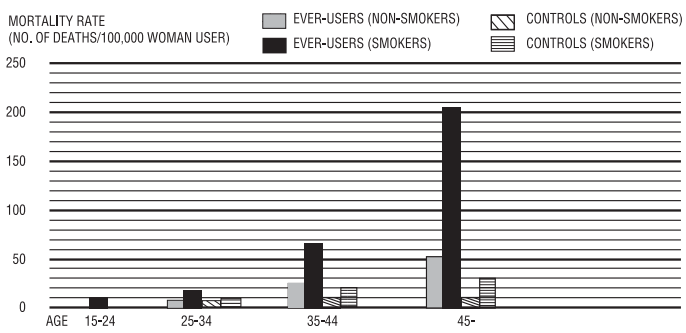
1. Thromboembolic Disorders and Other Vascular Problems

a. Myocardial Infarction

An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six (10 to 16). 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 (17). 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 (Table II) among women who use oral contraceptives.

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, Reference 18.

Oral contraceptives may compound the effects of well-known risk factors, such as hypertension, diabetes, hyperlipidemias, age and obesity (19). In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intolerance, while estrogens may create a state of hyperinsulinism (20 to 24). 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.

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 (9, 10, 25 to 30). 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 (31). The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped (8).

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives (15,32). The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions (15,32). 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 to six weeks after delivery in women who elect not to breastfeed.

c. Cerebrovascular Disease

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 (greater than 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, while smoking interacted to increase the risk for hemorrhagic strokes (33 to 35).

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 (36). 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 (36). The attributable risk is also greater in older women (9).

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 (37 to 39). A decline in serum high-density lipoproteins (HDL) has been reported with many progestational agents (20 to 22). 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 progestin and the nature of the progestin used in the contraceptives. The amount and activity 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 oral contraceptive, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with the needs of the individual patient. New acceptors of oral contraceptive agents should be started on preparations containing the lowest dose of estrogen which produces satisfactory results for the patient.

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 5 or more years, but this increased risk was not demonstrated in other age groups (14). 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). However, both studies were performed with oral contraceptive formulations containing 50 mcg or higher of estrogens.

2. Estimates of Mortality from Contraceptive Use

One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraception at different ages (Table III). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception has its specific benefits and risks. The study concluded that with the exception of oral contraceptive users 35 and older who smoke and 40 and older who do not smoke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of a possible increase in risk of mortality with age for oral contraceptive users is based on data gathered in the 1970's but not reported until 1983 (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 (Porter JB, Hunter J, Jick H, et al. Oral contraceptives and nonfatal vascular disease. Obstet Gynecol 1985;66:1-4; and Porter JB, Hershel J, Walker AM. Mortality among oral contraceptive users. Obstet Gynecol 1987;70:29-32), 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.

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

* Deaths are birth related.
** Deaths are method related.

Adapted from H.W. Ory, Reference 41.

3. Carcinoma of the Reproductive Organs

Numerous epidemiological studies have been performed on the incidence of breast, endometrial, ovarian, and cervical cancer in women using oral contraceptives. Most of the studies on breast cancer and oral contraceptive use report that the use of oral contraceptives is not associated with an increase in the risk of developing breast cancer (42,44,89). Some studies have reported an increased risk of developing breast cancer in certain subgroups of oral contraceptive users, but the findings reported in these studies are not consistent (43,45 to 49,85 to 88).

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 (51 to 54). 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 and 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/100,000 for users, a risk that increases after four or more years of use (55). Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage (56, 57). Studies from Britain have shown an increased risk of developing hepatocellular carcinoma (58 to 60) in long-term (greater than 8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S., and the attributable risk (the excess incidence) of liver cancers in oral contraceptive users approaches less than one per million users.

5. Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications such as COCs. Discontinue Tarina Fe 1/20 EQ prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see **Contraindications**]*. Tarina Fe 1/20 EQ can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen.

6. 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.

7. Oral Contraceptive Use Before and During Early Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy (61 to 63). Studies also do not suggest a teratogenic effect, particularly insofar as cardiac anomalies and limb reduction defects are concerned (61,62,64,65), 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 if pregnancy is confirmed.

8. Gallbladder Disease

Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens (66,67). More recent studies, however, have shown that the relative risk of developing gallbladder disease among oral contraceptive users may be minimal (68 to 70). The recent findings of minimal risk may be related to the use of oral contraceptive formulations containing lower hormonal doses of estrogens and progestogens.

9. Carbohydrate and Lipid Metabolic Effects

Oral contraceptives have been shown to cause glucose intolerance in a significant percentage of users (23). Oral contraceptives containing greater than 75 mcg of estrogens cause hyperinsulinism, while lower doses of estrogen cause less glucose intolerance (71).

Progestogens increase insulin secretion and create insulin resistance, this effect varying with different progestational agents (23,72).

However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose (73). Because of these demonstrated effects, prediabetic and diabetic women should be carefully observed 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.

10. Elevated Blood Pressure

An increase in blood pressure has been reported in women taking oral contraceptives (74) and this increase is more likely in older oral contraceptive users (75) and with continued use (74). Data from the Royal College of General Practitioners (18) 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 (76) 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 (75), and there is no difference in the occurrence of hypertension among ever and never users (74,76,77).

11. 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.

12. Bleeding Irregularities

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

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

PRECAUTIONS

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

2. 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.

3. Lipid Disorders

Women who are being treated for hyperlipidemia 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.

4. 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.

5. 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.

6. Emotional Disorders

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

7. Contact Lenses

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

8. Drug Interactions

Effects of Other Drugs on Oral Contraceptives (78)

Rifampin: Metabolism of both norethindrone and ethinyl estradiol is increased by rifampin. A reduction in contraceptive effectiveness and increased incidence of breakthrough bleeding and menstrual irregularities have been associated with concomitant use of rifampin.

Anticonvulsants: Anticonvulsants such as phenobarbital, phenytoin, and carbamazepine, have been shown to increase the metabolism of ethinyl estradiol and/or norethindrone, which could result in a reduction in contraceptive effectiveness.

Troglitazone: Administration of troglitazone with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both by approximately 30%, which could result in a reduction in contraceptive effectiveness.

Antibiotics: Pregnancy while taking oral contraceptives has been reported when the oral contraceptives were administered with antimicrobials such as ampicillin, tetracycline, and griseofulvin. However, clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

Atorvastatin: Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%, respectively.

Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer Tarina Fe 1/20 EQ with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations(see **WARNINGS, Risk of Liver Enzyme Elevations with concomitant Hepatitis C Treatment**).

Other: Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol concentrations, possibly by inhibition of conjugation. A reduction in contraceptive effectiveness and increased incidence of breakthrough bleeding has been suggested with phenylbutazone.

Effects of Oral Contraceptives on Other Drugs

Oral contraceptive combinations containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporine, prednisolone, and theophylline have been reported with concomitant administration of oral contraceptives. In addition, oral contraceptives may induce the conjugation of other compounds. Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine, and clofibric acid have been noted when these drugs were administered with oral contraceptives.

9. 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), T_4 by column or by radioimmunoassay. Free T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered.
c. Other binding proteins may be elevated in serum.
d. Sex-binding globulins are increased and result in elevated levels of total circulating sex steroids and corticoids; however, free or biologically active levels remain unchanged.
e. Triglycerides may be increased.
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.

10. Carcinogenesis

See **WARNINGS** section.

11. Pregnancy

Teratogenic Effects

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

12. 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 but to use other forms of contraception until she has completely weaned her child.

13. Pediatric Use

Safety and efficacy of Tarina Fe 1/20 EQ has 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.

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 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

OVERDOSAGE

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

NON-CONTRACEPTIVE HEALTH BENEFITS

The following non-contraceptive health benefits related to the use of 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 (79 to 84).

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

The blister pack has been designed to make oral contraceptive dosing as easy and as convenient as possible. The tablets are arranged in four rows of seven tablets each, with the days of the week appearing on the blister pack above the first row of tablets.

Note: Each blister pack has been preprinted with the days of the week, starting with Sunday, to facilitate a Sunday-Start regimen. Six different day label stickers have been provided with

the Detailed Patient & Brief Summary Patient Package Insert in order to accommodate a Day-1 Start regimen. If the patient is using the Day-1 Start regimen, she should place the self-adhesive day label sticker that corresponds to her starting day over the preprinted days.

Important: The patient should be instructed to use an additional method of protection until after the first week of administration in the initial cycle when utilizing the Sunday-Start regimen.

The possibility of ovulation and conception prior to initiation of use should be considered.

Dosage and Administration for 28-Day Dosage Regimen

To achieve maximum contraceptive effectiveness, Tarina Fe 1/20 EQ should be taken exactly as directed and at intervals not exceeding 24 hours.

Tarina Fe 1/20 EQ provides a continuous administration regimen consisting of 21 **light yellow to yellow** tablets of norethindrone acetate and ethinyl estradiol and 7 **brown** non-hormone containing tablets of ferrous fumarate. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen and do not serve any therapeutic purpose. There is no need for the patient to count days between cycles because there are no "off-tablet days."

A. Sunday-Start Regimen: The patient begins taking the first **light yellow to yellow** tablet from the top row of the blister pack (labeled Sunday) on the first Sunday after menstrual flow begins. When the menstrual flow begins on Sunday, the first **light yellow to yellow** tablet is taken on the same day. The patient takes one **light yellow to yellow** tablet daily for 21 days. The last **light yellow to yellow** tablet in the blister pack will be taken on a Saturday. Upon completion of all 21 **light yellow to yellow** tablets, and without interruption, the patient takes one **brown** tablet daily for 7 days. Upon completion of this first course of tablets, the patient begins a second course of 28-day tablets, without interruption, the next day (Sunday), starting with the Sunday **light yellow to yellow** tablet in the top row. Adhering to this regimen of one **light yellow to yellow** tablet daily for 21 days, followed without interruption by one **brown** tablet daily for seven days, the patient will start all subsequent cycles on a Sunday.

B. Day-1 Start Regimen: The first day of menstrual flow is Day 1. The patient places the self-adhesive day label sticker that corresponds to her starting day over the preprinted days on the blister pack. She starts taking one **light yellow to yellow** tablet daily, beginning with the first **light yellow to yellow** tablet in the top row. After the last **light yellow to yellow** tablet (at the end of the third row) has been taken, the patient will then take the brown tablets for a week (7 days). For all subsequent cycles, the patient begins a new 28 tablet regimen on the eighth day after taking her last **light yellow to yellow** tablet, again starting with the first tablet in the top row after placing the appropriate day label sticker over the preprinted days on the blister pack. Following this regimen of 21 **light yellow to yellow** tablets and 7 **brown** tablets, the patient will start all subsequent cycles on the same day of the week as the first course.

Tablets should be taken regularly with a meal or at bedtime. It should be stressed that efficacy of medication depends on strict adherence to the dosage schedule.

Special Notes on Administration

Menstruation usually begins two or three days, but may begin as late as the fourth or fifth day, after the **brown** tablets have been started. In any event, the next course of tablets should be started without interruption. If spotting occurs while the patient is taking **light yellow to yellow** tablets, continue medication without interruption.

If the patient forgets to take one or more **light yellow to yellow** tablets, the following is suggested:

One tablet is missed
- take tablet as soon as remembered
- take next tablet at the regular time

Two consecutive tablets are missed (week 1 or week 2)
- take **two** tablets as soon as remembered
- take **two** tablets the next day
- use another birth control method for seven days following the missed tablets

Two consecutive tablets are missed (week 3)

Sunday-Start Regimen
- take **one** tablet daily until Sunday
- discard remaining tablets
- start new pack of tablets immediately (Sunday)
- use another birth control method for seven days following the missed tablets

Day-1 Start Regimen
- discard remaining tablets
- start new pack of tablets that same day
- use another birth control method for seven days following the missed tablets

Three (or more) consecutive tablets are missed

Sunday-Start Regimen
- take **one** tablet daily until Sunday
- discard remaining tablets
- start new pack of tablets immediately (Sunday)
- use another birth control method for seven days following the missed tablets

Day-1 Start Regimen
- discard remaining tablets
- start new pack of tablets that same day
- use another birth control method for seven days following the missed tablets

The possibility of ovulation occurring increases with each successive day that scheduled **light yellow to yellow** tablets are missed. While there is little likelihood of ovulation occurring if only one **light yellow to yellow** tablet is missed, the possibility of spotting or bleeding is increased. This is particularly likely to occur if two or more consecutive **light yellow to yellow** tablets are missed.

If the patient forgets to take any of the seven **brown** tablets in week four, those **brown** tablets that were missed are discarded and one **brown** tablet is taken each day until the pack is empty. A back-up birth control method is not required during this time. A new pack of tablets should be started no later than the eighth day after the last **light yellow to yellow** tablet was taken.

In the rare case of bleeding which resembles menstruation, the patient should be advised to discontinue medication and then begin taking tablets from a new blister pack on the next Sunday or the first day (Day-1), depending on her regimen. Persistent bleeding which is not controlled by this method indicates the need for reexamination of the patient, at which time nonfunctional causes should be considered.

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 two consecutive periods, pregnancy should be ruled out before continuing the contraceptive regimen.

After several months on treatment, bleeding may be reduced to a point of virtual absence. This reduced flow may occur as a result of medication, in which event it is not indicative of pregnancy.

HOW SUPPLIED

Tarina Fe 1/20 EQ® (norethindrone acetate and ethinyl estradiol tablets USP, 1 mg/20 mcg and ferrous fumarate tablets, 75 mg) are light yellow to yellow, round, flat-faced, beveled-edge, uncoated tablets, debossed with 'S' on one side and '64' on other side of the tablet. Each brown mottled, round, flat-faced beveled-edge tablet contains 75 mg ferrous fumarate and is debossed with 'S' on one side and '57' on other side of the tablet. The ferrous fumarate tablets are present to facilitate ease of drug administration via a 28-day regimen, are non-hormonal, and do not serve any therapeutic purpose.

1 pouch of 28 tablets	NDC 50102-228-21
Carton of 3 pouches	NDC 50102-228-23

Store at 20º to 25ºC (68º to 77ºF) [see USP Controlled Room Temperature].

REFERENCES

1. Back DJ, Breckenridge AM, Crawford FE, McIver M, Orme ML'E, Rowe PH and Smith E: Kinetics of norethindrone in women II. Single-dose kinetics. Clin Pharmacol Ther 1978;24:448-453.
2. Hümpel M, Nieuweboer B, Wendt H and Speck U: Investigations of pharmacokinetics of ethinyloestradiol to specific consideration of a possible first-pass effect in women. Contraception 1979;19:421-432.
3. Back DJ, Breckenridge AM, Crawford FE, MacIver M, Orme ML'E, Rowe PH and Watts MJ. An investigation of the pharmacokinetics of ethynylestradiol in women using radioimmunoassay. Contraception 1979;20:263-273.
4. Hammond GL, Lähteenmäki PLA, Lähteenmäki P and Luukkainen T. Distribution and percentages of non-protein bound contraceptive steroids in human serum. J Steriod Biochem 1982;17:375-380.
5. Fotherby K. Pharmacokinetics and metabolism of progestins in humans, in Pharmacology of the contraceptive steroids, Goldzieher JW, Fotherby K (eds), Raven Press, Ltd., New York, 1994; 99-126.
6. Goldzieher JW. Pharmacokinetics and metabolism of ethynyl estrogens, in Pharmacology of the contraceptive steroids, Goldzieher JW, Fotherby K (eds), Raven Press Ltd., New York, 1994; 127-151.
7. Hatcher RA, et al. 1998. Contraceptive Technology, Seventeenth Edition. New York: Irvington Publishers.
8. Stadel, B.V.: Oral contraceptives and cardiovascular disease. (Pt. 1). *New England Journal of Medicine*, 305:612-618, 1981.
9. Stadel, B.V.: Oral contraceptives and cardiovascular disease. (Pt. 2). *New England Journal of Medicine*, 305:672-677, 1981.
10. Adam, S.A., and M. Thorogood: Oral contraception and myocardial infarction revisited: The effects of new preparations and prescribing patterns. *Brit. J. Obstet. and Gynec.*, 88:838-845, 1981.
11. Mann, J.I., and W.H. Inman: Oral contraceptives and death from myocardial infarction. *Brit. Med. J.*, 2(5965):245-248, 1975.
12. Mann, J.I., M.P. Vessey, M. Thorogood, and R. Doll: Myocardial infarction in young women with special reference to oral contraceptive practice. *Brit. Med. J.*, 2(5956):241-245, 1975.
13. Royal College of General Practitioners' Oral Contraception Study: Further analyses of mortality in oral contraceptive users. *Lancet*, 1:541-546, 1981.
14. Slone, D., S. Shapiro, D.W. Kaufman, L. Rosenberg, O.S. Miettinen, and P.D. Stolley: Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. *N.E.J.M.*, 305:420-424, 1981.
15. Vessey, M.P.: Female hormones and vascular disease: An epidemiological overview. *Brit. J. Fam. Plann.*, 6:1-12, 1980.
16. Russell-Briefel, R.G., T.M. Ezzati, R. Fulwood, J.A. Perlman, and R.S. Murphy: Cardiovascular risk status and oral contraceptive use, United States, 1976-80. *Preventive Medicine*, 15:352-362, 1986.
17. Goldbaum, G.M., J.S. Kendrick, G.C. Hogelin, and E.M. Gentry: The relative impact of smoking and oral contraceptive use on women in the United States. *J.A.M.A.*, 258:1339-1342, 1987.
18. Layde, P.M., and V. Beral: Further analyses of mortality in oral contraceptive users: Royal College General Practitioners' Oral Contraception Study. (Table 5) *Lancet*, 1:541-546, 1981.
19. Knopp, R.H.: Arteriosclerosis risk: The roles of oral contraceptives and postmenopausal estrogens. *J. of Reprod. Med.*, 31(9)(Supplement): 913-921, 1986.
20. Krauss, R.M., S. Roy, D.R. Mishell, J. Casagrande, and M.C. Pike: Effects of two low-dose oral contraceptives on serum lipids and lipoproteins: Differential changes in high-

density lipoproteins subclasses. *Am. J. Obstet. Gyn.*, 145:446-452, 1983.
21. Wahl, P., C. Walden, R. Knopp, J. Hoover, R. Wallace, G. Heiss, and B. Rifkind: Effect of estrogen/progestin potency on lipid/lipoprotein cholesterol. *N.E.J.M.*, 308:862-867, 1983.
22. Wynn, V., and R. Niththyananthan: The effect of progestin in combined oral contraceptives on serum lipids with special reference to high-density lipoproteins. *Am. J. Obstet. and Gyn.*, 142:766-771, 1982.
23. Wynn, V., and I. Godsland: Effects of oral contraceptives on carbohydrate metabolism. *J. Reprod. Medicine*, 31 (9)(Supplement): 892-897, 1986.
24. LaRosa, J.C.: Atherosclerotic risk factors in cardiovascular disease. *J. Reprod. Med.*, 31(9)(Supplement): 906-912, 1986.
25. Inman, W.H., and M.P. Vessey: Investigations of death from pulmonary, coronary, and cerebral thrombosis and embolism in women of child-bearing age. *Brit. Med. J.*, 2(5599): 193-199, 1968.
26. Maguire, M.G., J. Tonascia, P.E. Sartwell, P.D. Stolley, and M.S. Tockman: Increased risk of thrombosis due to oral contraceptives: A further report. *Am. J. Epidemiology*, 110(2): 188-195, 1979.
27. Pettiti, D.B., J. Wingerd, F. Pellegrin, and S. Ramacharan: Risk of vascular disease in women: Smoking, oral contraceptives, noncontraceptive estrogens, and other factors. *J.A.M.A.*, 242:1150-1154, 1979.
28. Vessey, M.P., and R. Doll: Investigation of relation between use of oral contraceptives and thromboembolic disease. *Brit. Med. J.*, 2(5599): 199-205, 1968.
29. Vessey, M.P., and R. Doll: Investigation of relation between use of oral contraceptives and thromboembolic disease: A further report. *Brit. Med. J.*, 2(5658): 651-657, 1969.
30. Porter, J.B., J.R. Hunter, D.A. Danielson, H. Jick, and A. Stergachis: Oral contraceptives and non-fatal vascular disease: Recent experience. *Obstet. and Gyn.*, 59(3):299-302, 1982.
31. Vessey, M., R. Doll, R. Peto, B. Johnson, and P. Wiggins: A long-term follow-up study of women using different methods of contraception: An interim report. *J. Biosocial. Sci.*, 8:375-427, 1976.
32. Royal College of General Practitioners: Oral contraceptives, venous thrombosis, and varicose veins. *J. of Royal College of General Practitioners*, 28:393-399, 1978.
33. Collaborative Group for the study of stroke in young women: Oral contraception and increased risk of cerebral ischemia or thrombosis. *N.E.J.M.*, 288:871-878, 1973.
34. Petitti, D.B., and J. Wingerd: Use of oral contraceptives, cigarette smoking, and risk of subarachnoid hemorrhage. *Lancet*, 2:234-236, 1978.
35. Inman, W.H.: Oral contraceptives and fatal subarachnoid hemorrhage. *Brit. Med. J.*, 2(6203): 1468-70, 1979.
36. Collaborative Group for the study of stroke in young women: Oral contraceptives and stroke in young women: Associated risk factors. *J.A.M.A.*, 231:718-722, 1975.
37. Inman, W.H., M.P. Vessey, B. Westerholm, and A. Engelund: Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. *Brit. Med. J.*, 2:203-209, 1970.
38. Meade, T.W., G. Greenberg, and S.G. Thompson: Progestogens and cardiovascular reactions associated with oral contraceptives and a comparison of the safety of 50 and 35 mcg oestrogen preparations. *Brit. Med. J.*, 280(6224): 1157-1161, 1980.
39. Kay, C.R.: Progestogens and arterial disease: Evidence from the Royal College of General Practitioners' study. *Amer. J. Obstet. Gyn.*, 142:762-765, 1982.
40. Royal College of General Practitioners: Incidence of arterial disease among oral contraceptive users. *J. Coll. Gen. Pract.*, 33:75-82, 1983.
41. Ory, H.W: Mortality associated with fertility and fertility control:1983. *Family Planning Perspectives*, 15:50-56, 1983.
42. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Oral-contraceptive use and the risk of breast cancer. *N.E.J.M.*, 315: 405-411, 1986.
43. Pike, M.C., B.E. Henderson, M.D. Krailo, A. Duke, and S. Roy: Breast cancer in young women and use of oral contraceptives: Possible modifying effect of formulation and age at use. *Lancet*, 2:926-929, 1983.
44. Paul, C., D.G. Skegg, G.F.S. Spears, and J.M. Kaldor: Oral contraceptives and breast cancer: A national study. *Brit. Med. J.*, 293:723-725, 1986.
45. Miller, D.R., L. Rosenberg, D.W. Kaufman, D. Schottenfeld, P.D. Stolley, and S. Shapiro: Breast cancer risk in relation to early oral contraceptive use. *Obstet. Gynec.*, 68:863-868, 1986.
46. Olson, H., K.L. Olson, T.R. Moller, J. Ranstam, P. Holm: Oral contraceptive use and breast cancer in young women in Sweden (letter). *Lancet*, 2:748-749, 1985.
47. McPherson, K., M. Vessey, A. Neil, R. Doll, L. Jones, and M. Roberts: Early contraceptive use and breast cancer: Results of another case-control study. *Brit. J. Cancer*, 56: 653-660, 1987.
48. Huggins, G.R., and P.F. Zucker: Oral contraceptives and neoplasia: 1987 update. *Fertil. Steril.*, 47:733-761, 1987.
49. McPherson, K., and J.O. Drife: The pill and breast cancer: Why the uncertainty? *Brit. Med. J.*, 293:709-710, 1986.
50. Shapiro, S.: Oral contraceptives: Time to take stock. *N.E.J.M.*, 315:450-451, 1987.
51. Ory, H., Z. Naib, S.B. Conger, R.A. Hatcher, and C.W. Tyler: Contraceptive choice and prevalence of cervical dysplasia and carcinoma *in situ*. *Am. J. Obstet. Gynec.*, 124:573-577, 1976.
52. Vessey, M.P., M. Lawless, K. McPherson, D. Yeates: Neoplasia of the cervix uteri and contraception: A possible adverse effect of the pill. *Lancet*, 2:930, 1983.
53. Brinton, L.A., G.R. Huggins, H.F. Lehman, K. Malli, D.A. Savitz, E. Trapido, J. Rosenthal, and R. Hoover: Long-term use of oral contraceptives and risk of invasive cervical cancer. *Int. J. Cancer*, 38:339-344, 1986.
54. WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Invasive cervical cancer and combined oral contraceptives. *Brit. Med. J.*, 290:961-965, 1985.
55. Rooks, J.B., H.W. Ory, K.G. Ishak, L.T. Strauss, J.R. Greenspan, A.P. Hill, and C.W. Tyler: Epidemiology of hepatocellular adenoma: The role of oral contraceptive use. *J.A.M.A.*, 242:644-648, 1979.
56. Bein, N.N., and H.S. Goldsmith: Recurrent massive hemorrhage from benign hepatic tumors secondary to oral contraceptives. *Brit. J. Surg.*, 64:433-435, 1977.
57. Klatskin, G.: Hepatic tumors: Possible relationship to use of oral contraceptives. *Gastroenterology*, 73:386-394, 1977.
58. Henderson, B.E., S. Preston-Martin, H.A. Edmondson, R.L. Peters, and M.C. Pike: Hepatocellular carcinoma and oral contraceptives. *Brit. J. Cancer*, 48:437-440, 1983.
59. Neuberger, J., D. Forman, R. Doll, and R. Williams: Oral contraceptives and hepatocellular carcinoma. *Brit. Med. J.*, 292:1355-1357, 1986.
60. Forman, D., T.J. Vincent, and R. Doll: Cancer of the liver and oral contraceptives. *Brit. Med. J.*, 292:1357-1361, 1986.
61. Harlap, S., and J. Eldor: Births following oral contraceptive failures. *Obstet. Gynec.*, 55:447-452, 1980.
62. Savolainen, E., E. Saksela, and L. Saxen: Teratogenic hazards of oral contraceptives analyzed in a national malformation register. *Amer. J. Obstet. Gynec.*, 140:521-524, 1981.
63. Janerich, D.T., J.M. Piper, and D.M. Glebatis: Oral contraceptives and birth defects. *Am. J. Epidemiology*, 112:73-79, 1980.
64. Ferencz, C., G.M. Matanoski, P.D. Wilson, J.D. Rubin, C.A. Neill, and R. Gutberlet: Maternal hormone therapy and congenital heart disease. *Teratology*, 21:225-239, 1980.
65. Rothman, K.J., D.C. Fyler, A. Goldbatt, and M.B. Kreidberg: Exogenous hormones and other drug exposures of children with congenital heart disease. *Am. J. Epidemiology*, 109:433-439, 1979.
66. Boston Collaborative Drug Surveillance Program: Oral contraceptives and venous thromboembolic disease, surgically confirmed gallbladder disease, and breast tumors. *Lancet*, 1:1399-1404, 1973.
67. Royal College of General Practitioners: *Oral Contraceptives and Health*. New York, Pittman, 1974, 100p.
68. Layde, P.M., M.P. Vessey, and D. Yeates: Risk of gallbladder disease: A cohort study of young women attending family planning clinics. *J. of Epidemiol. and Comm. Health*, 36: 274-278, 1982.
69. Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO): Prevalence of gallstone disease in an Italian adult female population. *Am. J. Epidemiol.*, 119:796-805, 1984.
70. Strom, B.L., R.T. Tamragouri, M.L. Morse, E.L. Lazar, S.L. West, P.D. Stolley, and J.K. Jones: Oral contraceptives and other risk factors for gallbladder disease. *Clin. Pharmacol.* Ther., 39:335-341, 1986.
71. Wynn, V., P.W. Adams, I.F. Godsland, J. Melrose, R. Niththyananthan, N.W. Oakley, and A. Seedj: Comparison of effects of different combined oral-contraceptive formulations on carbohydrate and lipid metabolism. *Lancet*, 1:1045-1049, 1979.
72. Wynn, V.: Effect of progesterone and progestins on carbohydrate metabolism. In Progesterone and Progestin. Edited by C.W. Bardin, E. Milgrom, P. Mauvis-Jarvis. New York, *Raven Press*, pp. 395-410, 1983.
73. Perlman, J.A., R. G. Roussell-Briefel, T.M. Ezzati, and G. Lieberknecht: Oral glucose tolerance and the potency of oral contraceptive progestogens. *J. Chronic Dis.*, 38:857-864, 1985.
74. Royal College of General Practitioners' Oral Contraception Study: Effect on hypertension and benign breast disease of progestogen component in combined oral contraceptives. *Lancet*, 1:624, 1977.
75. Fisch, I.R., and J. Frank: Oral contraceptives and blood pressure. *J.A.M.A.*, 237:2499-2503, 1977.
76. Laragh, A.J.: Oral contraceptive induced hypertension: Nine years later. *Amer. J. Obstet. Gynecol.*, 126:141-147, 1976.
77. Ramcharan, S., E. Peritz, F.A. Pellegrin, and W.T. Williams: Incidence of hypertension in the Walnut Creek Contraceptive Drug Study cohort. In Pharmacology of Steroid Contraceptive Drugs. Edited by S. Garattini and H.W. Berendes. New York, *Raven Press*, pp. 277-288, 1977. (Monographs of the Mario Negri Institute for Pharmacological Research, Milan.)
78. Back DJ, Orme ML'E. Drug interactions, in Pharmacology of the contraceptive steroids. Goldzieher JW, Fotherby K (eds), Raven Press, Ltd., New York, 1994, 407-425.
79. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Oral contraceptive use and the risk of ovarian cancer. *J.A.M.A.*, 249:1596-1599, 1983.
80. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development: Combination oral contraceptive use and the risk of endometrial cancer. *J.A.M.A.*, 257:796-800, 1987.
81. Ory, H.W.: Functional ovarian cysts and oral contraceptives: Negative association confirmed surgically. *J.A.M.A.*, 228:68-69, 1974.
82. Ory, H.W., P. Cole, B. Macmahon, and R. Hoover: Oral contraceptives and reduced risk of benign breast disease. *N.E.J.M.*, 294:41-422, 1976.
83. Ory, H.W.: The noncontraceptive health benefits from oral contraceptive use. *Fam. Plann. Perspectives*, 14:182-184, 1982.
84. Ory, H.W., J.D. Forrest, and R. Lincoln: Making Choices: Evaluating the health risks and benefits of birth control methods. New York, The Alan Guttmacher Institute, p. 1, 1983.
85. Miller, D.R., L. Rosenberg, D.W. Kaufman, P. Stolley, M.E. Warshauer, and S. Shapiro: Breast cancer before age 45 and oral contraceptive use: new findings. *Am. J. Epidemiol.*, 129:269-280, 1989.
86. Kay, C.R., and P.C. Hannaford: Breast cancer and the pill: a further report from the Royal College of General Practitioners Oral Contraception Study. *Br. J. Cancer*, 58:675-680, 1988.
87. Stadel, B.V., S. Lai, J.J. Schlesselman, and P. Murray: Oral contraceptives and premenopausal breast cancer in nulliparous women. *Contraception*, 38:287-299, 1988.
88. UK National Case--Control Study Group: Oral contraceptive use and breast cancer risk in young women. *Lancet*, 973-982, 1989.

89. Romieu, I., W.C. Willett, G.A. Colditz, M.J. Stampfer, B. Rosner, C.H. Hennekens, and F.E. Speizer: Prospective study of oral contraceptive use and risk of breast cancer in women. *J. Natl. Cancer Inst.*, 81:1313-1321, 1989.

The patient labeling for oral contraceptive drug product is set forth below:

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

BRIEF SUMMARY PATIENT PACKAGE INSERT

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, 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 should be strongly advised not to smoke.

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

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

1. Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack or angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences.
2. 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 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.

Most of the studies to date on breast cancer and pill use have found no increase in the risk of developing breast cancer, although some studies have reported an increased risk of developing breast cancer in certain groups of women. However, some studies have found an increase in the risk of developing cancer of the cervix in women taking the pill, but this finding may be related to differences in sexual behavior or other factors not related to use of the pill. Therefore, there is insufficient evidence to rule out the possibility that the pill may cause cancer of the breast or cervix.

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

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

INSTRUCTIONS TO PATIENT

Blister Pack

The Tarina Fe 1/20 EQ blister pack has been designed to make oral contraceptive dosing as easy and as convenient as possible. The tablets are arranged in four rows of seven tablets each with the days of the week appearing above the first row of tablets.

Each **light yellow to yellow** tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol.

Each **brown** tablet contains 75 mg ferrous fumarate, and is intended to help you remember to take the tablets correctly. These brown tablets are not intended to have any health benefit.

DIRECTIONS

To remove a tablet, press down on it with your thumb or finger. The tablet will drop through the back of the blister pack. Do not press with your thumbnail, fingernail, or any other sharp object.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

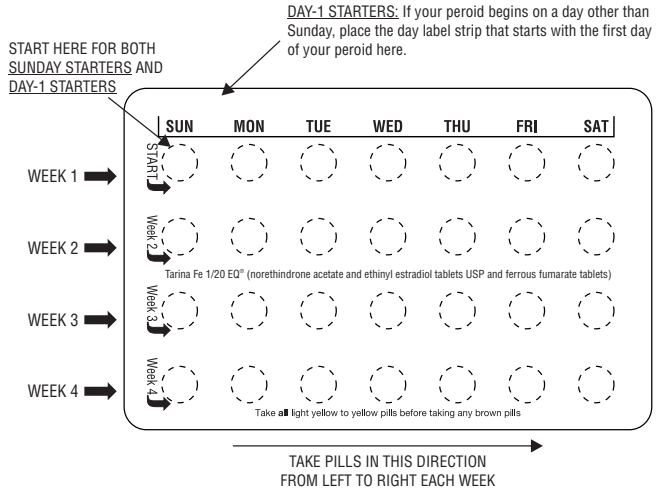
BEFORE YOU START TAKING YOUR PILLS:

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 have spotting or light bleeding or 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 birth control pills may not work as well. Use a back-up birth control method (such as condoms or foam) 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-Day pill pack has 21 "active" light yellow to yellow pills (with hormones) to take for 3 weeks, followed by 1 week of reminder brown pills (without hormones).
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills (follow the arrows), and
   3) the week numbers as shown in the following picture:

Tarina Fe 1/20 EQ - contains **21 LIGHT YELLOW TO YELLOW PILLS** for **WEEKS 1, 2 and 3**. **WEEK 4** will contain **7 BROWN PILLS ONLY**.



4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms or foam) 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. Pick the day label sticker that starts with the first day of your period. (This is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins.)
2. Place this day label sticker on the blister pack over the area that has the days of the week (starting with Sunday) printed on the blister pack.
3. Take the first "active" light yellow to yellow pill of the first pack during the first 24 hours

of your period.

4. 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" light yellow to yellow 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 or foam 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:**
   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** light yellow to yellow "active" pill:

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

If you **MISS 2** light yellow to yellow "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 COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or foam) as a back-up method of birth control until you have taken a light yellow to yellow "active" pill every day for 7 days.

If you **MISS 2** light yellow to yellow "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 COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or foam) as a back-up method of birth control until you have taken a light yellow to yellow "active" pill every day for 7 days.

If you **MISS 3 OR MORE** light yellow to yellow "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 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 COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or foam) as a back-up method of birth control until you have taken a light yellow to yellow "active" pill every day for 7 days.

A REMINDER

IF YOU FORGET ANY OF THE 7 BROWN "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 LIGHT YELLOW TO YELLOW "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

Based on his or her assessment of your medical needs, your doctor or healthcare provider has prescribed this drug for you. Do not give this drug to anyone else.

Keep this and all drugs out of the reach of children.

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

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.

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

DETAILED PATIENT PACKAGE INSERT

What You Should Know About Oral Contraceptives

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 leaflet 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 leaflet is not a replacement for a careful discussion between you and your healthcare 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 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

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

In comparison, typical failure rates for other 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: 20 to 40%
Condom alone (male): 14%
Condom alone (female): 21%
Periodic abstinence: 25%
Withdrawal: 19%
No method: 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 should be 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)
- Take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.
- 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:

- 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 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 breastfeeding. If you are breastfeeding, you should wait until you have weaned your child before using the pill. (See also the section on **Breastfeeding** in **GENERAL PRECAUTIONS**.)

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 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, a possible but not definite association has been found with the pill and liver cancers in two 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 contraceptive use increases the risk of developing cancer of the reproductive organs. Studies to date of women taking the pill have reported conflicting findings on whether pill use increases the risk of developing cancer of the breast or cervix. Most of the studies on breast cancer and pill use have found no overall increase in the risk of developing breast cancer, although some studies have reported an increased risk of developing breast cancer in certain groups of women. 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 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.

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

* Deaths are birth related.
** Deaths are method related.

In the above table, the risk of death from any birth control method is less than the risk of childbirth, except for oral contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke. It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7 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 exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.

The suggestion that women over 40 who don't smoke should not take oral contraceptives is based on information from older higher 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 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 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.

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 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, or 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 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 of any medication taken during pregnancy.

2. While Breastfeeding

If you are breastfeeding, 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 breastfeeding. You should use another method of contraception since breastfeeding provides only partial protection from becoming pregnant, and this partial protection decreases significantly as you breastfeed 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), carbamazepine, and phenytoin (Dilantin® is one brand of this drug); troglitazone; phenylbutazone; and possibly certain antibiotics. You may need to use additional contraception when you take drugs which can make oral contraceptives less effective.
Birth control pills interact with certain drugs. These drugs include acetaminophen, clofibric acid, cyclosporine, morphine, prednisolone, salicylic acid, temazepam, and theophylline. You should tell your doctor if you are taking any of these medications.

5. **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.**

INSTRUCTIONS TO PATIENT

Blister Pack

The Tarina Fe 1/20 EQ blister pack has been designed to make oral contraceptive dosing as easy and as convenient as possible. The tablets are arranged in four rows of seven tablets each, with the days of the week appearing above the first row of tablets.

Each **light yellow to yellow** tablet contains 1 mg norethindrone acetate and 20 mcg ethinyl estradiol.

Each **brown** tablet contains 75 mg ferrous fumarate and is intended to help you remember to take the tablets correctly. These brown tablets are not intended to have any health benefit.

DIRECTIONS

To remove a tablet, press down on it with your thumb or finger. The tablet will drop through the back of the blister pack. Do not press with your thumbnail, fingernail, or any other sharp object.

HOW TO TAKE THE PILL

IMPORTANT POINTS TO REMEMBER

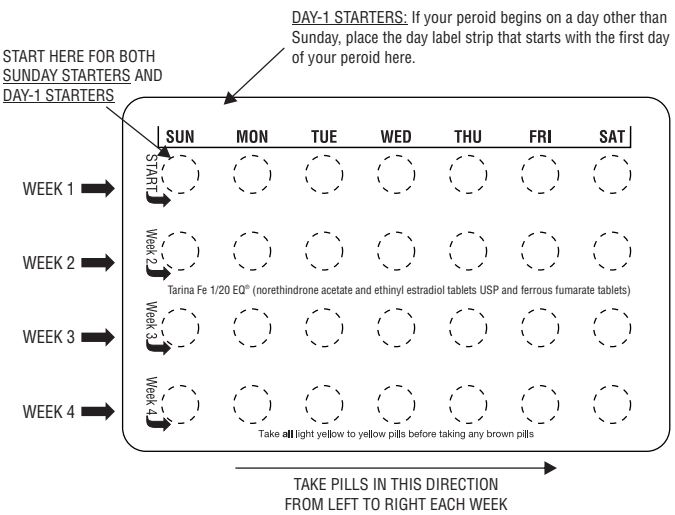
BEFORE YOU START TAKING YOUR PILLS:

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 have spotting or light bleeding or 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 birth control pills may not work as well. Use a back-up birth control method (such as condoms or foam) 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-Day pill pack has 21 "active" light yellow to yellow pills (with hormones) to take for 3 weeks, followed by 1 week of reminder brown pills (without hormones).
3. ALSO FIND:
   1) where on the pack to start taking pills,
   2) in what order to take the pills (follow the arrows), and
   3) the week numbers as shown in the following picture:

Tarina Fe 1/20 EQ - contains **21 LIGHT YELLOW TO YELLOW PILLS** for **WEEKS 1, 2 and 3**. **WEEK 4** will contain **7 BROWN PILLS ONLY**.



4. BE SURE YOU HAVE READY AT ALL TIMES:
   ANOTHER KIND OF BIRTH CONTROL (such as condoms or foam) 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. Pick the day label sticker that starts with the first day of your period. (This is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins.)
2. Place this day label sticker on the blister pack over the area that has the days of the week (starting with Sunday) printed on the blister pack.
3. Take the first "active" light yellow to yellow pill of the first pack during the first 24 hours of your period.
4. 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" light yellow to yellow 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 or foam 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:**
   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** light yellow to yellow "active" pill:

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

If you **MISS 2** light yellow to yellow "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 COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or foam) as a back-up method of birth control until you have taken a light yellow to yellow "active" pill every day for 7 days.

If you **MISS 2** light yellow to yellow "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 COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or foam) as a back-up method of birth control until you have taken a light yellow to yellow "active" pill every day for 7 days.

If you **MISS 3 OR MORE** light yellow to yellow "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 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 COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or foam) as a back-up method of birth control until you have taken a light yellow to yellow "active" pill every day for 7 days.

A REMINDER

IF YOU FORGET ANY OF THE 7 BROWN "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 LIGHT YELLOW TO YELLOW "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 1% (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 and examine you before prescribing oral contraceptives. The physical examination may be delayed to another time if you request it and your 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 oral contraceptives may provide certain benefits. They are:

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

If you want more information about birth control pills, ask your doctor or pharmacist. They have a more technical leaflet called the “Physician Insert,” which you may wish to read.

Remembering to take tablets according to schedule is stressed because of its importance in providing you the greatest degree of protection.

MISSED MENSTRUAL PERIODS FOR DOSAGE REGIMEN

At times there may be no menstrual period after a cycle of pills. Therefore, if you miss one menstrual period but 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 miss a menstrual period, *you may be pregnant* and should stop taking oral contraceptives until your doctor or healthcare provider determines whether or not you are pregnant. Until you can get to your doctor or healthcare provider, use another form of contraception. If two consecutive menstrual periods are missed, you should stop taking pills until it is determined whether or not you are pregnant. Although there does not appear to be any increase in birth defects in newborn babies if you become pregnant while using oral contraceptives, you should discuss the situation with your doctor or healthcare provider.

Periodic Examination

Your doctor or healthcare provider will take a complete medical and family history before prescribing oral contraceptives. At that time and about once a year thereafter, he or she will generally examine your blood pressure, breasts, abdomen, and pelvic organs (including a Papanicolaou smear, i.e., test for cancer).

Keep this and all drugs out of the reach of children.

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

To report SUSPECTED ADVERSE REACTIONS, contact the Afaxys Health and Safety Team at 1-855-888-2467 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 02/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Tri-VyLibra safely and effectively. See full prescribing information for Tri-VyLibra.

Tri-VyLibra® (norgestimate and ethinyl estradiol) tablets, for oral use
Initial U.S. Approval: 1989

WARNING: CIGARETTE SMOKING and SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **Tri-VyLibra is contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. (4)**

----------RECENT MAJOR CHANGES----------

Contraindications (4)	08/2017
Warnings and Precautions (5.3)	08/2017

----------INDICATIONS AND USAGE----------

Tri-VyLibra is estrogen/progestin COC, indicated for use by women to prevent pregnancy. (1.1)

Tri-VyLibra is also indicated for the treatment of moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche.

Tri-VyLibra should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control. (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Take one tablet daily by mouth at the same time every day. (2.2)
- Take tablets in the order directed on the blister pack. (2.2)
- Do not skip or delay tablet intake. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tri-VyLibra consists of 28 round, biconvex tablets in the following order (3):

- 7 white, coated tablets each containing 0.180 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 light blue, coated tablets each containing 0.215 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark blue, coated tablets each containing 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 green, uncoated tablets (inert)

----------CONTRAINDICATIONS----------

- A high risk of arterial or venous thrombotic diseases (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

----------WARNINGS AND PRECAUTIONS----------

- Thromboembolic Disorders and Other Vascular Problems: Stop Tri-VyLibra if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue Tri-VyLibra if jaundice occurs. (5.2)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop Tri-VyLibra if blood pressure rises significantly. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Tri-VyLibra. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue Tri-VyLibra if indicated. (5.7)
- Bleeding Irregularities and Amenorrhea: Evaluate irregular bleeding or amenorrhea. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions reported during clinical trials (≥2%) were: headache/migraine, breast issues (including breast pain, enlargement, and discharge), vaginal infection, abdominal/gastrointestinal pain, mood disorders (including mood alteration and depression), genital discharge, changes in weight (including weight increased or decreased). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Afaxys Pharma, LLC at 1-855-888-2467 or to FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING and SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

Tri-VyLibra tablets are indicated for use by females of reproductive potential to prevent pregnancy *[see Clinical Studies (14)]*.

1.2 Acne

Tri-VyLibra is indicated for the treatment of moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. Tri-VyLibra should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 How to Start Tri-VyLibra

Tri-VyLibra is available in blister pack *[see How Supplied/Storage and Handling (16)]*. Tri-VyLibra may be started using either a Day 1 start or a Sunday start (see Table 1). For the first cycle of a Sunday Start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

2.2 How to Take Tri-VyLibra

Table 1: Instructions for Administration of Tri-VyLibra

Starting COCs in women not currently using hormonal contraception (Day 1 Start or Sunday Start) **Important:** Consider the possibility of ovulation and conception prior to initiation of this product. **Tablet Color:** • Tri-VyLibra active tablets are white (Day 1 to Day 7), light blue (Day 8 to Day 14) and dark blue (Day 15 to Day 21). • Tri-VyLibra has green inactive tablets (Day 22 to Day 28).	**Day 1 Start:** • Take first active tablet without regard to meals on the first day of menses. • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one **green** inactive tablet daily for 7 days and at the same time of day that active tablets were taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last inactive tablet)
	Sunday Start: • Take first active tablet without regard to meals on the first Sunday after the onset of menses. **Due to the potential risk of becoming pregnant, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of Tri-VyLibra.** • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one **green** inactive tablet daily for the following 7 days and at the same time of day that active tablets were taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the Sunday after taking the last inactive tablet) and additional non-hormonal contraceptive is not needed.
Switching to Tri-VyLibra from another oral contraceptive	Start on the same day that a new pack of the previous oral contraceptive would have started.
Switching from another contraceptive method to Tri-VyLibra	**Start Tri-VyLibra:**
• **Transdermal patch**	• On the day when next application would have been scheduled
• **Vaginal ring**	• On the day when next insertion would have been scheduled
• **Injection**	• On the day when next injection would have been scheduled
• **Intrauterine contraceptive**	• On the day of removal • If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraceptive (such as condoms and spermicide) is needed for the first seven days of the first cycle pack.
• **Implant**	• On the day of removal

Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-Approved Patient Labeling.

Starting Tri-VyLibra after Abortion or Miscarriage

First-trimester

- After a first-trimester abortion or miscarriage, Tri-VyLibra may be started immediately. An additional method of contraception is not needed if Tri-VyLibra is started immediately.
- If Tri-VyLibra is not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of her first cycle pack of Tri-VyLibra.

Second-trimester

- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start Tri-VyLibra, following the instructions in Table 1 for Day 1 or Sunday start, as desired. If using Sunday start, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of Tri-VyLibra. *[see Contraindications (4), Warnings and Precautions (5.1), and FDA-Approved Patient Labeling.]*

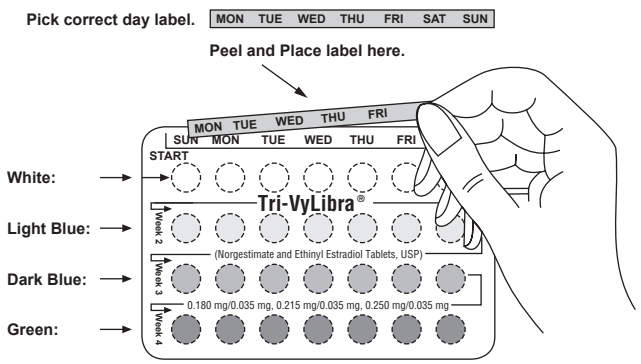
Starting Tri-VyLibra after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with Tri-VyLibra following the instructions in Table 1 for women not currently using hormonal contraception.
- Tri-VyLibra is not recommended for use in lactating women *[see Use in Specific Populations (8.3)]*.
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of Tri-VyLibra. *[See Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1 and 8.3), and FDA-Approved Patient Labeling]*.

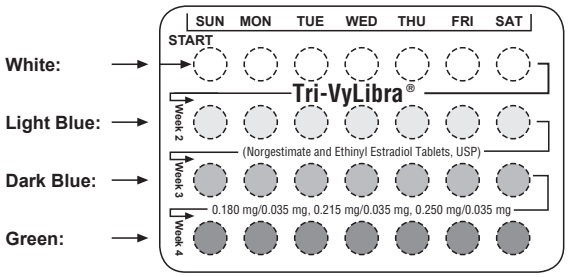
How to Use the Blister Pack:

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

1. Pick the Days of the Week Sticker that starts the first day of your period. (This is the day you begin bleeding or spotting, even if it is midnight when bleeding begins.) When you have picked the right sticker, throw away the others and place the sticker on the blister pack over the preprinted days of the week and make sure it lines up with the pills.



2. Your blister pack containing 28 individually sealed pills. Note that the pills are arranged in four numbered rows of 7 pills, with the pre-printed days of the week printed above them. There are 7 white "active" pills, 7 light blue "active" pills, 7 dark blue "active" pills, and 7 green "reminder" pills. Refer to the sample of the blister pack below:



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

Three Ways to Remember in What Order to take the Pills

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

3. Always finish all your pills.

2.3 Missed Tablets

Table 2: Instructions for Missed Tri-VyLibra Tablets	
• If one active tablet is missed in Weeks 1, 2, or 3	Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.
• If two active tablets are missed in Week 1 or Week 2	Take the two missed tablets as soon as possible and the next two active tablets the next day. Continue taking one tablet a day until the pack is finished. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**
• If two active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	Day 1 start: Throw out the rest of the pack and start a new pack that same day. Sunday start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**

2.4 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting or diarrhea occurs within 3 to 4 hours after taking an active tablet, handle this as a missed tablet *[see FDA-Approved Patient Labeling]*.

2.5 Tri-VyLibra Use for Acne

The timing of initiation of dosing with Tri-VyLibra for acne should follow the guidelines for use of Tri-VyLibra as an oral contraceptive. Consult the DOSAGE AND ADMINISTRATION section (2.1) for instructions.

3 DOSAGE FORMS AND STRENGTHS

Tri-VyLibra tablets are available in blister packs. Each blister pack contains 28 tablets in the following order:

- 7 white, round, biconvex, coated tablets, debossed with "S" on one side and "19" on other side of the tablet contains 0.180 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 light blue, round, biconvex, coated tablets, debossed with "S" on one side and "21" on other side of the tablet contains 0.215 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 dark blue, round, biconvex, coated tablets, debossed with "S" on one side and "22" on other side of the tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 green, round, mottled biconvex, uncoated tablets (non-hormonal placebo) debossed with "S" on one side and "24" on other side of the tablet contains inert ingredients

4 CONTRAINDICATIONS

Do not prescribe Tri-VyLibra to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or migraine headaches with aura *[see Warnings and Precautions (5.7)]*
    - Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.7)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.2)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.11)]*
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

- Stop Tri-VyLibra if an arterial thrombotic event or venous thromboembolic (VTE) event occurs.
- Stop Tri-VyLibra if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately *[see Adverse Reactions (6.2)]*.
- If feasible, stop Tri-VyLibra at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during and following prolonged immobilization.
- Start Tri-VyLibra no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued.
- Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.
- Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function

Do not use Tri-VyLibra in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver *[see Contraindications (4)]*. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Tri-VyLibra if jaundice develops.

Liver Tumors

Tri-VyLibra is contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)]*. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the risk of liver cancers in COC users is less than one case per million users.

5.3 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as COCs. Discontinue Tri-VyLibra prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. Tri-VyLibra can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.4 High Blood Pressure

Tri-VyLibra is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop Tri-VyLibra if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may worsen existing gallbladder disease. A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC related cholestasis.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who take Tri-VyLibra. COCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache

If a woman taking Tri-VyLibra develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Tri-VyLibra if indicated.

Consider discontinuation of Tri-VyLibra in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event).

5.8 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or

occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different contraceptive product.

In clinical trials of Tri-VyLibra, the frequency and duration of breakthrough bleeding and/or spotting was assessed in 4,826 patients (35,546 evaluable cycles). A total of 231 (4.8%) women discontinued Tri-VyLibra, at least in part, due to bleeding or spotting. Based on data from the clinical trials, 13 to 38% of women using Tri-VyLibra experienced unscheduled bleeding per cycle in the first year. The percent of women who experienced breakthrough/unscheduled bleeding tended to decrease over time.

Amenorrhea and Oligomenorrhea

Women who use Tri-VyLibra may experience amenorrhea. Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was pre-existent.

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.9 COC 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. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue Tri-VyLibra use if pregnancy is confirmed.

Administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Carefully observe women with a history of depression and discontinue Tri-VyLibra if depression recurs to a serious degree.

5.11 Carcinoma of Breast and Cervix

- Tri-VyLibra is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see Contraindications (4)]*.

  There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.
- Some studies suggest that COC use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

5.12 Effect on Binding Globulins

The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.15 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Tri-VyLibra.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in labeling:

- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of Tri-VyLibra was evaluated in 4,826 healthy women of child-bearing potential who participated in 6 clinical trials and received at least 1 dose of Tri-VyLibra for contraception. Two trials were randomized active-controlled trials and 4 were uncontrolled open-label trials. In 3 trials, subjects were followed for up to 24 cycles; in 2 trials, subjects were followed for up to 12 cycles; and in 1 trial, subjects were followed for up to 6 cycles.

Common Adverse Reactions (≥ 2% of subjects): The most common adverse reactions reported by at least 2% of the 4,826 women were the following in order of decreasing incidence: headache/migraine (33.6%), breast issues (including breast pain, enlargement, and discharge) (8.0%), vaginal infection (7.1%), abdominal/gastrointestinal pain (5.6%), mood disorders (including mood alteration and depression) (3.8%), genital discharge (3.2%), and changes in weight (including weight fluctuation, increased or decreased) (2.5%).

Adverse Reactions Leading to Study Discontinuation: Over the trials, between 9 to 27% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions (≥1%) leading to discontinuation were: metrorrhagia (4.3%), nausea/vomiting (2.8%), headache/migraine (2.4%), mood disorders (including depression and mood altered) (1.1%), and weight increased (1.1%).

Serious Adverse Reactions: breast cancer (1 subject), carcinoma of the cervix *in situ* (1 subject), hypertension (1 subject), and migraine (2 subjects).

6.2 Postmarketing Experience

The following additional adverse drug reactions have been reported from worldwide postmarketing experience with norgestimate/ethinyl estradiol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and Infestations: Urinary tract infection;

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Breast cancer, benign breast neoplasm, hepatic adenoma, focal nodular hyperplasia, breast cyst;

Immune System Disorders: Hypersensitivity;

Metabolism and Nutrition Disorders: Dyslipidemia;

Psychiatric Disorders: Anxiety, insomnia;

Nervous System Disorders: Syncope, convulsion, paresthesia, dizziness;

Eye Disorders: Visual impairment, dry eye, contact lens intolerance;

Ear and Labyrinth Disorders: Vertigo;

Cardiac Disorders: Tachycardia, palpitations;

Vascular Events: Deep vein thrombosis, pulmonary embolism, retinal vascular thrombosis, hot flush;

Arterial Events: Arterial thromboembolism, myocardial infarction, cerebrovascular accident;

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea;

Gastrointestinal Disorders: Pancreatitis, abdominal distension, diarrhea, constipation;

Hepatobiliary Disorders: Hepatitis;

Skin and Subcutaneous Tissue Disorders: Angioedema, erythema nodosum, hirsutism, night sweats, hyperhidrosis, photosensitivity reaction, urticaria, pruritus, acne;

Musculoskeletal, Connective Tissue, and Bone Disorders: Muscle spasms, pain in extremity, myalgia, back pain;

Reproductive System and Breast Disorders: Ovarian cyst, suppressed lactation, vulvovaginal dryness;

General Disorders and Administration Site Conditions: Chest pain, asthenic conditions.

7 DRUG INTERACTIONS

Consult the labeling of concurrently used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

No drug-drug interaction studies were conducted with Tri-VyLibra.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances decreasing the plasma concentrations of COCs:

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of COCs and potentially diminish the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between hormonal contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Colesevelam: Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of EE. The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Substances increasing the plasma concentrations of COCs:

Co-administration of atorvastatin or rosuvastatin and certain COCs containing ethinyl estradiol (EE) increase AUC values for EE by approximately 20 to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV

protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

7.2 Effects of Combined Oral Contraceptives on Other Drugs

- COCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations.
- COCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

  Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs.

7.3 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

7.4 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer Tri-VyLibra with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations *[see Warnings and Precautions (5.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

Do not administer COCs to induce withdrawal bleeding as a test for pregnancy. Do not use COCs during pregnancy to treat threatened or habitual abortion.

8.3 Nursing Mothers

Advise the nursing mother to use other forms of contraception, when possible, until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of Tri-VyLibra Tablets have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

There was no significant difference between Tri-VyLibra tablets and placebo in mean change in total lumbar spine (L1-L4) and total hip bone mineral density between baseline and Cycle 13 in 123 adolescent females with anorexia nervosa in a double-blind, placebo-controlled, multicenter, one-year treatment duration clinical trial for the Intent To Treat (ITT) population.

8.5 Geriatric Use

Tri-VyLibra has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

The pharmacokinetics of Tri-VyLibra has not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. *[See Contraindications (4) and Warnings and Precautions (5.2).]*

8.7 Renal Impairment

The pharmacokinetics of Tri-VyLibra has not been studied in women with renal impairment.

10 OVERDOSAGE

There have been no reports of serious ill effects from overdosage of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

11 DESCRIPTION

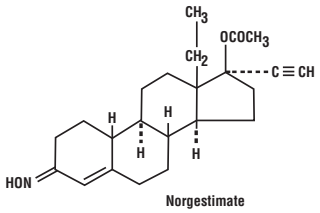
Tri-VyLibra is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. Norgestimate is designated as (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime,(17α)-(+)-) and ethinyl estradiol is designated as (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol).

Each active white tablet contains 0.180 mg of norgestimate USP and 0.035 mg of ethinyl estradiol USP. Inactive ingredients include croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

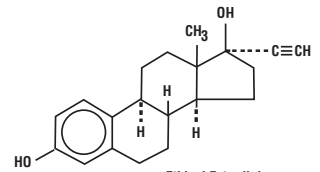
Each active light blue tablet contains 0.215 mg of norgestimate USP and 0.035 mg of ethinyl estradiol USP. Inactive ingredients include croscarmellose sodium, FD&C #2/ Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Each active dark blue tablet contains 0.250 mg of norgestimate USP and 0.035 mg of ethinyl estradiol USP. Inactive ingredients include croscarmellose sodium, FD&C #2/ Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Each green tablet contains only inert ingredients, as follows: anhydrous lactose, FD&C Blue No. 2 aluminum lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, and povidone.



Norgestimate



Ethinyl Estradiol

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

- Oral Contraception

  COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.
- Acne

  Acne is a skin condition with a multifactorial etiology, including androgen stimulation of sebum production. While the combination of ethinyl estradiol and norgestimate increases sex hormone-binding globulin (SHBG) and decreases free testosterone, the relationship between these changes and a decrease in the severity of facial acne in otherwise healthy women with this skin condition has not been established.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Tri-VyLibra.

12.3 Pharmacokinetics

Absorption

Norgestimate (NGM) and EE are rapidly absorbed following oral administration. NGM is rapidly and completely metabolized by first pass (intestinal and/or hepatic) mechanisms to norelgestromin (NGMN) and norgestrel (NG), which are the major active metabolites of norgestimate.

Peak serum concentrations of NGMN and EE are generally reached by 2 hours after administration of Tri-VyLibra. Accumulation following multiple dosing of the 250 mcg NGM / 35 mcg EE dose is approximately 2-fold for NGMN and EE compared with single dose administration. The pharmacokinetics of NGMN is dose-proportional following NGM doses of 180 mcg to 250 mcg. Steady-state concentration of EE is achieved by Day 7 of each dosing cycle. Steady-state concentrations of NGMN and NG are achieved by Day 21. Non-linear accumulation (approximately 8 fold) of NG is observed as a result of high-affinity binding to SHBG, which limits its biological activity (Table 3).

Table 3: Summary of NGMN, NG and EE pharmacokinetic parameters.

Mean (SD) Pharmacokinetic Parameters of Tri-VyLibra During a Three Cycle Study						
Analyte	Cycle	Day	C_{max}	t_{max} (h)	$AUC_{0\text{-}24h}$	$t_{1/2}$ (h)
NGMN	3	7	1.80 (0.46)	1.42 (0.73)	15.0 (3.88)	NC
		14	2.12 (0.56)	1.21 (0.26)	16.1 (4.97)	NC
		21	2.66 (0.47)	1.29 (0.26)	21.4 (3.46)	22.3 (6.54)
NG	3	7	1.94 (0.82)	3.15 (4.05)	34.8 (16.5)	NC
		14	3.00 (1.04)	2.21 (2.03)	55.2 (23.5)	NC
		21	3.66 (1.15)	2.58 (2.97)	69.3 (23.8)	40.2 (15.4)
EE	3	7	124 (39.5)	1.27 (0.26)	1130 (420)	NC
		14	128 (38.4)	1.32 (0.25)	1130 (324)	NC
		21	126 (34.7)	1.31 (0.56)	1090 (359)	15.9 (4.39)

C_{max} = peak serum concentration, t_{max} = time to reach peak serum concentration, $AUC_{0\text{-}24h}$ = area under serum concentration vs time curve from 0 to 24 hours, $t_{1/2}$ = elimination half-life, NC = not calculated.
NGMN and NG: C_{max} = ng/mL, $AUC_{0\text{-}24h}$ = h•ng/mL
EE: C_{max} = pg/mL, $AUC_{0\text{-}24h}$ = h•pg/mL

Food Effect

The effect of food on the pharmacokinetics of Tri-VyLibra has not been studied.

Distribution

NGMN and NG are highly bound (>97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while NG is bound primarily to SHBG. EE is extensively bound (>97%) to serum albumin and induces an increase in the serum concentrations of SHBG.

Metabolism

NGM is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. NGM's primary active metabolite is NGMN. Subsequent hepatic metabolism of

NGMN occurs and metabolites include NG, which is also active, and various hydroxylated and conjugated metabolites. Although NGMN and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, under the recommended dosing regimen, the *in vivo* concentrations of NGMN and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant (K_i). EE is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Excretion

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.2, 5.11) and Use in Specific Populations (8.1).]

14 CLINICAL STUDIES

14.1 Contraception

In four clinical trials with Tri-VyLibra, 4,756 women aged 15 to 41 years were studied for 24 cycles, providing a total of 45,244 cycles of exposure. The racial demographic was about 87 to 90% Caucasian, 6 to 10% African-American, with the remainder Asian (≤1%) or Other (2 to 5%). There were no exclusions on the basis of weight; the weight range for women treated was 80 to 310 lbs, with a mean weight of about 132 lbs. The pregnancy rate was approximately 1 pregnancy per 100 women-years.

14.2 Acne

Tri-VyLibra was evaluated for the treatment of acne vulgaris in two randomized, double-blind, placebo-controlled, multicenter, six- (28 day) cycle studies. Two hundred twenty-one patients received Tri-VyLibra and 234 patients received placebo. Mean age at enrollment for both groups was 28 years. At the end of 6 months, the mean total lesion count changed from 55 to 31 (42% reduction) in patients treated with Tri-VyLibra and from 54 to 38 (27% reduction) in patients similarly treated with placebo. Table 4 summarizes the changes in lesion count for each type of lesion. Based on the investigator's global assessment conducted at the final visit, patients treated with Tri-VyLibra showed a statistically significant improvement in total lesions compared to those treated with placebo.

Table 4: Acne Vulgaris Indication. Combined Results: Two Multicenter, Placebo-Controlled Trials. Observed Means at Six Months (LOCF)* and at Baseline. Intent-to-Treat Population.

	Tri-VyLibra (N=221)		Placebo (N=234)		Difference in Counts between Tri-VyLibra and Placebo at 6 Months
# of Lesions	Counts	% Reduction	Counts	% Reduction	
INFLAMMATORY LESIONS					
Baseline Mean	19		19		
Sixth Month Mean	10	48%	13	30%	3 (95% CI: -1.2, 5.1)
NON-INFLAMMATORY LESIONS					
Baseline Mean	36		35		
Sixth Month Mean	22	34%	25	21%	3 (95% CI: -0.2, 7.8)
TOTAL LESIONS					
Baseline Mean	55		54		7 (95% CI: 2.0, 11.9)
Sixth Month Mean	31	42%	38	27%	

*LOCF: Last Observation Carried Forward

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Tri-VyLibra tablets are available in a blister pack.

Each blister pack (28 tablets) contains in the following order:

- 7 white, round, biconvex, coated tablets, debossed with "S" on one side and "19" on other side of the tablet contains 0.180 mg norgestimate USP and 0.035 mg ethinyl estradiol USP
- 7 light blue, round, biconvex, coated tablets, debossed with "S" on one side and "21" on other side of the tablet contains 0.215 mg norgestimate USP and 0.035 mg ethinyl estradiol USP
- 7 dark blue, round, biconvex, coated tablets, debossed with "S" on one side and "22" on other side of the tablet contains 0.250 mg norgestimate USP and 0.035 mg ethinyl estradiol USP
- 7 green, round, mottled biconvex, uncoated tablets (non-hormonal Placebo), debossed with "S" on one side and "24" on other side of the tablet.

The blister packs are available in the following packages:

- The blister packs are packaged in mono cartons

Carton of 1 Blister Pack	NDC 50102-233-11
Carton of 3 Blister packaged in mono cartons	NDC 50102-233-13

16.2 Storage Conditions

- **Store at** 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
- Protect from light.
- Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs *[see Boxed Warning]*.
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC *[see Warnings and Precautions (5.1)]*.
- Tri-VyLibra does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- Tri-VyLibra is not to be used during pregnancy; if pregnancy occurs during use of Tri-VyLibra instruct the patient to stop further use *[see Warnings and Precautions (5.9)]*.
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed *[see Dosage and Administration (2.2)]*.
- Use a back-up or alternative method of contraception when enzyme inducers are used with Tri-VyLibra *[see Drug Interactions (7.1)]*.
- COCs may reduce breast milk production; this is less likely to occur if breastfeeding is well established *[see Use in Specific Populations (8.3)]*.
- Women who start COCs postpartum, and who have not yet had a period, should use an additional method of contraception until they have taken an active tablet for 7 consecutive days *[see Dosage and Administration (2.2)]*.
- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea at the time of the first missed period. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles *[see Warnings and Precautions (5.8)]*.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 12/2020

Patient Information

Tri-VyLibra
(norgestimate and ethinyl estradiol tablets USP)

What is the most important information I should know about Tri-VyLibra?

Do not use Tri-VyLibra if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from hormonal birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

What is Tri-VyLibra?

Tri-VyLibra is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

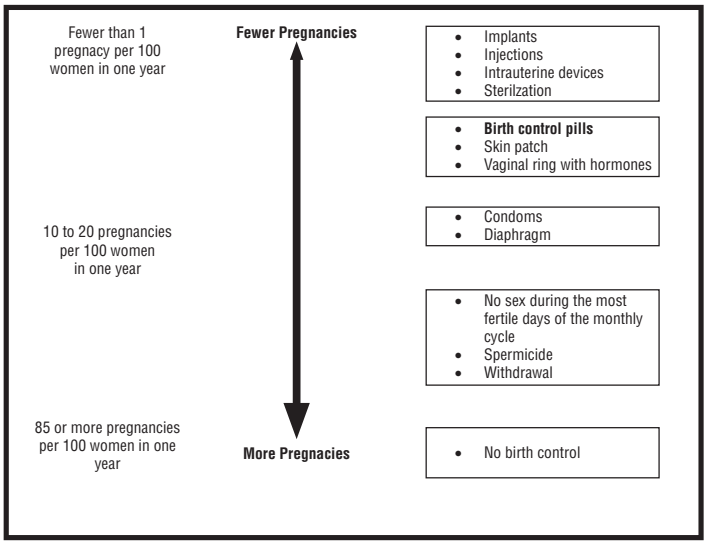
Tri-VyLibra is also used to treat moderate acne vulgaris in females 15 years of age and older, who have no known history of allergies or problems taking birth control pills, and have started their menstrual cycle ("period"). Tri-VyLibra should only be used to treat acne in women who want to take birth control pills to prevent pregnancy.

How does Tri-VyLibra work for contraception?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of clinical studies, about 1 out of 100 women may get pregnant during the first year they use Tri-VyLibra.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



Who should not take Tri-VyLibra?

Do not take Tri-VyLibra if you:

- smoke and are over 35 years of age
- had blood clots in your arms, legs, lungs, or eyes
- had a problem with your blood that makes it clot more than normal
- have certain heart valve problems or irregular heart beat that increases your risk of having blood clots
- had a stroke
- had a heart attack
- have high blood pressure that cannot be controlled by medicine
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or any migraine headaches if you are over 35 years of age
- have liver problems, including liver tumors
- take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.
- have any unexplained vaginal bleeding
- are pregnant
- had breast cancer or any cancer that is sensitive to female hormones

If any of these conditions happen while you are taking Tri-VyLibra, stop taking Tri-VyLibra right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking Tri-VyLibra.

What should I tell my healthcare provider before taking Tri-VyLibra?

Tell your healthcare provider if you:

- are pregnant or think you may be pregnant
- are depressed now or have been depressed in the past
- had yellowing of your skin or eyes (jaundice) caused by pregnancy (cholestasis of pregnancy)
- are breastfeeding or plan to breastfeed. Tri-VyLibra may decrease the amount of breast milk you make. A small amount of the hormones in Tri-VyLibra may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Tri-VyLibra may affect the way other medicines work, and other medicines may affect how well Tri-VyLibra works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Tri-VyLibra?

Read the Instructions for Use at the end of this Patient Information.

What are the possible serious side effects of Tri-VyLibra?

- **Like pregnancy, Tri-VyLibra may cause serious side effects, including blood clots in your lungs, heart attack, or a stroke that may lead to death. Some other examples of serious blood clots include blood clots in the legs or eyes.**

Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age. Serious blood clots are more likely to happen when you:

- first start taking birth control pills
- restart the same or different birth control pills after not using them for a month or more

Call your healthcare provider or go to a hospital emergency room right away if you have:

- leg pain that will not go away
- a sudden, severe headache unlike your usual headaches
- sudden severe shortness of breath
- weakness or numbness in your arm or leg
- sudden change in vision or blindness
- trouble speaking
- chest pain

Other serious side effects include:

- **liver problems, including:**
  - rare liver tumors
  - jaundice (cholestasis), especially if you previously had cholestasis of pregnancy. Call your healthcare provider if you have yellowing of your skin or eyes.
- **high blood pressure.** You should see your healthcare provider for a yearly check of your blood pressure.
- **gallbladder problems**
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood**
- **new or worsening headaches including migraine headaches**
- **irregular or unusual vaginal bleeding and spotting between your menstrual periods, especially during the first 3 months of taking Tri-VyLibra.**
- **depression**
- **possible cancer in your breast and cervix**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider if you have a swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher is you have a history of angioedema.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Women who tend to get chloasma should avoid spending a long time in sunlight, tanning booths, and under sun lamps while taking Tri-VyLibra. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of Tri-VyLibra?

- headache (migraine)
- breast pain or tenderness, enlargement or discharge
- stomach pain, discomfort, and gas
- vaginal infections and discharge
- mood changes, including depression
- nervousness
- changes in weight
- skin rash

These are not all the possible side effects of Tri-VyLibra. For more information, ask your healthcare provider or pharmacist.

You may report side effects to the FDA at 1-800-FDA-1088.

What else should I know about taking Tri-VyLibra?

- If you are scheduled for any lab tests, tell your healthcare provider you are taking Tri-VyLibra. Certain blood tests may be affected by Tri-VyLibra.
- Tri-VyLibra does not protect against HIV infection (AIDS) and other sexually transmitted infections.

How should I store Tri-VyLibra?

- Store Tri-VyLibra at room temperature between 20° to 25°C (68° to 77°F).
- Keep Tri-VyLibra and all medicines out of the reach of children.
- Store away from light.

General information about the safe and effective use of Tri-VyLibra.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Tri-VyLibra for a condition for which it was not prescribed. Do not give Tri-VyLibra to other people, even if they have the same symptoms that you have.

This Patient Information summarizes the most important information about Tri-VyLibra. You can ask your pharmacist or healthcare provider for information about Tri-VyLibra that is written for health professionals.

For more information, call Afaxys Pharma, LLC at 1-855-888-2467

Do birth control pills cause cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What if I want to become pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

What should I know about my period when taking Tri-VyLibra?

Your periods may be lighter and shorter than usual. Some women may miss a period. Irregular vaginal bleeding or spotting may happen while you are taking Tri-VyLibra, especially during the first few months of use. This usually is not a serious problem. It is important to continue taking your pills on a regular schedule to prevent a pregnancy.

What are the ingredients in Tri-VyLibra?

Active ingredients: Each white, light blue, and dark blue pill contains norgestimate and ethinyl estradiol.

Inactive ingredients:

White pills: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Light blue pills: croscarmellose sodium, FD&C#2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Dark blue pills: croscarmellose sodium, FD&C#2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Green pills: anhydrous lactose, FD&C Blue No. 2 aluminum lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, and povidone.

Instructions For Use

Tri-VyLibra

(norgestimate and ethinyl estradiol tablets USP)

Important Information about taking Tri-VyLibra

- Take **1** pill every day at the same time. Take the pills in the order directed on your blister pack.
- Do not skip your pills, even if you do not have sex often. If you miss pills (including starting the pack late) **you could get pregnant**. The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take Tri-VyLibra, talk to your healthcare provider. When you first start taking Tri-VyLibra, spotting or light bleeding in between your periods may occur. Contact your healthcare provider if this does not go away after a few months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking Tri-VyLibra. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If your nausea does not go away, call your healthcare provider.
- Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills (see **What should I do if I miss any Tri-VyLibra pills?** below), you could also feel a little sick to your stomach.
- It is not uncommon to miss a period. However, if you miss a period and have not taken Tri-VyLibra according to directions, or miss **2** periods in a row, or feel like you may be pregnant, call your healthcare provider. If you have a positive pregnancy test, you should stop taking Tri-VyLibra.
- If you have vomiting or diarrhea within **3 to 4** hours of taking your pill, take another pill of the same color from your extra blister pack. If you do not have an extra blister pack, take the next pill in your blister pack. Continue taking all your remaining pills in order. Start the first pill of your next blister pack the day after finishing your current blister pack. This will be 1 day earlier than originally scheduled. Continue on your new schedule.
- If you have vomiting or diarrhea for more than 1 day, your birth control pills may not work as well. Use an additional birth control method, like condoms and a spermicide, until you check with your healthcare provider.
- Stop taking Tri-VyLibra at least **4** weeks before you have major surgery and do not restart after the surgery without asking your healthcare provider. Be sure to use other forms of contraception (like condoms and spermicide) during this time period.

Before you start taking Tri-VyLibra:

- Decide what time of day you want to take your pill. It is important to take it at the same time every day and in the order as directed on your blister pack.
- Have backup contraception (condoms and spermicide) available and if possible, an extra full pack of pills as needed.

When should I start taking Tri-VyLibra?

If you start taking Tri-VyLibra and you have not used a hormonal birth control method before:

- There are 2 ways to start taking your birth control pills. You can either start on a Sunday (Sunday Start) or on the first day (Day 1) of your natural menstrual period (Day 1 Start). Your healthcare provider should tell you when to start taking your birth control pill.
- If you use the Sunday Start, use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days that you take Tri-VyLibra. You do not need back-up contraception if you use the Day 1 Start.

If you start taking Tri-VyLibra and you are switching from another birth control pill:

- Start your new Tri-VyLibra pack on the same day that you would start the next pack of your previous birth control method.
- Do not continue taking the pills from your previous birth control pack.

If you start taking Tri-VyLibra and previously used a vaginal ring or transdermal patch:

- Start using Tri-VyLibra on the day you would have reapplied the next ring or patch.

If you start taking Tri-VyLibra and you are switching from a progestin-only method such as an implant or injection:

- Start taking Tri-VyLibra on the day of removal of your implant or on the day when you would have had your next injection.

If you start taking Tri-VyLibra and you are switching from an intrauterine device or system (IUD or IUS):

- Start taking Tri-VyLibra on the day of removal of your IUD or IUS.
- You do not need back-up contraception if your IUD or IUS is removed on the first day (Day 1) of your period. If your IUD or IUS is removed on any other day, use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days that you take Tri-VyLibra.

Keep a calendar to track your period:

If this is the first time you are taking birth control pills, read, "**When should I start taking Tri-VyLibra?**" above.

Follow these instructions for either a **Sunday Start** or a **Day 1 Start**.

Sunday Start:

You will use a **Sunday Start** if your healthcare provider told you to take your first pill on a Sunday.

- Take pill **1** on the Sunday **after your period starts.**
- If your period starts on a Sunday, take pill "**1**" that day and refer to Day 1 Start instructions below.
- Take **1** pill every day in the order on the blister pack at the same time each day for **28** days.
- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack (Sunday). Take the first pill in the new pack whether or not you are having your period.
- Use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days of the first cycle that you take Tri-VyLibra.

Day 1 Start:

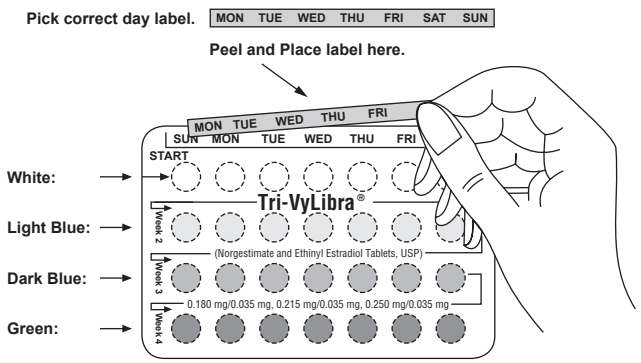
You will use a **Day 1 Start** if your doctor told you to take your first pill (Day 1) on the **first day of your period**.

- Take **1** pill every day in the order of the blister pack, at the same time each day, for **28** days.
- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack. Take the first pill in the new pack whether or not you are having your period.

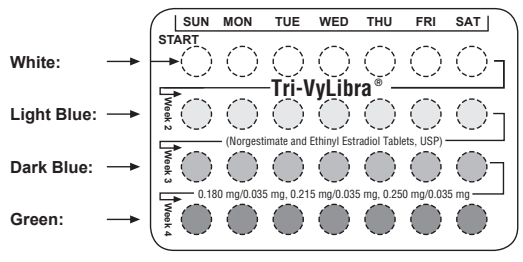
How to Use the Blister Pack:

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

1. Pick the Days of the Week Sticker that starts the first day of your period. (This is the day you begin bleeding or spotting, even if it is midnight when bleeding begins.) When you have picked the right sticker, throw away the others and place the sticker on the blister pack over the preprinted days of the week and make sure it lines up with the pills.



2. Your blister pack containing 28 individually sealed pills. Note that the pills are arranged in four numbered rows of 7 pills, with the pre-printed days of the week printed above them. There are 7 white "active" pills, 7 light blue "active" pills, 7 dark blue "active" pills, and 7 green "reminder" pills. Refer to the sample of the blister pack below:



3. After taking the last green pill, start a new blister pack the **very next day** no matter when your period started. You will be taking a pill every day without interruption. Anytime you start the pills later than directed, protect yourself by using another method of birth control until you have taken a pill a day for seven consecutive days. After taking the last green pill, start taking the first white pill from the blister pack the very next day.

4. Take the pills in each new package as before. Start with the white pill on row #1 and take one pill each day, left to right, until the last green pill has been taken.

Three Ways to Remember in What Order to take the Pills

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

What should I do if I miss any Tri-VyLibra pills?

If you miss 1 pill in Weeks 1, 2, or 3, follow these steps:

- 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.
- Then continue taking **1** pill every day until you finish the pack.
- You do not need to use a back-up birth control method if you have sex.

If you miss 2 pills in Week 1 or Week 2 of your pack, follow these steps:

- Take the 2 missed pills as soon as possible and the next 2 pills the next day.
- Then continue to take **1** pill every day until you finish the pack.
- Use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7 days** after missing your pills.

If you miss 2 pills in a row in Week 3, or you miss 3 or more pills in a row during Weeks 1, 2, or 3 of the pack, follow these steps:

- **If you are a Day 1 Starter:**
  - Throw out the rest of the pill pack and start a new pack that same day.
  - 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 healthcare provider because you might be pregnant.
  - You could become pregnant if you have sex during the first 7 days after you restart your pills. You MUST use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7** days after you restart your pills.
- **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.
  - Use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7** days after you restart your pills.

If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 12/2020

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRI-VYLIBRA® LO safely and effectively. See full prescribing information for TRI-VYLIBRA LO.

Tri-VyLibra Lo (norgestimate and ethinyl estradiol) tablets for oral use
Initial U.S. Approval: 1989

WARNING: CIGARETTE SMOKING and SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **Tri-VyLibra Lo is contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. (4)**

----------RECENT MAJOR CHANGES----------

Contraindications (4)	08/2017
Warnings and Precautions (5.3)	08/2017

----------INDICATIONS AND USAGE----------

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is an estrogen/progestin COC, indicated for use by women to prevent pregnancy. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Take one tablet daily by mouth at the same time every day. (2.2)
- Take tablets in the order directed on the blister pack. (2.2)
- Do not skip or delay tablet intake. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets USP) consists of 21 round, biconvex, coated tablets and 7 round, mottled, biconvex, uncoated tablets in the following order (3):

- 7 white to off white tablets each containing 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 pale blue to bluish white tablets each containing 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 blue to light blue tablets each containing 0.250 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 green tablets (inert)

----------CONTRAINDICATIONS----------

- A high risk of arterial or venous thrombotic diseases (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (4)

----------WARNINGS AND PRECAUTIONS----------

- Thromboembolic Disorders and Other Vascular Problems: Stop Tri-VyLibra Lo if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue Tri-VyLibra Lo if jaundice occurs. (5.2)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop Tri-VyLibra Lo if blood pressure rises significantly. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking Tri-VyLibra Lo. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue Tri-VyLibra Lo if indicated. (5.7)
- Bleeding Irregularities and Amenorrhea: Evaluate irregular bleeding or amenorrhea. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions reported during clinical trials (≥2%) were: headache/migraine, nausea/vomiting, breast issues, abdominal pain, menstrual disorders, mood disorders, acne, vulvovaginal infection, abdominal distension, weight increased, fatigue. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Afaxys Pharma, LLC at 1-855-888-2467 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 01/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING and SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke *[see Contraindications (4)].*

1 INDICATIONS AND USAGE

1.1 Oral Contraception

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is indicated for use by females of reproductive potential to prevent pregnancy *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 How to Start Tri-VyLibra Lo (Norgestimate and Ethinyl Estradiol Tablets)

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is dispensed in a blister pack *[see How Supplied/Storage and Handling (16)]*. Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) may be started using either a Day 1 start or a Sunday start (see Table 1). For the first cycle of a Sunday Start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

2.2 How to Take Tri-VyLibra Lo (Norgestimate and Ethinyl Estradiol Tablets)

Table 1: Instructions for Administration of Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets)

Starting COCs in women not currently using hormonal contraception (Day 1 Start or Sunday Start) **Important:** Consider the possibility of ovulation and conception prior to initiation of this product. **Tablet Color:** • Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) active tablets are white to off white (Day 1 to Day 7), pale blue to bluish white (Day 8 to Day 14) and blue to light blue (Day 15 to Day 21). • Tri-VyLibra Lo inactive tablets are green (Day 22 to Day 28).	**Day 1 Start:** • Take first active tablet without regard to meals on the first day of menses. • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one **green** inactive tablet daily for 7 days and at the same time of day that active tablets were taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last inactive tablet) **Sunday Start:** • Take first active tablet without regard to meals on the first Sunday after the onset of menses. **Due to the potential risk of becoming pregnant, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets).** • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one **green** inactive tablet daily for the following 7 days and at the same time of day that active tablets were taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the Sunday after taking the last inactive tablet) and additional non-hormonal contraceptive is not needed.
Switching to Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) from another oral contraceptive	Start on the same day that a new pack of the previous oral contraceptive would have started.
Switching from another contraceptive method to Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets)	**Start Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets):**
• **Transdermal patch**	• On the day when next application would have been scheduled
• **Vaginal ring**	• On the day when next insertion would have been scheduled
• **Injection**	• On the day when next injection would have been scheduled
• **Intrauterine contraceptive**	• On the day of removal • If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraceptive (such as condoms and spermicide) is needed for the first seven days of the first cycle pack.
• **Implant**	• On the day of removal
Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-Approved Patient Labeling.	

Starting Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) after Abortion or Miscarriage

First-trimester

- After a first-trimester abortion or miscarriage, Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) may be started immediately. An additional method of contraception is not needed if Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is started immediately.
- If Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of her first cycle pack of Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets).

Second-trimester

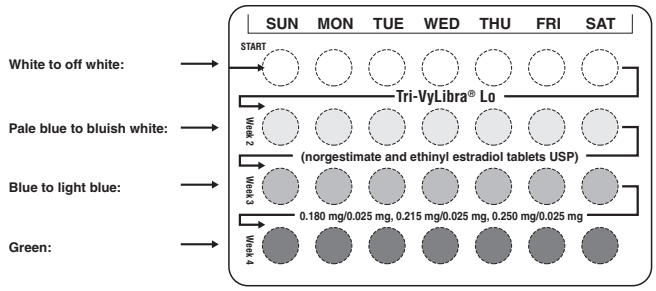
- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets), following the instructions in Table 1 for Day 1 or Sunday start, as desired. If using Sunday start, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets). *[see Contraindications (4), Warnings and Precautions (5.1), and FDA-Approved Patient Labeling.]*

Starting Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) following the instructions in Table 1 for women not currently using hormonal contraception.
- Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) is not recommended for use in lactating women *[see Use in Specific Populations (8.3)]*.
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets). *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1 and 8.3), and FDA-Approved Patient Labeling]*.

Blister Pack:

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. The 28-pill pack has 21 white to off white, pale blue to bluish white, and blue to light blue "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of green "reminder" 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.



4. Be sure you have ready at all times:
   Another kind of birth control (such as condoms or spermicide) to use as a back-up method in case you miss pills.
   An extra, full pill pack.

You have a choice of which day to start taking your first pack of pills. Tri-VyLibra Lo is available in a blister pack which is preset for a Sunday Start. Day 1 Start stickers are also provided. Decide with your healthcare professional which is the best day for you. Pick a time of day that will be easy to remember.

Sunday Start:

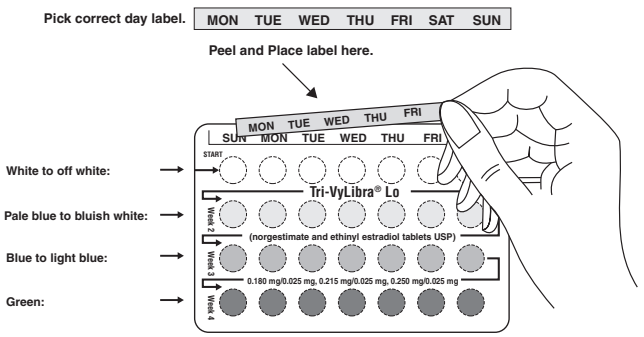
Take the first white to off white "active" pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

Use another method of birth control (such as condoms or spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

Day 1 Start:

Take the first white to off white "active" pill of the first pack during the first 24 hours of your period.

1. Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins).
2. Place this day label strip in the cycle tablet over the area that has the days of the week (starting with Sunday) imprinted in the plastic.



Note: If the first day of your period is a Sunday, you can skip steps #1 and #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.

2.3 Missed Tablets

Table 2: Instructions for Missed Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets)

• If one active tablet is missed in Weeks 1, 2, or 3	Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.
• If two active tablets are missed in Week 1 or Week 2	Take the two missed tablets as soon as possible and the next two active tablets the next day. Continue taking one tablet a day until the pack is finished. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**
• If two active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	Day 1 start: Throw out the rest of the pack and start a new pack that same day. Sunday start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**

2.4 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting or diarrhea occurs within 3 to 4 hours after taking an active tablet, handle this as a missed tablet *[see FDA-Approved Patient Labeling]*.

3 DOSAGE FORMS AND STRENGTHS

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets USP) is available in a blister pack. Each blister pack contains 28 tablets in the following order:

- 7 white to off white, round, biconvex, coated tablets, debossed with "S" on one side and "15" on other side of the tablet contains 0.180 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 pale blue to bluish white, round, biconvex, coated tablets, debossed with "S" on one side and "16" on other side of the tablet contains 0.215 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 blue to light blue, round, biconvex, coated tablets, debossed with "S" on one side and "17" on other side of the tablet contains 0.250 mg norgestimate and 0.025 mg ethinyl estradiol
- 7 green, round, mottled, biconvex, uncoated tablets, debossed with "S" on one side and "24" on other side of the tablet contains inert ingredients

4 CONTRAINDICATIONS

Do not prescribe Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets) to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or migraine headaches with aura *[see Warnings and Precautions (5.7)]*
    - Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.7)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.2)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9)* and *Use in Specific Populations (8.1)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.11)]*
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

- Stop Tri-VyLibra Lo if an arterial thrombotic event or venous thrombotic (VTE) event occurs.
- Stop Tri-VyLibra Lo if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately *[see Adverse Reactions (6.2)]*.
- If feasible, stop Tri-VyLibra Lo at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during and following prolonged immobilization.
- Start Tri-VyLibra Lo no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued.
- Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.
- Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function

Do not use Tri-VyLibra Lo in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver *[see Contraindications (4)]*. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue Tri-VyLibra Lo if jaundice develops.

Liver Tumors

Tri-VyLibra Lo is contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)]*. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the risk of liver cancers in COC users is less than one case per million users.

5.3 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as COCs. Discontinue Tri-VyLibra Lo prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. Tri-VyLibra Lo can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.4 High Blood Pressure

Tri-VyLibra Lo is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop Tri-VyLibra Lo if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension

increases with increasing concentrations of progestin.

5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may worsen existing gallbladder disease. A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC related cholestasis.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who take Tri-VyLibra Lo. COCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache

If a woman taking Tri-VyLibra Lo develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue Tri-VyLibra Lo if indicated.

Consider discontinuation of Tri-VyLibra Lo in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event).

5.8 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different contraceptive product.

In the clinical trial of Tri-VyLibra Lo, the frequency and duration of unscheduled bleeding and/or spotting was assessed in 1,673 women (11,015 evaluable cycles). A total of 3 (0.2%) women discontinued Tri-VyLibra Lo, at least in part, due to bleeding or spotting. Based on data from the clinical trials, 7 to 17% of women using Tri-VyLibra Lo experienced unscheduled bleeding per cycle in the first year. The percent of women who experienced unscheduled bleeding tended to decrease over time.

Amenorrhea and Oligomenorrhea

Women who use Tri-VyLibra Lo may experience amenorrhea. Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was pre-existent.

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.9 COC 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. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue Tri-VyLibra Lo use if pregnancy is confirmed.

Administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Carefully observe women with a history of depression and discontinue Tri-VyLibra Lo if depression recurs to a serious degree.

5.11 Carcinoma of Breast and Cervix

- Tri-VyLibra Lo is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see Contraindications (4)]*.

  There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.
- Some studies suggest that COC use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

5.12 Effect on Binding Globulins

The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.15 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking Tri-VyLibra Lo.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in labeling:

- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of Tri-VyLibra Lo was evaluated in 1,723 subjects who participated in a randomized, partially blinded, multicenter, active-controlled clinical trial of Tri-VyLibra Lo for contraception. This trial examined healthy, nonpregnant, volunteers aged 18 to 45 (nonsmoker if 35 to 45 years of age), who were sexually active with regular coitus. Subjects were followed for up to 13 28-day cycles.

Common Adverse Reactions (≥ 2% of subjects): The most common adverse reactions reported by at least 2% of the 1,723 women using the 28-day regimen were the following in order of decreasing incidence: headache/migraine (30.5%), nausea/vomiting (16.3%); breast issues (including tenderness, pain, enlargement, swelling, discharge, discomfort, cyst, and nipple pain) (10.3%), abdominal pain (9.2%), menstrual disorders (including dysmenorrhea, menstrual discomfort, menstrual disorder) (9.2%), mood disorders (including depression, mood altered, mood swings and depressed mood) (7.6%); acne (5.1%), vulvovaginal infection (3.5%), abdominal distension (2.8%), weight increased (2.4%), fatigue (2.1%).

Adverse Reactions Leading to Study Discontinuation: In the clinical trial of Tri-VyLibra Lo 4% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions leading to discontinuation were headache/migraine (1.2%), nausea/vomiting (0.7%), cervical dysplasia (0.7%), abdominal pain (0.4%), ovarian cyst (0.3%), acne (0.2%), flatulence (0.2%) and depression (0.2%).

Serious Adverse Reactions: carcinoma of the cervix *in situ* (1 subject) and cervical dysplasia (1 subject).

6.2 Postmarketing Experience

The following additional adverse drug reactions have been reported from worldwide postmarketing experience with norgestimate/ethinyl estradiol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and Infestations: Urinary tract infection

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps): Breast cancer, benign breast neoplasm, hepatic adenoma, focal nodular hyperplasia, breast cyst

Immune System Disorders: Hypersensitivity

Metabolism and Nutrition Disorders: Dyslipidemia

Psychiatric Disorders: Anxiety, insomnia

Nervous System Disorders: Syncope, convulsion, paresthesia, dizziness

Eye Disorders: Visual impairment, dry eye, contact lens intolerance

Ear and Labyrinth Disorders: Vertigo

Cardiac Disorders: Tachycardia, palpitations

Vascular Events: Deep vein thrombosis, pulmonary embolism, retinal vascular thrombosis, hot flush

Arterial Events: Arterial thromboembolism, myocardial infarction, cerebrovascular accident

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Gastrointestinal Disorders: Pancreatitis, abdominal distension, diarrhea, constipation

Hepatobiliary Disorders: Hepatitis

Skin and Subcutaneous Tissue Disorders: Angioedema, erythema nodosum, hirsutism, night sweats, hyperhidrosis, photosensitivity reaction, urticaria, pruritus, acne

Musculoskeletal, Connective Tissue, and Bone Disorders: Muscle spasms, pain in extremity, myalgia, back pain

Reproductive System and Breast Disorders: Ovarian cyst, suppressed lactation, vulvovaginal dryness

General Disorders and Administration Site Conditions: Chest pain, asthenic conditions.

7 DRUG INTERACTIONS

Consult the labeling of concurrently used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

No drug-drug interaction studies were conducted with Tri-VyLibra Lo.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances Decreasing the Plasma Concentrations of COCs

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of COCs and potentially diminish the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of COCs include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant and products containing St. John's wort. Interactions between COCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Colesevelam: Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of ethinyl estradiol (EE). The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Substances Increasing the Plasma Concentrations of COCs

Co-administration of atorvastatin or rosuvastatin and certain COCs containing EE increase AUC values for EE by approximately 20 to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Human Immunodeficiency Virus (HIV)/Hepatitis C Virus (HCV) Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

7.2 Effects of Combined Oral Contraceptives on Other Drugs

- COCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations.
- COCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

  Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs.

7.3 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

7.4 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer Tri-VyLibra Lo with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations *[see Warnings and Precautions (5.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

Do not administer COCs to induce withdrawal bleeding as a test for pregnancy. Do not use COCs during pregnancy to treat threatened or habitual abortion.

8.3 Nursing Mothers

Advise the nursing mother to use other forms of contraception, when possible, until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of Tri-VyLibra Lo tablets have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

Tri-VyLibra Lo has not been studied in postmenopausal women and is not indicated in this population.

8.6 Hepatic Impairment

The pharmacokinetics of Tri-VyLibra Lo has not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded *[see Contraindications (4)* and *Warnings and Precautions (5.2).]*

8.7 Renal Impairment

The pharmacokinetics of Tri-VyLibra Lo has not been studied in women with renal impairment.

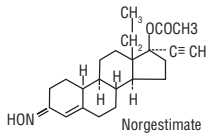
10 OVERDOSAGE

There have been no reports of serious ill effects from overdosage of oral contraceptives, including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

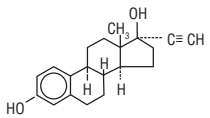
11 DESCRIPTION

Tri-VyLibra Lo is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. Norgestimate is designated as (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)-) and ethinyl estradiol is designated as (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol).

- Each active white to off white tablet contains 0.180 mg of norgestimate USP and 0.025 mg of ethinyl estradiol USP. Inactive ingredients include croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.
- Each active pale blue to bluish white tablet contains 0.215 mg of norgestimate USP and 0.025 mg of ethinyl estradiol USP. Inactive ingredients include croscarmellose sodium, FD&C Blue #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.
- Each active blue to light blue tablet contains 0.250 mg of norgestimate USP and 0.025 mg of ethinyl estradiol USP. Inactive ingredients include croscarmellose sodium, FD&C Blue #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.
- Each green placebo tablet contains only inert ingredients, as follows: anhydrous lactose, FD&C Blue No. 2 aluminum lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, and povidone.



Norgestimate



Ethinyl Estradiol

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with Tri-VyLibra Lo.

12.3 Pharmacokinetics

Absorption

Norgestimate (NGM) and EE are rapidly absorbed following oral administration. NGM is rapidly and completely metabolized by first pass (intestinal and/or hepatic) mechanisms to norelgestromin (NGMN) and norgestrel (NG), which are the major active metabolites of NGM.

Mean pharmacokinetic parameters for NGMN, NG and EE during three cycles of administration of Tri-VyLibra Lo are summarized in Table 3.

Peak serum concentrations of NGMN and EE were generally reached by 2 hours after administration of Tri-VyLibra Lo. Accumulation following multiple dosing of the 0.180 mg NGM / 0.025 mg EE dose is approximately 1.5 to 2 fold for NGMN and approximately 1.5 fold for EE compared with single dose administration, in agreement with that predicted based on linear kinetics of NGMN and EE. The pharmacokinetics of NGMN is dose proportional following NGM doses of 0.180 to 0.250 mg. Steady-state conditions for NGMN following each NGM dose and for EE were achieved during the three cycle study. Non-linear accumulation (4.5 to 14.5 fold) of NG was observed as a result of high affinity binding to SHBG, which limits its biological activity.

Table 3 Summary of NGMN, NG and EE pharmacokinetic parameters.

Table 3: Mean (SD) Pharmacokinetic Parameters of Tri-VyLibra Lo During a Three Cycle Study

Analyte[1]	Cycle	Day	C_{max}	t_{max}(h)	AUC_{0-24h}	$t_{1/2}$(h)
NGMN[(2-4)]	**1**	**1**	**0.91** (0.27)	**1.8** (1)	**5.86** (1.54)	**NC**
	3	**7**	**1.42** (0.43)	**1.8** (0.7)	**11.3** (3.2)	**NC**
		14	**1.57** (0.39)	**1.8** (0.7)	**13.9** (3.7)	**NC**
		21	**1.82** (0.54)	**1.5** (0.7)	**16.1** (4.8)	**28.1** (10.6)
NG[(2-4)]	**1**	**1**	**0.32** (0.14)	**2** (1.1)	**2.44** (2.04)	**NC**
	3	**7**	**1.64** (0.89)	**1.9** (0.9)	**27.9** (18.1)	**NC**
		14	**2.11** (1.13)	**4** (6.3)	**40.7** (24.8)	**NC**
		21	**2.79** (1.42)	**1.7** (1.2)	**49.9** (27.6)	**36.4** (10.2)
EE[(2,3,5)]	**1**	**1**	**55.6** (18.1)	**1.7** (0.5)	**421** (118)	**NC**
	3	**7**	**91.1** (36.7)	**1.3** (0.3)	**782** (329)	**NC**
		14	**96.9** (38.5)	**1.3** (0.3)	**796** (273)	**NC**
		21	**95.9** (38.9)	**1.3** (0.6)	**771** (303)	**17.7** (4.4)

[1] NGMN = Norelgestromin, NG = norgestrel, EE = ethinyl estradiol
[2] C_{max} = peak serum concentration, t_{max} = time to reach peak serum concentration, AUC_{0-24h} = area under serum concentration vs. time curve from 0 to 24 hours, $t_{1/2}$ = elimination half-life.
[3] units for all analytes; h = hours
[4] units for NGMN and NG – C_{max} = ng/mL, AUC_{0-24h} = h•ng/mL
[5] units for EE only – C_{max} = pg/mL, AUC_{0-24h} = h•pg/mL
NC = not calculated

Food Effect

The effect of food on the pharmacokinetics of Tri-VyLibra Lo has not been studied.

Distribution

NGMN and NG are highly bound (>97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while NG is bound primarily to SHBG. EE is extensively bound (>97%) to serum albumin and induces an increase in the serum concentrations of SHBG.

Metabolism

NGM is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. NGM's primary active metabolite is NGMN. Subsequent hepatic metabolism of NGMN occurs and metabolites include NG, which is also active and various hydroxylated and conjugated metabolites. Although NGMN and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, under the recommended dosing regimen, the *in vivo* concentrations of NGMN and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant (K_i). EE is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Excretion

Following 3 cycles of administration of Tri-VyLibra Lo, the mean (± SD) elimination half-life values, at steady-state, for NGMN, NG and EE were 28.1 (± 10.6) hours, 36.4 (± 10.2) hours and 17.7 (± 4.4) hours, respectively (Table 2). The metabolites of NGMN and EE are eliminated by renal and fecal pathways.

Use in Specific Populations

Effects of Body Weight, Body Surface Area, and Age

The effects of body weight, body surface area, age and race on the pharmacokinetics of NGMN, NG and EE were evaluated in 79 healthy women using pooled data following single dose administration of NGM 0.180 or 0.250 mg / EE 0.025 mg tablets in four pharmacokinetic studies. Increasing body weight and body surface area were each associated with decreases in C_{max} and AUC_{0-24h} values for NGMN and EE and increases in CL/F (oral clearance) for EE. Increasing body weight by 10 kg is predicted to reduce the following parameters: NGMN C_{max} by 9% and AUC_{0-24h} by 19%, NG C_{max} by 12% and AUC_{0-24h} by 46%, EE C_{max} by 13% and AUC_{0-24h} by 12%. These changes were statistically significant. Increasing age was associated with slight decreases (6% with increasing age by 5 years) in C_{max} and AUC_{0-24h} for NGMN and were statistically significant, but there was no significant effect for NG or EE. Only a small to moderate fraction (5 to 40%) of the overall variability in the pharmacokinetics of NGMN and EE following Tri-VyLibra Lo tablets may be explained by any or all of the above demographic parameters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.2, 5.11) and Use in Specific Populations (8.1).]

14 CLINICAL STUDIES

In an active controlled clinical trial lasting 12 months, 1,673 women, 18 to 45 years old completed 11,003 cycles of Tri-VyLibra Lo use and a total of 20 pregnancies were reported in Tri-VyLibra Lo users. The racial demographic of those treated with Tri-VyLibra Lo was: Caucasian (86%), African-American (6%), Asian (2%), and Other (6%). There were no exclusions on the basis of weight; the weight range for women treated was 90 to 240 lbs, with a mean weight of about 142 lbs. The pregnancy rate in women aged 18 to 35 years was approximately 2.6 pregnancies per 100 woman-years of use.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Tri-VyLibra Lo (norgestimate and ethinyl estradiol tablets USP) Tablets are available in a blister pack.

Each blister pack (28 tablets) contains in the following order:

- 7 white to off white, round, biconvex, coated tablets (active), debossed with "S" on one side and "15" on other side of the tablet contains 0.180 mg, norgestimate USP and 0.025 mg ethinyl estradiol USP
- 7 pale blue to bluish white, round, biconvex, coated tablets (active), debossed with "S" on one side and "16" on other side of the tablet contains 0.215 mg norgestimate USP and 0.025 mg ethinyl estradiol USP
- 7 blue to light blue, round, biconvex, coated tablets (active), debossed with "S" on one side and "17" on other side of the tablet contains 0.250 mg norgestimate USP and 0.025 mg ethinyl estradiol USP
- 7 green, round, mottled, biconvex, uncoated tablets (non-hormonal placebo), debossed with "S" on one side and "24" on other side of the tablet contains inert ingredients

The blister packs are available in the following packages:

- The blister packs are packaged in mono cartons

Carton of 1 Blister Pack	NDC 50102-231-11
Carton of 3 Blister Packs packaged in mono cartons	NDC 50102-231-13

16.2 Storage Conditions

- **Store at** 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
- Protect from light.
- Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instruction for Use).

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs *[see Boxed Warning]*.
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC *[see Warnings and Precautions (5.1)]*.
- Tri-VyLibra Lo does not protect against HIV infection (AIDS) and other sexually transmitted infections.
- Tri-VyLibra Lo is not to be used during pregnancy; if pregnancy occurs during use of Tri-VyLibra Lo instruct the patient to stop further use *[see Warnings and Precautions (5.9)]*.
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed *[see Dosage and Administration (2.2)]*.
- Use a back-up or alternative method of contraception when enzyme inducers are used with Tri-VyLibra Lo *[see Drug Interactions (7.1)]*.
- COCs may reduce breast milk production, this is less likely to occur if breastfeeding is well established *[see Use in Specific Populations (8.3)]*.
- Women who start COCs postpartum; and who have not yet had a period, should use an additional method of contraception until they have taken a white to off white tablet for 7 consecutive days *[see Dosage and Administration (2.2)]*.
- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea at the time of the first missed period. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles *[see Warnings and Precautions (5.8)]*.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 01/2021

Patient Information
Tri-VyLibra Lo
(norgestimate and ethinyl estradiol tablets USP)

What is the most important information I should know about Tri-VyLibra Lo?

Do not use Tri-VyLibra Lo if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from hormonal birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

What is Tri-VyLibra Lo?

Tri-VyLibra Lo is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

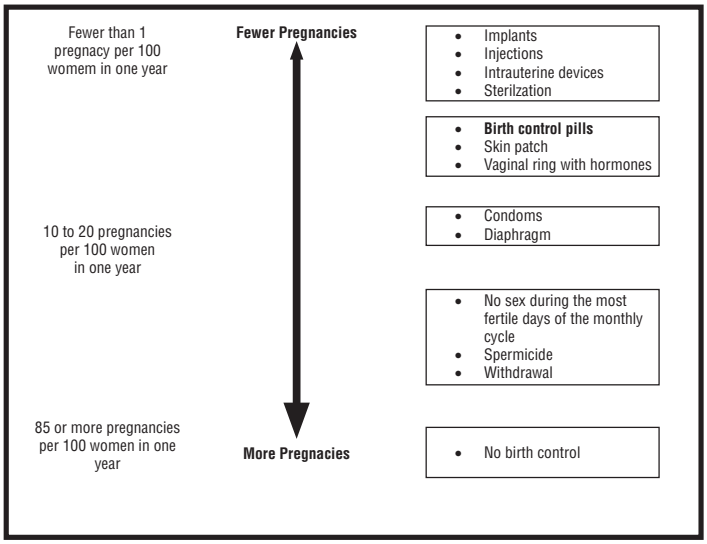
How does Tri-VyLibra Lo work for contraception?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results from the clinical study, about 3 out of 100 women may get pregnant during the first year they use Tri-VyLibra Lo.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use

birth control and are trying to get pregnant.



Who should not take Tri-VyLibra Lo?

Do not take Tri-VyLibra Lo if you:

- smoke and are over 35 years of age
- had blood clots in your arms, legs, lungs, or eyes
- had a problem with your blood that makes it clot more than normal
- have certain heart valve problems or irregular heart beat that increases your risk of having blood clots
- had a stroke
- had a heart attack
- have high blood pressure that cannot be controlled by medicine
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or any migraine headaches if you are over 35 years of age
- have liver problems, including liver tumors
- take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.
- have any unexplained vaginal bleeding
- are pregnant
- had breast cancer or any cancer that is sensitive to female hormones

If any of these conditions happen while you are taking Tri-VyLibra Lo, stop taking Tri-VyLibra Lo right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking Tri-VyLibra Lo.

What should I tell my healthcare provider before taking Tri-VyLibra Lo?

Tell your healthcare provider if you:

- are pregnant or think you may be pregnant
- are depressed now or have been depressed in the past
- had yellowing of your skin or eyes (jaundice) caused by pregnancy (cholestasis of pregnancy)
- are breastfeeding or plan to breastfeed. Tri-VyLibra Lo may decrease the amount of breast milk you make. A small amount of the hormones in Tri-VyLibra Lo may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

Tri-VyLibra Lo may affect the way other medicines work, and other medicines may affect how well Tri-VyLibra Lo works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take Tri-VyLibra Lo?

Read the Instructions for Use at the end of this Patient Information.

What are the possible serious side effects of Tri-VyLibra Lo?

- **Like pregnancy, Tri-VyLibra Lo may cause serious side effects, including blood clots in your lungs, heart attack, or a stroke that may lead to death. Some other examples of serious blood clots include blood clots in the legs or eyes.**

Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age. Serious blood clots are more likely to happen when you:

- first start taking birth control pills
- restart the same or different birth control pills after not using them for a month or more

Call your healthcare provider or go to a hospital emergency room right away if you have:

- leg pain that will not go away
- sudden severe shortness of breath
- sudden change in vision or blindness
- chest pain
- a sudden, severe headache unlike your usual headaches
- weakness or numbness in your arm or leg
- trouble speaking

Other serious side effects include:

- **liver problems, including:**
  - rare liver tumors
  - jaundice (cholestasis), especially if you previously had cholestasis of pregnancy. Call your healthcare provider if you have yellowing of your skin or eyes.
- **high blood pressure.** You should see your healthcare provider for a yearly check of your blood pressure.
- **gallbladder problems**
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood**
- **new or worsening headaches including migraine headaches**
- **irregular or unusual vaginal bleeding and spotting between your menstrual periods, especially during the first 3 months of taking Tri-VyLibra Lo.**
- **depression**
- **possible cancer in your breast and cervix**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider if you have a swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher is you have a history of angioedema.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Women who tend to get chloasma should avoid spending a long time in sunlight, tanning booths, and under sun lamps while taking Tri-VyLibra Lo. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of Tri-VyLibra Lo?

- headache (including migraine)
- nausea and vomiting
- breast problems
  - tenderness, pain and discomfort
  - enlargement and swelling
  - discharge
  - nipple pain
- stomach pain
- pain with your periods (menstrual cycle)
- mood changes, including depression
- acne
- vaginal infections
- bloating
- weight gain
- fatigue

These are not all the possible side effects of Tri-VyLibra Lo. For more information, ask your healthcare provider or pharmacist.

You may report side effects to the FDA at 1-800-FDA-1088.

What else should I know about taking Tri-VyLibra Lo?

- If you are scheduled for any lab tests, tell your healthcare provider you are taking Tri-VyLibra Lo. Certain blood tests may be affected by Tri-VyLibra Lo.
- Tri-VyLibra Lo does not protect against HIV infection (AIDS) and other sexually transmitted infections.

How should I store Tri-VyLibra Lo?

- Store Tri-VyLibra Lo at room temperature between 20°C to 25°C (68°F to 77°F).
- Keep Tri-VyLibra Lo and all medicines out of the reach of children.
- Store away from light.

General information about the safe and effective use of Tri-VyLibra Lo.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Tri-VyLibra Lo for a condition for which it was not prescribed. Do not give Tri-VyLibra Lo to other people, even if they have the same symptoms that you have.

This Patient Information summarizes the most important information about Tri-VyLibra Lo. You can ask your pharmacist or healthcare provider for information about Tri-VyLibra Lo that is written for health professionals.

For more information, call Afaxys Pharma, LLC at 855-888-2467.

Do birth control pills cause cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What if I want to become pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

What should I know about my period when taking Tri-VyLibra Lo?

Your periods may be lighter and shorter than usual. Some women may miss a period. Irregular vaginal bleeding or spotting may happen while you are taking Tri-VyLibra Lo,

especially during the first few months of use. This usually is not a serious problem. It is important to continue taking your pills on a regular schedule to prevent a pregnancy.

What are the ingredients in Tri-VyLibra Lo?

Active ingredients: Each white to off white, pale blue to bluish white, and blue to light blue pill contains norgestimate and ethinyl estradiol.

Inactive ingredients:

White to off white pills: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Pale blue to bluish white pills: croscarmellose sodium, FD&C Blue #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Blue to light blue pills: croscarmellose sodium, FD&C Blue #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Green pills: anhydrous lactose, FD&C Blue No. 2 aluminum lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, and povidone.

Instructions For Use
Tri-VyLibra Lo
(norgestimate and ethinyl estradiol tablets USP)

Important Information about taking Tri-VyLibra Lo

- Take **1** pill every day at the same time. Take the pills in the order directed on your pill blister pack.
- Do not skip your pills, even if you do not have sex often. If you miss pills (including starting the pack late) **you could get pregnant**. The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take Tri-VyLibra Lo, talk to your healthcare provider. When you first start taking Tri-VyLibra Lo, spotting or light bleeding in between your periods may occur. Contact your healthcare provider if this does not go away after a few months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking Tri-VyLibra Lo. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If your nausea does not go away, call your healthcare provider.
- Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills (see **What should I do if I miss any Tri-VyLibra Lo pills?** below), you could also feel a little sick to your stomach.
- It is not uncommon to miss a period. However, if you miss a period and have not taken Tri-VyLibra Lo according to directions, or miss **2** periods in a row, or feel like you may be pregnant, call your healthcare provider. If you have a positive pregnancy test, you should stop taking Tri-VyLibra Lo.
- If you have vomiting or diarrhea within **3 to 4** hours of taking your pill, take another pill of the same color from your extra pill blister pack. If you do not have an extra pill blister pack, take the next pill in your pill blister pack. Continue taking all your remaining pills in order. Start the first pill of your next pill blister pack the day after finishing your current pill blister pack. This will be 1 day earlier than originally scheduled. Continue on your new schedule.
- If you have vomiting or diarrhea for more than 1 day, your birth control pills may not work as well. Use an additional birth control method, like condoms and a spermicide, until you check with your healthcare provider.
- Stop taking Tri-VyLibra Lo at least **4** weeks before you have major surgery and do not restart after the surgery without asking your healthcare provider. Be sure to use other forms of contraception (like condoms and spermicide) during this time period.

Before you start taking Tri-VyLibra Lo:

- Decide what time of day you want to take your pill. It is important to take it at the same time every day and in the order as directed on your pill blister pack.
- Have backup contraception (condoms and spermicide) available and if possible, an extra full pack of pills as needed.

When should I start taking Tri-VyLibra Lo?

If you start taking Tri-VyLibra Lo and you have not used a hormonal birth control method before:

- There are 2 ways to start taking your birth control pills. You can either start on a Sunday (Sunday Start) or on the first day (Day 1) of your natural menstrual period (Day 1 Start). Your healthcare provider should tell you when to start taking your birth control pill.
- If you use the Sunday Start, use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days that you take Tri-VyLibra Lo. You do not need back-up contraception if you use the Day 1 Start.

If you start taking Tri-VyLibra Lo and you are switching from another birth control pill:

- Start your new Tri-VyLibra Lo pack on the same day that you would start the next pack of your previous birth control method.
- Do not continue taking the pills from your previous birth control pack.

If you start taking Tri-VyLibra Lo and previously used a vaginal ring or transdermal patch:

- Start using Tri-VyLibra Lo on the day you would have reapplied the next ring or patch.

If you start taking Tri-VyLibra Lo and you are switching from a progestin-only method such as an implant or injection:

- Start taking Tri-VyLibra Lo on the day of removal of your implant or on the day when you would have had your next injection.

If you start taking Tri-VyLibra Lo and you are switching from an intrauterine device or system (IUD or IUS):

- Start taking Tri-VyLibra Lo on the day of removal of your IUD or IUS.
- You do not need back-up contraception if your IUD or IUS is removed on the first day (Day 1) of your period. If your IUD or IUS is removed on any other day, use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days that you take Tri-VyLibra Lo.

Keep a calendar to track your period:
If this is the first time you are taking birth control pills, read, "**When should I start taking Tri-VyLibra Lo?**" above. Follow these instructions for either a **Sunday Start** or a **Day 1 Start**.

Sunday Start:

You will use a **Sunday Start** if your healthcare provider told you to take your first pill on a Sunday.

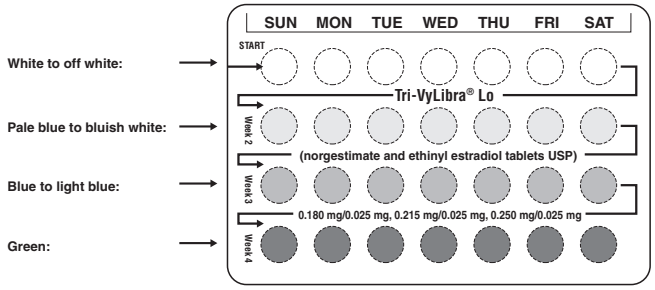
- Take pill **1** on the Sunday **after your period starts.**
- If your period starts on a Sunday, take pill "**1**" that day and refer to Day 1 Start instructions below.
- Take **1** pill every day in the order on the pill blister pack at the same time each day for **28** days.
- After taking the last pill on **Day 28** from the pill blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack (Sunday). Take the first pill in the new pack whether or not you are having your period.
- Use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days of the first cycle that you take Tri-VyLibra Lo.

Day 1 Start:
You will use a **Day 1 Start** if your doctor told you to take your first pill (Day 1) on the **first day of your period**.

- Take **1** pill every day in the order of the pill blister pack, at the same time each day, for **28** days.
- After taking the last pill on **Day 28** from the pill blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack. Take the first pill in the new pack whether or not you are having your period.

Tri-VyLibra Lo comes in Blister Pack.

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. The 28-pill pack has 21 white to off white, pale blue to bluish white, and blue to light blue "active" pills (with hormones) to take for 3 weeks. This is followed by 1 week of green "reminder" 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.



4. Be sure you have ready at all times:
   Another kind of birth control (such as condoms or spermicide) to use as a back-up method in case you miss pills.
   An extra, full pill pack.

You have a choice of which day to start taking your first pack of pills. Tri-VyLibra Lo is available in a blister pack which is preset for a Sunday Start. Day 1 Start stickers are also provided. Decide with your healthcare professional which is the best day for you. Pick a time of day that will be easy to remember.

Sunday Start:

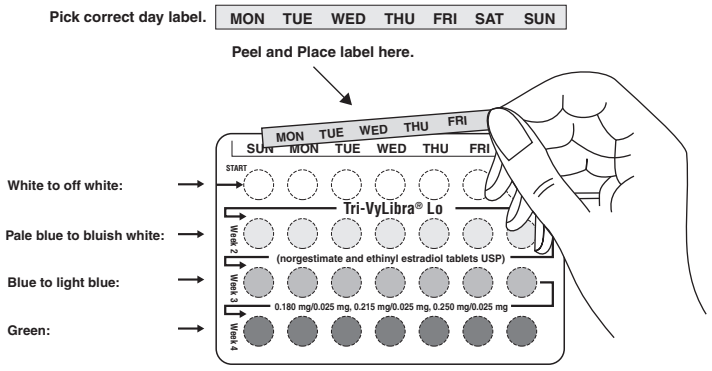
Take the first white to off white "active" pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.

Use another method of birth control (such as condoms or spermicide) as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days).

Day 1 Start:

Take the first white to off white "active" pill of the first pack during the first 24 hours of your period.

1. Pick the day label strip that starts with the first day of your period (this is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins).
2. Place this day label strip in the cycle tablet over the area that has the days of the week (starting with Sunday) imprinted in the plastic.



Note: If the first day of your period is a Sunday, you can skip steps #1 and #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 should I do if I miss any Tri-VyLibra Lo pills?

If you miss 1 pill in Weeks 1, 2, or 3, follow these steps:

- 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.
- Then continue taking **1** pill every day until you finish the pack.
- You do not need to use a back-up birth control method if you have sex.

If you miss 2 pills in Week 1 or Week 2 of your pack, follow these steps:

- Take the 2 missed pills as soon as possible and the next 2 pills the next day.
- Then continue to take **1** pill every day until you finish the pack.
- Use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7 days** after missing your pills.

If you miss 2 pills in a row in Week 3, or you miss 3 or more pills in a row during Weeks 1, 2, or 3 of the pack, follow these steps:

- **If you are a Day 1 Starter:**
  - Throw out the rest of the pill pack and start a new pack that same day.
  - 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 healthcare provider because you might be pregnant.
  - You could become pregnant if you have sex during the first 7 days after you restart your pills. You MUST use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7** days after you restart your pills.
- **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.
  - Use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7** days after you restart your pills.

If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

Revised: 01/2021

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VyLibra safely and effectively. See full prescribing information for VyLibra.

VyLibra® (norgestimate and ethinyl estradiol) tablets, for oral use
Initial U.S. Approval: 1989

WARNING: CIGARETTE SMOKING and SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

- **VyLibra is contraindicated in women over 35 years old who smoke. (4)**
- **Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. (4)**

----------RECENT MAJOR CHANGES ----------

Contraindications (4)
08/2017
Warnings and Precautions (5.3)
08/2017

----------INDICATIONS AND USAGE----------

VyLibra is estrogen/progestin COCs, indicated for use by women to prevent pregnancy. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Take one tablet daily by mouth at the same time every day. (2.2)
- Take tablets in the order directed on the blister pack. (2.2)
- Do not skip or delay tablet intake. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

VyLibra consists of 28 round, biconvex tablets in the following order (3):

- 21 dark blue, coated tablets each containing 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 green, uncoated tablets (inert)

- **----------CONTRAINDICATIONS----------**

- A high risk of arterial or venous thrombotic diseases (4)
- Liver tumors or liver disease (4)
- Undiagnosed abnormal uterine bleeding (4)
- Pregnancy (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Co-administration with Hepatitis C drug combinations containing ombitasvir/ paritaprevir/ritonavir, with or without dasabuvir (4)

----------WARNINGS AND PRECAUTIONS----------

- Thromboembolic Disorders and Other Vascular Problems: Stop VyLibra if a thrombotic event occurs. Stop at least 4 weeks before and through 2 weeks after major surgery. Start no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue VyLibra if jaundice occurs. (5.2)
- High blood pressure: If used in women with well-controlled hypertension, monitor blood pressure and stop VyLibra if blood pressure rises significantly. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking VyLibra. Consider an alternate contraceptive method for women with uncontrolled dyslipidemia. (5.6)
- Headache: Evaluate significant change in headaches and discontinue VyLibra if indicated. (5.7)
- Bleeding Irregularities and Amenorrhea: Evaluate irregular bleeding or amenorrhea. (5.8)

----------ADVERSE REACTIONS----------

The most common adverse reactions reported during clinical trials (≥2%) were: headache/ migraine, abdominal/gastrointestinal pain, vaginal infection, genital discharge, breast issues (including breast pain, discharge, and enlargement), mood disorders (including depression and mood altered), flatulence, nervousness, rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Afaxys Pharma, LLC at 1-855-888-2467 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up or alternative method of contraception when enzyme inducers are used with COCs. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

Nursing mothers: Not recommended; can decrease milk production. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING and SERIOUS CARDIOVASCULAR EVENTS

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs are contraindicated in women who are over 35 years of age and smoke *[see Contraindications (4)]*.

1 INDICATIONS AND USAGE

1.1 Oral Contraceptive

VyLibra tablets are indicated for use by females of reproductive potential to prevent pregnancy *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 How to Start VyLibra

VyLibra is available in blister pack *[see How Supplied/Storage and Handling (16)]*. VyLibra

may be started using either a Day 1 start or a Sunday start (see Table 1). For the first cycle of a Sunday Start regimen, an additional method of contraception should be used until after the first 7 consecutive days of administration.

2.2 How to Take VyLibra

Table 1: Instructions for Administration of VyLibra

Starting COCs in women not currently using hormonal contraception (Day 1 Start or Sunday Start) **Important:** Consider the possibility of ovulation and conception prior to initiation of this product. **Tablet Color:** • VyLibra active tablets are dark blue (Day 1 to Day 21). • VyLibra has green inactive tablets (Day 22 to Day 28).	**Day 1 Start:** • Take first active tablet without regard to meals on the first day of menses. • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one **green** inactive tablet daily for 7 days and at the same time of day that active tablets were taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the day after taking the last inactive tablet)
	Sunday Start: • Take first active tablet without regard to meals on the first Sunday after the onset of menses. **Due to the potential risk of becoming pregnant, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of VyLibra.** • Take subsequent active tablets once daily at the same time each day for a total of 21 days. • Take one **green** inactive tablet daily for the following 7 days and at the same time of day that active tablets were taken. • Begin each subsequent pack on the same day of the week as the first cycle pack (i.e., on the Sunday after taking the last inactive tablet) and additional non-hormonal contraceptive is not needed.
Switching to VyLibra from another oral contraceptive	Start on the same day that a new pack of the previous oral contraceptive would have started.
Switching from another contraceptive method to VyLibra	**Start VyLibra:**
• **Transdermal patch**	• On the day when next application would have been scheduled
• **Vaginal ring**	• On the day when next insertion would have been scheduled
• **Injection**	• On the day when next injection would have been scheduled
• **Intrauterine contraceptive**	• On the day of removal • If the IUD is not removed on first day of the patient's menstrual cycle, additional non-hormonal contraceptive (such as condoms and spermicide) is needed for the first seven days of the first cycle pack.
• **Implant**	• On the day of removal
Complete instructions to facilitate patient counseling on proper tablet usage are located in the FDA-Approved Patient Labeling.	

Starting VyLibra after Abortion or Miscarriage

First-trimester

- After a first-trimester abortion or miscarriage, VyLibra may be started immediately. An additional method of contraception is not needed if VyLibra is started immediately.
- If VyLibra is not started within 5 days after termination of the pregnancy, the patient should use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of her first cycle pack of VyLibra.

Second-trimester

- Do not start until 4 weeks after a second-trimester abortion or miscarriage, due to the increased risk of thromboembolic disease. Start VyLibra, following the instructions in Table 1 for Day 1 or Sunday start, as desired. If using Sunday start, use additional non-hormonal contraception (such as condoms and spermicide) for the first seven days of the patient's first cycle pack of VyLibra. *[see Contraindications (4), Warnings and Precautions (5.1), and FDA-Approved Patient Labeling.]*

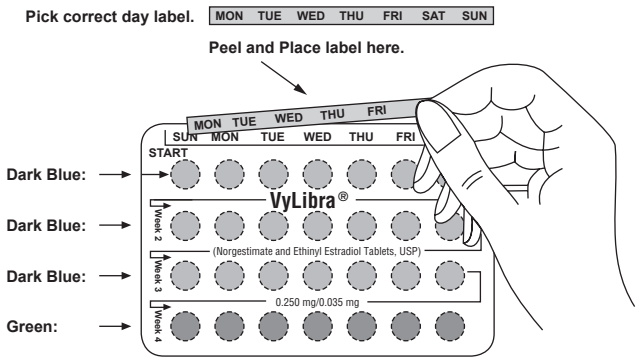
Starting VyLibra after Childbirth

- Do not start until 4 weeks after delivery, due to the increased risk of thromboembolic disease. Start contraceptive therapy with VyLibra following the instructions in Table 1 for women not currently using hormonal contraception.
- VyLibra is not recommended for use in lactating women *[see Use in Specific Populations (8.3)]*.
- If the woman has not yet had a period postpartum, consider the possibility of ovulation and conception occurring prior to use of VyLibra. *[See Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1 and 8.3), and FDA-Approved Patient Labeling]*.

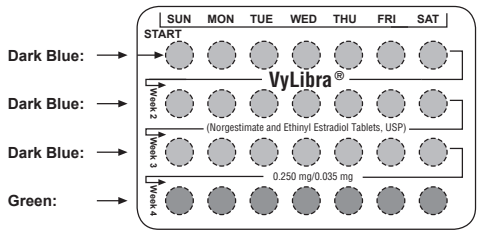
How to Use the Blister Pack:

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

1. Pick the Days of the Week Sticker that starts the first day of your period. (This is the day you begin bleeding or spotting, even if it is midnight when bleeding begins.) When you have picked the right sticker, throw away the others and place the sticker on the blister pack over the preprinted days of the week and make sure it lines up with the pills.



2. Your blister pack containing 28 individually sealed pills. Note that the pills are arranged in four numbered rows of 7 pills, with the pre-printed days of the week printed above them. There are 21 dark blue "active" pills and 7 green "reminder" pills. Refer to the sample of the blister pack below:



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

Three Ways to Remember in What Order to take the Pills

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

2.3 Missed Tablets

Table 2: Instructions for Missed VyLibra Tablets

• If one active tablet is missed in Weeks 1, 2, or 3	Take the tablet as soon as possible. Continue taking one tablet a day until the pack is finished.
• If two active tablets are missed in Week 1 or Week 2	Take the two missed tablets as soon as possible and the next two active tablets the next day. Continue taking one tablet a day until the pack is finished. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**

Table 2: Instructions for Missed VyLibra Tablets

• If two active tablets are missed in the third week or three or more active tablets are missed in a row in Weeks 1, 2, or 3	Day 1 start: Throw out the rest of the pack and start a new pack that same day. Sunday start: Continue taking one tablet a day until Sunday, then throw out the rest of the pack and start a new pack that same day. **Additional non-hormonal contraception (such as condoms and spermicide) should be used as back-up if the patient has sex within 7 days after missing tablets.**

2.4 Advice in Case of Gastrointestinal Disturbances

In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting or diarrhea occurs within 3 to 4 hours after taking an active tablet, handle this as a missed tablet *[see FDA-Approved Patient Labeling]*.

3 DOSAGE FORMS AND STRENGTHS

VyLibra tablets are available in blister packs. Each blister pack contains 28 tablets in the following order:

- 21 dark blue, round, biconvex, coated tablet debossed with "S" on one side and "22" on other side of the tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 green round, mottled biconvex, uncoated tablets (non-hormonal placebo) debossed with "S" on one side and "24" on other side of the tablet contains inert ingredients

4 CONTRAINDICATIONS

Do not prescribe VyLibra to women who are known to have the following conditions:

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
  - Smoke, if over age 35 *[see Boxed Warning and Warnings and Precautions (5.1)]*
  - Have deep vein thrombosis or pulmonary embolism, now or in the past *[see Warnings and Precautions (5.1)]*
  - Have inherited or acquired hypercoagulopathies *[see Warnings and Precautions (5.1)]*
  - Have cerebrovascular disease *[see Warnings and Precautions (5.1)]*
  - Have coronary artery disease *[see Warnings and Precautions (5.1)]*
  - Have thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation) *[see Warnings and Precautions (5.1)]*
  - Have uncontrolled hypertension *[see Warnings and Precautions (5.4)]*
  - Have diabetes mellitus with vascular disease *[see Warnings and Precautions (5.6)]*
  - Have headaches with focal neurological symptoms or migraine headaches with aura *[see Warnings and Precautions (5.7)]*
- Women over age 35 with any migraine headaches *[see Warnings and Precautions (5.7)]*
- Liver tumors, benign or malignant, or liver disease *[see Warnings and Precautions (5.2)]*
- Undiagnosed abnormal uterine bleeding *[see Warnings and Precautions (5.8)]*
- Pregnancy, because there is no reason to use COCs during pregnancy *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*
- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past *[see Warnings and Precautions (5.11)]*
- Use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to the potential for ALT elevations *[see Warnings and Precautions (5.3)]*

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Other Vascular Problems

- Stop VyLibra if an arterial thrombotic event or venous thromboembolic (VTE) event occurs.
- Stop VyLibra if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately *[see Adverse Reactions (6.2)]*.
- If feasible, stop VyLibra at least 4 weeks before and through 2 weeks after major surgery or other surgeries known to have an elevated risk of VTE as well as during and following prolonged immobilization.
- Start VyLibra no earlier than 4 weeks after delivery, in women who are not breastfeeding. The risk of postpartum VTE decreases after the third postpartum week, whereas the risk of ovulation increases after the third postpartum week.
- The use of COCs increases the risk of VTE. However, pregnancy increases the risk of VTE as much or more than the use of COCs. The risk of VTE in women using COCs is 3 to 9 cases per 10,000 woman-years. The risk of VTE is highest during the first year of use of COCs and when restarting hormonal contraception after a break of 4 weeks or longer. The risk of thromboembolic disease due to COCs gradually disappears after use is discontinued.
- Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events. COCs have been shown to increase both the relative and attributable risks of cerebrovascular events (thrombotic and hemorrhagic strokes). This risk increases with age, particularly in women over 35 years of age who smoke.
- Use COCs with caution in women with cardiovascular disease risk factors.

5.2 Liver Disease

Impaired Liver Function

Do not use VyLibra in women with liver disease, such as acute viral hepatitis or severe (decompensated) cirrhosis of liver *[see Contraindications (4)]*. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. Discontinue VyLibra if jaundice develops.

Liver Tumors

VyLibra is contraindicated in women with benign and malignant liver tumors *[see Contraindications (4)]*. Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

Studies have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) COC users. However, the risk of liver cancers in COC users is less than one case per million users.

5.3 Risk of Liver Enzyme Elevations with Concomitant Hepatitis C Treatment

During clinical trials with the Hepatitis C combination drug regimen that contains ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN), including some cases greater than 20 times the ULN, were significantly more frequent in women using ethinyl estradiol-containing medications, such as COCs. Discontinue VyLibra prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir *[see Contraindications (4)]*. VyLibra can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

5.4 High Blood Pressure

VyLibra is contraindicated in women with uncontrolled hypertension or hypertension with vascular disease *[see Contraindications (4)]*. For women with well-controlled hypertension, monitor blood pressure and stop VyLibra if blood pressure rises significantly.

An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women with extended duration of use. The incidence of hypertension increases with increasing concentrations of progestin.

5.5 Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among COC users. Use of COCs may worsen existing gallbladder disease. A past history of COC-related cholestasis predicts an increased risk with subsequent COC use. Women with a history of pregnancy-related cholestasis may be at an increased risk for COC related cholestasis.

5.6 Carbohydrate and Lipid Metabolic Effects

Carefully monitor prediabetic and diabetic women who take VyLibra. COCs may decrease glucose tolerance.

Consider alternative contraception for women with uncontrolled dyslipidemia. A small proportion of women will have adverse lipid changes while on COCs.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs.

5.7 Headache

If a woman taking VyLibra develops new headaches that are recurrent, persistent, or severe, evaluate the cause and discontinue VyLibra if indicated.

Consider discontinuation of VyLibra in the case of increased frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event).

5.8 Bleeding Irregularities and Amenorrhea

Unscheduled Bleeding and Spotting

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different contraceptive product.

In clinical trials of VyLibra, the frequency and duration of breakthrough bleeding and/or spotting was assessed in 1,647 patients (21,275 evaluable cycles). A total of 100 (7.5%) women discontinued VyLibra, at least in part, due to bleeding or spotting. Based on data from the clinical trials, 14 to 34% of women using VyLibra experienced unscheduled bleeding per cycle in the first year. The percent of women who experienced breakthrough/unscheduled bleeding tended to decrease over time.

Amenorrhea and Oligomenorrhea

Women who use VyLibra may experience amenorrhea. Some women may experience amenorrhea or oligomenorrhea after discontinuation of COCs, especially when such a condition was pre-existent.

If scheduled (withdrawal) bleeding does not occur, consider the possibility of pregnancy. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

5.9 COC 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. Studies also do not suggest a teratogenic effect, particularly in so far as cardiac anomalies and limb reduction defects are concerned, when oral contraceptives are taken inadvertently during early pregnancy. Discontinue VyLibra use if pregnancy is confirmed.

Administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy *[see Use in Specific Populations (8.1)]*.

5.10 Depression

Carefully observe women with a history of depression and discontinue VyLibra if depression recurs to a serious degree.

5.11 Carcinoma of Breast and Cervix

- VyLibra is contraindicated in women who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see Contraindications (4)]*.

  There is substantial evidence that COCs do not increase the incidence of breast cancer. Although some past studies have suggested that COCs might increase the incidence of breast cancer, more recent studies have not confirmed such findings.
- Some studies suggest that COC use has been associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors.

5.12 Effect on Binding Globulins

The estrogen component of COCs may raise the serum concentrations of thyroxine-binding globulin, sex hormone-binding globulin, and cortisol-binding globulin. The dose of replacement thyroid hormone or cortisol therapy may need to be increased.

5.13 Monitoring

A woman who is taking COCs should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.14 Hereditary Angioedema

In women with hereditary angioedema, exogenous estrogens may induce or exacerbate symptoms of angioedema.

5.15 Chloasma

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking VyLibra.

6 ADVERSE REACTIONS

The following serious adverse reactions with the use of COCs are discussed elsewhere in labeling:

- Serious cardiovascular events and stroke *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Vascular events *[see Warnings and Precautions (5.1)]*
- Liver disease *[see Warnings and Precautions (5.2)]*

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of VyLibra was evaluated in 1,647 healthy women of child-bearing potential who participated in 3 clinical trials and received at least 1 dose of VyLibra for contraception. Two trials were randomized active-controlled trials and 1 was an uncontrolled open-label trial. In all 3 trials, subjects were followed for up to 24 cycles.

Common Adverse Reactions (≥ 2% of subjects): The most common adverse reactions reported by at least 2% of the 1,647 women were the following in order of decreasing incidence: headache/migraine (32.9%), abdominal/gastrointestinal pain (7.8%), vaginal infection (8.4%), genital discharge (6.8%), breast issues (including breast pain, discharge, and enlargement) (6.3%), mood disorders (including depression and mood altered) (5.0%), flatulence (3.2%), nervousness (2.9%), and rash (2.6%).

Adverse Reactions Leading to Study Discontinuation: Over the three trials, between 11 to 21% of subjects discontinued the trial due to an adverse reaction. The most common adverse reactions (≥1%) leading to discontinuation were: metrorrhagia (6.9%), nausea/vomiting (5.0%), headache (4.1%), mood disorders (including depression and mood altered) (2.4%), premenstrual syndrome (1.7%), hypertension (1.4%), breast pain (1.4%), nervousness (1.3%), amenorrhea (1.1%), dysmenorrhea (1.1%), weight increased (1.1%), and flatulence (1.1%).

Serious Adverse Reactions: breast cancer (1 subject), mood disorders including depression, irritability, and mood swings (1 subject), myocardial infarction (1 subject), and venous thromboembolic events including pulmonary embolism (1 subject) and deep vein thrombosis (DVT) (1 subject).

6.2 Postmarketing Experience

The following additional adverse drug reactions have been reported from worldwide postmarketing experience with norgestimate/ethinyl estradiol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections and Infestations: Urinary tract infection;

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Breast cancer, benign breast neoplasm, hepatic adenoma, focal nodular hyperplasia, breast cyst;

Immune System Disorders: Hypersensitivity;

Metabolism and Nutrition Disorders: Dyslipidemia;

Psychiatric Disorders: Anxiety, insomnia;

Nervous System Disorders: Syncope, convulsion, paresthesia, dizziness;

Eye Disorders: Visual impairment, dry eye, contact lens intolerance;

Ear and Labyrinth Disorders: Vertigo;

Cardiac Disorders: Tachycardia, palpitations;

Vascular Events: Deep vein thrombosis, pulmonary embolism, retinal vascular thrombosis, hot flush;

Arterial Events: Arterial thromboembolism, myocardial infarction, cerebrovascular accident;

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea;

Gastrointestinal Disorders: Pancreatitis, abdominal distension, diarrhea, constipation;

Hepatobiliary Disorders: Hepatitis;

Skin and Subcutaneous Tissue Disorders: Angioedema, erythema nodosum, hirsutism, night sweats, hyperhidrosis, photosensitivity reaction, urticaria, pruritus, acne;

Musculoskeletal, Connective Tissue, and Bone Disorders: Muscle spasms, pain in extremity, myalgia, back pain;

Reproductive System and Breast Disorders: Ovarian cyst, suppressed lactation, vulvovaginal dryness;

General Disorders and Administration Site Conditions: Chest pain, asthenic conditions.

7 DRUG INTERACTIONS

Consult the labeling of concurrently used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

No drug-drug interaction studies were conducted with VyLibra.

7.1 Effects of Other Drugs on Combined Oral Contraceptives

Substances decreasing the plasma concentrations of COCs:

Drugs or herbal products that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of COCs and potentially diminish the effectiveness of COCs or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include phenytoin, barbiturates, carbamazepine, bosentan, felbamate, griseofulvin, oxcarbazepine, rifampicin, topiramate, rifabutin, rufinamide, aprepitant, and products containing St. John's wort. Interactions between hormonal contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative method of contraception or a back-up method when enzyme inducers are used with COCs, and to continue back-up contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.

Colesevelam: Colesevelam, a bile acid sequestrant, given together with a COC, has been shown to significantly decrease the AUC of EE. The drug interaction between the contraceptive and colesevelam was decreased when the two drug products were given 4 hours apart.

Substances increasing the plasma concentrations of COCs:

Co-administration of atorvastatin or rosuvastatin and certain COCs containing ethinyl estradiol (EE) increase AUC values for EE by approximately 20 to 25%. Ascorbic acid and acetaminophen may increase plasma EE concentrations, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole, voriconazole, fluconazole, grapefruit juice, or ketoconazole may increase plasma hormone concentrations.

Human immunodeficiency virus (HIV)/Hepatitis C virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors:

Significant changes (increase or decrease) in the plasma concentrations of estrogen and/or progestin have been noted in some cases of co-administration with HIV protease inhibitors (decrease [e.g., nelfinavir, ritonavir, darunavir/ritonavir, (fos)amprenavir/ritonavir, lopinavir/ritonavir, and tipranavir/ritonavir] or increase [e.g., indinavir and atazanavir/ritonavir])/HCV protease inhibitors (decrease [e.g., boceprevir and telaprevir]) or with non-nucleoside reverse transcriptase inhibitors (decrease [e.g., nevirapine] or increase [e.g., etravirine]).

7.2 Effects of Combined Oral Contraceptives on Other Drugs

- COCs containing EE may inhibit the metabolism of other compounds (e.g., cyclosporine, prednisolone, theophylline, tizanidine, and voriconazole) and increase their plasma concentrations.
- COCs have been shown to decrease plasma concentrations of acetaminophen, clofibric acid, morphine, salicylic acid, temazepam and lamotrigine. Significant decrease in plasma concentration of lamotrigine has been shown, likely due to induction of lamotrigine glucuronidation. This may reduce seizure control; therefore, dosage adjustments of lamotrigine may be necessary.

  Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because the serum concentration of thyroid-binding globulin increases with use of COCs.

7.3 Interference with Laboratory Tests

The use of contraceptive steroids may influence the results of certain laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins.

7.4 Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation

Do not co-administer VyLibra with HCV drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir, due to potential for ALT elevations *[see Warnings and Precautions (5.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

There is little or no increased risk of birth defects in women who inadvertently use COCs during early pregnancy. Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb reduction defects) following exposure to low dose COCs prior to conception or during early pregnancy.

Do not administer COCs to induce withdrawal bleeding as a test for pregnancy. Do not use COCs during pregnancy to treat threatened or habitual abortion.

8.3 Nursing Mothers

Advise the nursing mother to use other forms of contraception, when possible, until she has weaned her child. COCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. Small amounts of oral contraceptive steroids and/or metabolites are present in breast milk.

8.4 Pediatric Use

Safety and efficacy of VyLibra Tablets have been established in women of reproductive age. Efficacy is expected to be the same for post-pubertal adolescents under the age of 18 and for users 18 years and older. Use of this product before menarche is not indicated.

8.5 Geriatric Use

VyLibra has not been studied in postmenopausal women and are not indicated in this population.

8.6 Hepatic Impairment

The pharmacokinetics of VyLibra has not been studied in subjects with hepatic impairment. However, steroid hormones may be poorly metabolized in patients with hepatic impairment. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal and COC causation has been excluded. *[See Contraindications (4) and Warnings and Precautions (5.2).]*

8.7 Renal Impairment

The pharmacokinetics of VyLibra has not been studied in women with renal impairment.

10 OVERDOSAGE

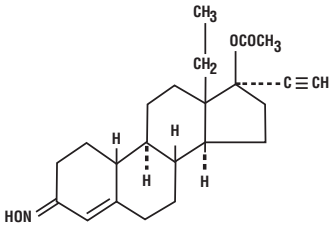
There have been no reports of serious ill effects from overdosage of oral contraceptives,

including ingestion by children. Overdosage may cause withdrawal bleeding in females and nausea.

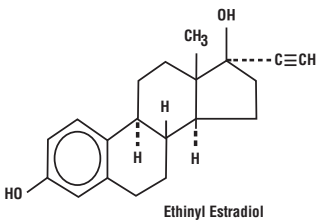
11 DESCRIPTION

VyLibra is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol. Norgestimate is designated as (18,19-Dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-, oxime,(17α)-(+)-) and ethinyl estradiol is designated as (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol).

- Each active dark blue coated tablet contains 0.250 mg of norgestimate and 0.035 mg of ethinyl estradiol. Inactive ingredients include croscarmellose sodium, FD&C #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.
- Each green placebo tablet containing only inert ingredients, as follows: Anhydrous lactose, FD&C Blue No. 2 aluminum lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, and povidone.



Norgestimate



Ethinyl Estradiol

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

- Oral Contraception

  COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted with VyLibra.

12.3 Pharmacokinetics

Absorption

Norgestimate (NGM) and EE are rapidly absorbed following oral administration. NGM is rapidly and completely metabolized by first pass (intestinal and/or hepatic) mechanisms to norelgestromin (NGMN) and norgestrel (NG), which are the major active metabolites of norgestimate.

Peak serum concentrations of NGMN and EE are generally reached by 2 hours after administration of VyLibra. Accumulation following multiple dosing of the 250 mcg NGM / 35 mcg EE dose is approximately 2-fold for NGMN and EE compared with single dose administration. The pharmacokinetics of NGMN is dose-proportional following NGM doses of 180 mcg to 250 mcg. Steady-state concentration of EE is achieved by Day 7 of each dosing cycle. Steady-state concentrations of NGMN and NG are achieved by Day 21. Non-linear accumulation (approximately 8 fold) of NG is observed as a result of high-affinity binding to SHBG, which limits its biological activity (Table 3).

Table 3: Summary of NGMN, NG and EE pharmacokinetic parameters.

Mean (SD) Pharmacokinetic Parameters of VyLibra During a Three Cycle Study						
Analyte	Cycle	Day	C_{max}	tmax (h)	AUC_{0-24h}	t1/2 (h)
NGMN	1	1	1.78 (0.397)	1.19 (0.250)	9.90 (3.25)	18.4 (5.91)
	3	21	2.19 (0.655)	1.43 (0.680)	18.1 (5.53)	24.9 (9.04)
NG	1	1	0.649 (0.49)	1.42 (0.69)	6.22 (2.46)	37.8 (14.0)
	3	21	2.65 (1.11)	1.67 (1.32)	48.2 (20.5)	45.0 (20.4)
EE	1	1	92.2 (24.5)	1.2 (0.26)	629 (138)	10.1 (1.90)
	3	21	147 (41.5)	1.13 (0.23)	1210 (294)	15 (2.36)

C_{max} = peak serum concentration, t_{max} = time to reach peak serum concentration, AUC_{0-24h} = area under serum concentration vs. time curve from 0 to 24 hours, $t_{1/2}$ = elimination half-life, NC = not calculated.
NGMN and NG: C_{max} = ng/mL, AUC_{0-24h} = h•ng/mL
EE: C_{max} = pg/mL, AUC_{0-24h} = h•pg/mL

Food Effect

The effect of food on the pharmacokinetics of VyLibra has not been studied.

Distribution

NGMN and NG are highly bound (>97%) to serum proteins. NGMN is bound to albumin and not to SHBG, while NG is bound primarily to SHBG. EE is extensively bound (>97%) to serum albumin and induces an increase in the serum concentrations of SHBG.

Metabolism

NGM is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. NGM's primary active metabolite is NGMN. Subsequent hepatic metabolism of NGMN occurs and metabolites include NG, which is also active, and various hydroxylated and conjugated metabolites. Although NGMN and its metabolites inhibit a variety of P450 enzymes in human liver microsomes, under the recommended dosing regimen, the *in vivo* concentrations of NGMN and its metabolites, even at the peak serum levels, are relatively low compared to the inhibitory constant (K_i). EE is also metabolized to various hydroxylated products and their glucuronide and sulfate conjugates.

Excretion

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See Warnings and Precautions (5.2, 5.11) and Use in Specific Populations (8.1).]

14 CLINICAL STUDIES

14.1 Contraception

In three U.S. clinical trials with VyLibra, 1,651 women aged 18 to 38 years were studied for up to 24 cycles, proving a total of 24,272 cycles of exposure. The racial demographic was about 73 to 86% Caucasian, 8 to 13% African-American, 6 to 14% Hispanic with the remainder Asian or Other (≤1%). There were no exclusions on the basis of weight; the weight range for women treated was 82 to 303 lbs, with a mean weight of about 135 lbs. The pregnancy rate was approximately 1 pregnancy per 100 women-years.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

VyLibra (norgestimate and ethinyl estradiol tablets USP 0.250 mg/0.035 mg) are available in a blister pack.

Each blister pack (28 tablets) contains in the following order:

- 21 dark blue, round, biconvex, coated tablet debossed with "S" on one side and "22" on other side of the tablet contains 0.250 mg norgestimate and 0.035 mg ethinyl estradiol
- 7 green round, mottled, biconvex, uncoated tablets, debossed with "S" on one side and "24" on other side of the tablet contains inert ingredients

The blister packs are available in the following packages:

- The Blister Packs are packaged in mono cartons

Carton of 1 Blister Pack	NDC 50102-235-11
Carton of 3 Blister Packs packaged in mono cartons	NDC 50102-235-13

16.2 Storage Conditions

- **Store at** 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
- Protect from light.
- Κεεπ ουτ οφ τηε ρεαχη οφ χηιλδρεν.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

Counsel patients about the following information:

- Cigarette smoking increases the risk of serious cardiovascular events from COC use, and that women who are over 35 years old and smoke should not use COCs *[see Boxed Warning]*.
- Increased risk of VTE compared to non-users of COCs is greatest after initially starting a COC or restarting (following a 4-week or greater pill-free interval) the same or a different COC *[see Warnings and Precautions (5.1)]*.
- VyLibra do not protect against HIV infection (AIDS) and other sexually transmitted infections.
- VyLibra is not to be used during pregnancy; if pregnancy occurs during use of VyLibra instruct the patient to stop further use *[see Warnings and Precautions (5.9)]*.
- Take one tablet daily by mouth at the same time every day. Instruct patients what to do in the event tablets are missed *[see Dosage and Administration (2.2)]*.
- Use a back-up or alternative method of contraception when enzyme inducers are used with VyLibra *[see Drug Interactions (7.1)]*.
- COCs may reduce breast milk production; this is less likely to occur if breastfeeding is well established *[see Use in Specific Populations (8.3)]*.
- Women who start COCs postpartum, and who have not yet had a period, should use an additional method of contraception until they have taken an active tablet for 7 consecutive days *[see Dosage and Administration (2.2)]*.
- Amenorrhea may occur. Consider pregnancy in the event of amenorrhea at the time of the first missed period. Rule out pregnancy in the event of amenorrhea in two or more consecutive cycles *[see Warnings and Precautions (5.8)]*.

Patient Information

VyLibra (Norgestimate and Ethinyl Estradiol Tablets USP 0.250 mg/0.035 mg)

What is the most important information I should know about VyLibra?

Do not use VyLibra if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects from hormonal birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.

What is VyLibra?

VyLibra is a birth control pill (oral contraceptive) used by women to prevent pregnancy.

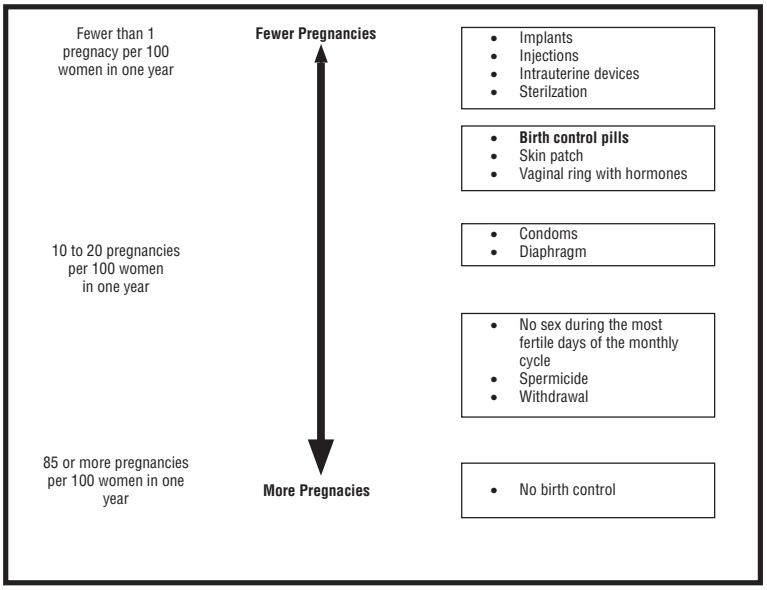
How does VyLibra work for contraception?

Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The better you follow the directions, the less chance you have of getting pregnant.

Based on the results of clinical studies, about 1 out of 100 women may get pregnant during

the first year they use VyLibra.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



Who should not take VyLibra?

Do not take VyLibra if you:

- smoke and are over 35 years of age
- had blood clots in your arms, legs, lungs, or eyes
- had a problem with your blood that makes it clot more than normal
- have certain heart valve problems or irregular heart beat that increases your risk of having blood clots
- had a stroke
- had a heart attack
- have high blood pressure that cannot be controlled by medicine
- have diabetes with kidney, eye, nerve, or blood vessel damage
- have certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision, or any migraine headaches if you are over 35 years of age
- have liver problems, including liver tumors
- take any Hepatitis C drug combination containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.
- have any unexplained vaginal bleeding
- are pregnant
- had breast cancer or any cancer that is sensitive to female hormones

If any of these conditions happen while you are taking VyLibra, stop taking VyLibra right away and talk to your healthcare provider. Use non-hormonal contraception when you stop taking VyLibra.

What should I tell my healthcare provider before taking VyLibra?

Tell your healthcare provider if you:

- are pregnant or think you may be pregnant
- are depressed now or have been depressed in the past
- had yellowing of your skin or eyes (jaundice) caused by pregnancy (cholestasis of pregnancy)
- are breastfeeding or plan to breastfeed. VyLibra may decrease the amount of breast milk you make. A small amount of the hormones in VyLibra may pass into your breast milk. Talk to your healthcare provider about the best birth control method for you while breastfeeding.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.

VyLibra may affect the way other medicines work, and other medicines may affect how well VyLibra works.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take VyLibra?

Read the Instructions for Use at the end of this Patient Information.

What are the possible serious side effects of VyLibra?

- **Like pregnancy, VyLibra may cause serious side effects, including blood clots in your lungs, heart attack, or a stroke that may lead to death. Some other examples of serious blood clots include blood clots in the legs or eyes.**

Serious blood clots can happen especially if you smoke, are obese, or are older than 35 years of age. Serious blood clots are more likely to happen when you:

- first start taking birth control pills
- restart the same or different birth control pills after not using them for a month or more

Call your healthcare provider or go to a hospital emergency room right away if you have:

- leg pain that will not go away
- sudden severe shortness of breath
- sudden change in vision or blindness
- chest pain
- a sudden, severe headache unlike your usual headaches
- weakness or numbness in your arm or leg
- trouble speaking

Other serious side effects include:

- **liver problems, including:**
  - rare liver tumors
  - jaundice (cholestasis), especially if you previously had cholestasis of pregnancy. Call your healthcare provider if you have yellowing of your skin or eyes.
- **high blood pressure.** You should see your healthcare provider for a yearly check of your blood pressure.
- **gallbladder problems**
- **changes in the sugar and fat (cholesterol and triglycerides) levels in your blood**
- **new or worsening headaches including migraine headaches**
- **irregular or unusual vaginal bleeding and spotting between your menstrual periods, especially during the first 3 months of taking VyLibra.**
- **depression**
- **possible cancer in your breast and cervix**
- **swelling of your skin especially around your mouth, eyes, and in your throat (angioedema).** Call your healthcare provider if you have a swollen face, lips, mouth tongue or throat, which may lead to difficulty swallowing or breathing. Your chance of having angioedema is higher is you have a history of angioedema.
- **dark patches of skin around your forehead, nose, cheeks and around your mouth, especially during pregnancy (chloasma).** Women who tend to get chloasma should avoid spending a long time in sunlight, tanning booths, and under sun lamps while taking VyLibra. Use sunscreen if you have to be in the sunlight.

What are the most common side effects of VyLibra?

- headache (migraine)
- breast pain or tenderness, enlargement or discharge
- stomach pain, discomfort, and gas
- vaginal infections and discharge
- mood changes, including depression
- nervousness
- changes in weight
- skin rash

These are not all the possible side effects of VyLibra. For more information, ask your healthcare provider or pharmacist.

You may report side effects to the FDA at 1-800-FDA-1088.

What else should I know about taking VyLibra?

- If you are scheduled for any lab tests, tell your healthcare provider you are taking VyLibra. Certain blood tests may be affected by VyLibra.
- VyLibra does not protect against HIV infection (AIDS) and other sexually transmitted infections.

How should I store VyLibra?

- Store VyLibra at room temperature between 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
- Keep VyLibra and all medicines out of the reach of children.
- Store away from light.

General information about the safe and effective use of VyLibra.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VyLibra for a condition for which it was not prescribed. Do not give VyLibra to other people, even if they have the same symptoms that you have.

This Patient Information summarizes the most important information about VyLibra. You can ask your pharmacist or healthcare provider for information about VyLibra that is written for health professionals.

For more information, call Afaxys Pharma, LLC at 1-855-888-2467

Do birth control pills cause cancer?

Birth control pills do not seem to cause breast cancer. However, if you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

Women who use birth control pills may have a slightly higher chance of getting cervical cancer. However, this may be due to other reasons such as having more sexual partners.

What if I want to become pregnant?

You may stop taking the pill whenever you wish. Consider a visit with your healthcare provider for a pre-pregnancy checkup before you stop taking the pill.

What should I know about my period when taking VyLibra?

Your periods may be lighter and shorter than usual. Some women may miss a period. Irregular vaginal bleeding or spotting may happen while you are taking VyLibra, especially during the first few months of use. This usually is not a serious problem. It is important to continue taking your pills on a regular schedule to prevent a pregnancy.

What are the ingredients in VyLibra?

Active ingredients: Each dark blue pill contains norgestimate and ethinyl estradiol.

Inactive ingredients:

Dark blue pills: croscarmellose sodium, FD&C #2/Indigo carmine aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide.

Green pills: Anhydrous lactose, FD&C Blue No. 2 aluminum lake, ferric oxide yellow, magnesium stearate, microcrystalline cellulose, and povidone.

Instructions For Use

VyLibra (Norgestimate and Ethinyl Estradiol Tablets USP 0.250 mg/0.035 mg)

Important Information about taking VyLibra

- Take **1** pill every day at the same time. Take the pills in the order directed on your blister pack.
- Do not skip your pills, even if you do not have sex often. If you miss pills (including starting the pack late) **you could get pregnant**. The more pills you miss, the more likely you are to get pregnant.
- If you have trouble remembering to take VyLibra, talk to your healthcare provider. When you first start taking VyLibra, spotting or light bleeding in between your periods may occur. Contact your healthcare provider if this does not go away after a few months.
- You may feel sick to your stomach (nauseous), especially during the first few months of taking VyLibra. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If your nausea does not go away, call your healthcare provider.
- Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills (see **What should I do if I miss any VyLibra pills?** below), you could also feel a little sick to your stomach.
- It is not uncommon to miss a period. However, if you miss a period and have not taken VyLibra according to directions, or miss **2** periods in a row, or feel like you may be pregnant, call your healthcare provider. If you have a positive pregnancy test, you should stop taking VyLibra.
- If you have vomiting or diarrhea within **3 to 4** hours of taking your pill, take another pill of the same color from your extra blister pack. If you do not have an extra blister pack, take the next pill in your blister pack. Continue taking all your remaining pills in order. Start the first pill of your next blister pack the day after finishing your current blister pack. This will be 1 day earlier than originally scheduled. Continue on your new schedule.
- If you have vomiting or diarrhea for more than 1 day, your birth control pills may not work as well. Use an additional birth control method, like condoms and a spermicide, until you check with your healthcare provider.
- Stop taking VyLibra at least **4** weeks before you have major surgery and do not restart after the surgery without asking your healthcare provider. Be sure to use other forms of contraception (like condoms and spermicide) during this time period.

Before you start taking VyLibra:

- Decide what time of day you want to take your pill. It is important to take it at the same time every day and in the order as directed on your blister pack.
- Have backup contraception (condoms and spermicide) available and if possible, an extra full pack of pills as needed.

When should I start taking VyLibra?

If you start taking VyLibra and you have not used a hormonal birth control method before:

- There are 2 ways to start taking your birth control pills. You can either start on a Sunday (Sunday Start) or on the first day (Day 1) of your natural menstrual period (Day 1 Start). Your healthcare provider should tell you when to start taking your birth control pill.
- If you use the Sunday Start, use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days that you take VyLibra. You do not need back-up contraception if you use the Day 1 Start.

If you start taking VyLibra and you are switching from another birth control pill:

- Start your new VyLibra pack on the same day that you would start the next pack of your previous birth control method.
- Do not continue taking the pills from your previous birth control pack.

If you start taking VyLibra and previously used a vaginal ring or transdermal patch:

- Start using VyLibra on the day you would have reapplied the next ring or patch.

If you start taking VyLibra and you are switching from a progestin-only method such as an implant or injection:

- Start taking VyLibra on the day of removal of your implant or on the day when you would have had your next injection.

If you start taking VyLibra and you are switching from an intrauterine device or system (IUD or IUS):

- Start taking VyLibra on the day of removal of your IUD or IUS.
- You do not need back-up contraception if your IUD or IUS is removed on the first day (Day 1) of your period. If your IUD or IUS is removed on any other day, use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days that you take VyLibra.

Keep a calendar to track your period:

If this is the first time you are taking birth control pills, read, "**When should I start taking VyLibra?**" above. Follow these instructions for either a **Sunday Start** or a **Day 1 Start**.

Sunday Start:

You will use a **Sunday Start** if your healthcare provider told you to take your first pill on a Sunday.

- Take pill **1** on the Sunday **after your period starts.**
- If your period starts on a Sunday, take pill "**1**" that day and refer to Day 1 Start instructions below.
- Take **1** pill every day in the order on the blister pack at the same time each day for **28** days.
- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack (Sunday). Take the first pill in the new pack whether or not you are having your period.
- Use non-hormonal back-up contraception such as condoms and spermicide for the first **7** days of the first cycle that you take VyLibra.

Day 1 Start:

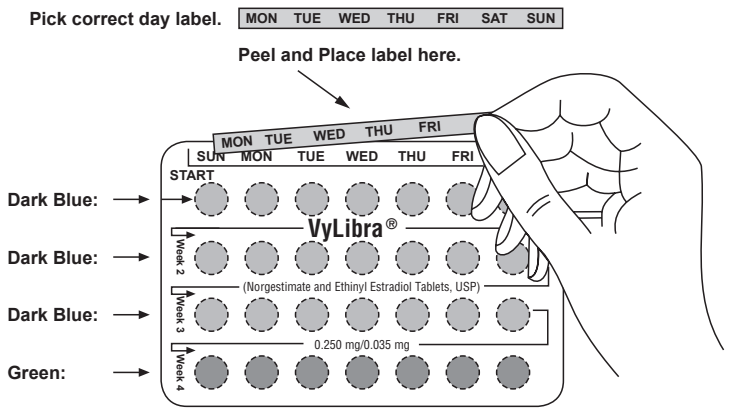
You will use a **Day 1 Start** if your doctor told you to take your first pill (Day 1) on the **first day of your period**.

- Take **1** pill every day in the order of the blister pack, at the same time each day, for **28** days.
- After taking the last pill on **Day 28** from the blister pack, start taking the first pill from a new pack, on the same day of the week as the first pack. Take the first pill in the new pack whether or not you are having your period.

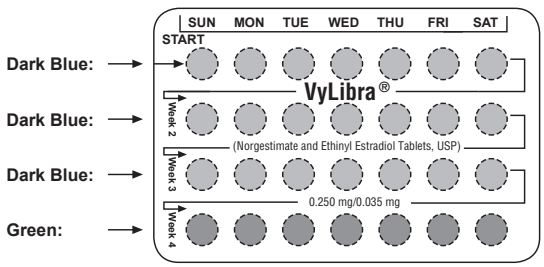
How to Use the Blister Pack:

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

1. Pick the Days of the Week Sticker that starts the first day of your period. (This is the day you begin bleeding or spotting, even if it is midnight when bleeding begins.) When you have picked the right sticker, throw away the others and place the sticker on the blister pack over the preprinted days of the week and make sure it lines up with the pills.



2. Your blister pack containing 28 individually sealed pills. Note that the pills are arranged in four numbered rows of 7 pills, with the pre-printed days of the week printed above them. There are 21 dark blue "active" pills and 7 green "reminder" pills. Refer to the sample of the blister pack below:



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

Three Ways to Remember in What Order to take the Pills

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

What should I do if I miss any VyLibra pills?

If you miss 1 pill in Weeks 1, 2, or 3, follow these steps:

- 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.

- Then continue taking **1** pill every day until you finish the pack.
- You do not need to use a back-up birth control method if you have sex.

If you miss 2 pills in Week 1 or Week 2 of your pack, follow these steps:

- Take the 2 missed pills as soon as possible and the next 2 pills the next day.
- Then continue to take **1** pill every day until you finish the pack.
- Use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7 days** after missing your pills.

If you miss 2 pills in a row in Week 3, or you miss 3 or more pills in a row during Weeks 1, 2, or 3 of the pack, follow these steps:

- **If you are a Day 1 Starter:**
  - o Throw out the rest of the pill pack and start a new pack that same day.
  - o 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 healthcare provider because you might be pregnant.
  - o You could become pregnant if you have sex during the first 7 days after you restart your pills. You MUST use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7** days after you restart your pills.
- **If you are a Sunday Starter:**
  - o 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.
  - o Use a non-hormonal birth control method (such as a condom and spermicide) as a back-up if you have sex during the first **7** days after you restart your pills.

If you have any questions or are unsure about the information in this leaflet, call your healthcare provider.

Manufactured For:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Manufactured by:
Aurobindo Pharma Limited
Unit-VII (SEZ)
Mahaboob Nagar (Dt)-509302, India

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 12/2020

PJPI0665B

HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use MEDROXYPROGESTERONE ACETATE INJECTABLE SUSPENSION safely and effectively. See full prescribing information for MEDROXYPROGESTERONE ACETATE INJECTABLE SUSPENSION.

MEDROXYPROGESTERONE ACETATE injectable suspension, for intramuscular use
Initial U.S. Approval: 1959

WARNING: LOSS OF BONE MINERAL DENSITY
***See full prescribing information for complete boxed warning*.**

- **Women who use medroxyprogesterone acetate injectable suspension may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. (5.1)**
- **It is unknown if use of medroxyprogesterone acetate injectable suspension during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. (5.1)**
- **Medroxyprogesterone acetate injectable suspension is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate. (1, 5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1) 12/2020

----------INDICATIONS AND USAGE----------

Medroxyprogesterone acetate is a progestin indicated for use by females of reproductive potential to prevent pregnancy. (1)

Limitations of Use:
The use of medroxyprogesterone acetate injectable suspension is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate. (1, 5.1)

----------DOSAGE AND ADMINISTRATION----------

The recommended dose is 150 mg of medroxyprogesterone acetate injectable suspension every 3 months (13 weeks) administered by deep, intramuscular (IM) injection in the gluteal or deltoid muscle. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

- Prefilled syringe: prefilled syringe is available packaged with 22-gauge x 1 ½ inch Terumo SurGuard® Needles. (3)

----------CONTRAINDICATIONS----------

- Known or suspected pregnancy or as a diagnostic test for pregnancy. (4)
- Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease. (4) Known or suspected malignancy of breast. (4)
- Known hypersensitivity to medroxyprogesterone acetate injectable suspension or any of its other ingredients. (4)
- Significant liver disease. (4)
- Undiagnosed vaginal bleeding. (4)

----------WARNINGS AND PRECAUTIONS----------

- Thromboembolic Disorders: Discontinue medroxyprogesterone acetate injectable suspension in patients who develop thrombosis. (5.2)
- Cancer Risks: Monitor women with a strong family history of breast cancer carefully. (5.3)
- Ectopic Pregnancy: Consider ectopic pregnancy if a woman using medroxyprogesterone acetate injectable suspension becomes pregnant or complains of severe abdominal pain. (5.4)
- Anaphylaxis and Anaphylactoid Reactions: Provide emergency medical treatment. (5.5)
- Liver Function: Discontinue medroxyprogesterone acetate injectable suspension if jaundice or disturbances of liver function develop. (5.7)
- Carbohydrate Metabolism: Monitor diabetic patients carefully. (5.12)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >5%) are: menstrual irregularities (bleeding or spotting) 57% at 12 months, 32% at 24 months, abdominal pain/discomfort 11%, weight gain > 10 lbs at 24 months 38%, dizziness 6%, headache 17%, nervousness 11%, decreased libido 6%. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Afaxys Pharma, LLC at 1-855-888-2467 or FDA at 1-800-FDA-1088 orwww.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of contraceptive drug products. Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with medroxyprogesterone acetate injectable suspension. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- *Nursing Mothers*: Detectable amounts of drug have been identified in the milk of mothers receiving medroxyprogesterone acetate injectable suspension. (8.3)
- *Pediatric Patients*: Medroxyprogesterone acetate injectable suspension is not indicated before menarche. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*** Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: LOSS OF BONE MINERAL DENSITY

- **Women who use medroxyprogesterone acetate injectable suspension may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible *[see Warnings and Precautions (5.1)]*.**
- **It is unknown if use of medroxyprogesterone acetate injectable suspension during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life *[see Warnings and Precautions (5.1)]*.**
- **Medroxyprogesterone acetate injectable suspension is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate *[see Indications and Usage (1) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

Medroxyprogesterone acetate injectable suspension is indicated for use by females of reproductive potential to prevent pregnancy.

Limitations of Use:
The use of medroxyprogesterone acetate injectable suspension is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prevention of Pregnancy

The 1 mL prefilled syringe of medroxyprogesterone acetate injectable suspension should be vigorously shaken just before use to ensure that the dose being administered represents a uniform suspension.

The recommended dose is 150 mg of medroxyprogesterone acetate injectable suspension every 3 months (13 weeks) administered by deep intramuscular (IM) injection using strict aseptic technique in the gluteal or deltoid muscle, rotating the sites with every injection. As with any IM injection, to avoid an inadvertent subcutaneous injection, body habitus should be assessed prior to each injection to determine if a longer needle is necessary particularly for gluteal IM injection.

Use for longer than 2 years is not recommended (unless other birth control methods are considered inadequate) due to the impact of long-term medroxyprogesterone acetate injectable suspension treatment on bone mineral density (BMD) *[see Warnings and Precautions (5.1)]*. Dosage does not need to be adjusted for body weight [*see Clinical Studies (14.1)]*.

To ensure the patient is not pregnant at the time of the first injection, the first injection should be given ONLY during the first 5 days of a normal menstrual period; ONLY within the first 5-days postpartum if not breast-feeding; and if exclusively breast-feeding, ONLY at the sixth postpartum week. If the time interval between injections is greater than 13 weeks, the physician should determine that the patient is not pregnant before administering the drug. The efficacy of medroxyprogesterone acetate injectable suspension depends on adherence to the dosage schedule of administration.

2.2 Switching From Other Methods of Contraception

When switching from other contraceptive methods, medroxyprogesterone acetate injectable suspension should be given in a manner that ensures continuous contraceptive coverage based upon the mechanism of action of both methods, (e.g., patients switching from oral contraceptives should have their first injection of medroxyprogesterone acetate injectable suspension on the day after the last active tablet or at the latest, on the day following the final inactive tablet).

3 DOSAGE FORMS AND STRENGTHS

Prefilled syringe is available packaged with 22-gauge x 1 1/2 inch Terumo SurGuard® Needles.

4 CONTRAINDICATIONS

The use of medroxyprogesterone acetate injectable suspension is contraindicated in the following conditions:

- Known or suspected pregnancy or as a diagnostic test for pregnancy.
- Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease *[see Warnings and Precautions (5.2)]*.
- Known or suspected malignancy of breast *[see Warnings and Precautions (5.3)]*.
- Known hypersensitivity to medroxyprogesterone acetate injectable suspension or any of its other ingredients *[see Warnings and Precautions (5.5)]*.
- Significant liver disease *[see Warnings and Precautions (5.7)]*.
- Undiagnosed vaginal bleeding *[see Warnings and Precautions (5.10)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Loss of Bone Mineral Density

Use of medroxyprogesterone acetate injectable suspension reduces serum estrogen levels and is associated with significant loss of bone mineral density (BMD). This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. It is unknown if use of medroxyprogesterone acetate injectable suspension by younger women will reduce peak bone mass and increase the risk for osteoporotic fracture in later life.

A study to assess the reversibility of loss of BMD in adolescents was conducted with medroxyprogesterone acetate injectable suspension. After discontinuing medroxyprogesterone acetate injectable suspension in these adolescents, mean BMD loss at the total hip and femoral neck did not fully recover by 5 years (60 months) post-treatment in the subgroup of adolescents who were treated for more than 2 years *[see Clinical Studies (14.3)]*. Similarly, in adults, there was only partial recovery of mean BMD at the total hip, femoral neck, and lumbar spine towards baseline by 2 years post-treatment *[See Clinical Studies (14.2)]*.

The use of medroxyprogesterone acetate injectable suspension is not recommended as a long-term (i.e., longer than 2 years) birth control method unless other options are considered inadequate. BMD should be evaluated when a woman needs to continue to use medroxyprogesterone acetate injectable suspension long-term. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity.

Other birth control methods should be considered in the risk/benefit analysis for the use of medroxyprogesterone acetate injectable suspension in women with osteoporosis risk factors. Medroxyprogesterone acetate injectable suspension can pose an additional risk in patients with risk factors for osteoporosis (e.g., metabolic bone disease, chronic alcohol and/or tobacco use, anorexia nervosa, strong family history of osteoporosis or chronic use of drugs that can reduce bone mass such as anticonvulsants or corticosteroids).

5.2 Thromboembolic Disorders

There have been reports of serious thrombotic events in women using medroxyprogesterone acetate injectable suspension (150 mg). However, medroxyprogesterone acetate injectable suspension has not been causally associated with the induction of thrombotic or thromboembolic disorders. Any patient who develops thrombosis while undergoing therapy with medroxyprogesterone acetate injectable suspension should discontinue treatment unless she has no other acceptable options for birth control.

Do not re-administer medroxyprogesterone acetate injectable suspension pending examination if there is a sudden partial or complete loss of vision or if there is a sudden onset of proptosis, diplopia, or migraine. Do not re-administer if examination reveals papilledema or retinal vascular lesions.

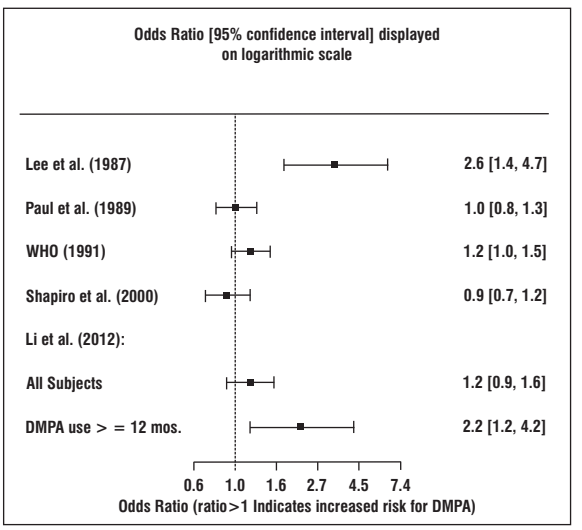
5.3 Cancer Risks

Breast Cancer

Women who have or have had a history of breast cancer should not use hormonal contraceptives, including medroxyprogesterone acetate injectable suspension, because breast cancer may be hormonally sensitive *[see Contraindications (4)]*. Women with a strong family history of breast cancer should be monitored with particular care.

The results of five large case-control studies[1,2] assessing the association between depomedroxyprogesterone acetate (DMPA) use and the risk of breast cancer are summarized in Figure 1. Three of the studies suggest a slightly increased risk of breast cancer in the overall population of users; these increased risks were statistically significant in one study. One recent US study[1] evaluated the recency and duration of use and found a statistically significantly increased risk of breast cancer in recent users (defined as last use within the past five years) who used DMPA for 12 months or longer; this is consistent with results of a previous study.

Figure 1 Risk estimates for breast cancer in DMPA users



Odds ratio estimates were adjusted for the following covariates:
Lee et al. (1987): age, parity, and socioeconomic status.
Paul et al. (1989): age, parity, ethnic group, and year of interview.
WHO (1991): age, center, and age at first live birth.
Shapiro et al. (2000): age, ethnic group, socioeconomic status, and any combined estrogen/progestogen oral contraceptive use.
Li et al. (2012): age, year, BMI, duration of OC use, number of full-term pregnancies, family history of breast cancer, and history of screening mammography.

Based on the published SEER-18 2011 incidence rate (age-adjusted to the 2000 U.S. Standard Population) of breast cancer for U.S. women, all races, age 20 to 49 years, a doubling of risk would increase the incidence of breast cancer in women who use medroxyprogesterone acetate injectable suspension from about 72 to about 144 cases per 100,000 women.

Cervical Cancer

A statistically nonsignificant increase in RR estimates of invasive squamous-cell cervical cancer has been associated with the use of medroxyprogesterone acetate injectable suspension in women who were first exposed before the age of 35 years (RR 1.22 to 1.28 and 95% CI 0.93 to 1.70). The overall, nonsignificant relative rate of invasive squamous-cell cervical cancer in women who ever used medroxyprogesterone acetate injectable suspension was estimated to be 1.11 (95% CI 0.96 to 1.29). No trends in risk with duration of use or times since initial or most recent exposure were observed.

Other Cancers

Long-term case-controlled surveillance of users of medroxyprogesterone acetate injectable suspension found no overall increased risk of ovarian or liver cancer.

5.4 Ectopic Pregnancy

Be alert to the possibility of an ectopic pregnancy among women using medroxyprogesterone acetate injectable suspension who become pregnant or complain of severe abdominal pain.

5.5 Anaphylaxis and Anaphylactoid Reaction

Anaphylaxis and anaphylactoid reaction have been reported with the use of medroxyprogesterone acetate injectable suspension. Institute emergency medical treatment if an anaphylactic reaction occurs.

5.6 Injection Site Reactions

Injection site reactions have been reported with use of medroxyprogesterone acetate injectable suspension *[see Adverse Reactions (6.2)]*. Persistent injection site reactions may occur after administration of medroxyprogesterone acetate injectable suspension due to inadvertent subcutaneous administration or release of the drug into the subcutaneous space while removing the needle *[see Dosage and Administration (2.1)]*.

5.7 Liver Function

Discontinue medroxyprogesterone acetate injectable suspension use if jaundice or acute or chronic disturbances of liver function develop. Do not resume use until markers of liver function return to normal and medroxyprogesterone acetate injectable suspension causation has been excluded.

5.8 Convulsions
There have been a few reported cases of convulsions in patients who were treated with medroxyprogesterone acetate injectable suspension. Association with drug use or pre-existing conditions is not clear.

5.9 Depression
Monitor patients who have a history of depression and do not readminister medroxyprogesterone acetate injectable suspension if depression recurs.

5.10 Bleeding Irregularities
Most women using medroxyprogesterone acetate injectable suspension experience disruption of menstrual bleeding patterns. Altered menstrual bleeding patterns include amenorrhea, irregular or unpredictable bleeding or spotting, prolonged spotting or bleeding, and heavy bleeding. Rule out the possibility of organic pathology if abnormal bleeding persists or is severe, and institute appropriate treatment.

As women continue using medroxyprogesterone acetate injectable suspension, fewer experience irregular bleeding and more experience amenorrhea. In clinical studies of medroxyprogesterone acetate injectable suspension, by month 12 amenorrhea was reported by 55% of women, and by month 24, amenorrhea was reported by 68% of women using medroxyprogesterone acetate injectable suspension.

5.11 Weight Gain
Women tend to gain weight while on therapy with medroxyprogesterone acetate injectable suspension. From an initial average body weight of 136 lb, women who completed 1 year of therapy with medroxyprogesterone acetate injectable suspension gained an average of 5.4 lb. Women who completed 2 years of therapy gained an average of 8.1 lb. Women who completed 4 years gained an average of 13.8 lb. Women who completed 6 years gained an average of 16.5 lb. Two percent of women withdrew from a large-scale clinical trial because of excessive weight gain.

5.12 Carbohydrate Metabolism
A decrease in glucose tolerance has been observed in some patients on medroxyprogesterone acetate injectable suspension treatment. Monitor diabetic patients carefully while receiving medroxyprogesterone acetate injectable suspension.

5.13 Lactation
Detectable amounts of drug have been identified in the milk of mothers receiving medroxyprogesterone acetate injectable suspension. In nursing mothers treated with medroxyprogesterone acetate injectable suspension, milk composition, quality, and amount are not adversely affected. Neonates and infants exposed to medroxyprogesterone from breast milk have been studied for developmental and behavioral effects through puberty. No adverse effects have been noted.

5.14 Fluid Retention
Because progestational drugs including medroxyprogesterone acetate injectable suspension may cause some degree of fluid retention, monitor patients with conditions that might be influenced by this condition, such as epilepsy, migraine, asthma, and cardiac or renal dysfunction.

5.15 Return of Fertility
Return to ovulation and fertility is likely to be delayed after stopping medroxyprogesterone acetate injectable suspension. In a large U.S. study of women who discontinued use of medroxyprogesterone acetate injectable suspension to become pregnant, data are available for 61% of them. Of the 188 women who discontinued the study to become pregnant, 114 became pregnant. Based on Life-Table analysis of these data, it is expected that 68% of women who do become pregnant may conceive within 12 months, 83% may conceive within 15 months, and 93% may conceive within 18 months from the last injection. The median time to conception for those who do conceive is 10 months following the last injection with a range of 4 to 31 months, and is unrelated to the duration of use. No data are available for 39% of the patients who discontinued medroxyprogesterone acetate injectable suspension to become pregnant and who were lost to follow-up or changed their mind.

5.16 Sexually Transmitted Diseases
Patients should be counseled that medroxyprogesterone acetate injectable suspension does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

5.17 Pregnancy
Although medroxyprogesterone acetate injectable suspension should not be used during pregnancy, there appears to be little or no increased risk of birth defects in women who have inadvertently been exposed to medroxyprogesterone acetate injections in early pregnancy. Neonates exposed to medroxyprogesterone acetate in-utero and followed to adolescence showed no evidence of any adverse effects on their health including their physical, intellectual, sexual or social development.

5.18 Monitoring
A woman who is taking hormonal contraceptive should have a yearly visit with her healthcare provider for a blood pressure check and for other indicated healthcare.

5.19 Interference With Laboratory Tests
The use of medroxyprogesterone acetate injectable suspension may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. *[See Drug Interactions (7.2).]*

6 ADVERSE REACTIONS
The following important adverse reactions observed with the use of medroxyprogesterone acetate injectable suspension are discussed in greater detail in the *Warnings and Precautions* section (5):
- Loss of Bone Mineral Density *[see Warnings and Precautions (5.1)]*
- Thromboembolic disease *[see Warnings and Precautions (5.2)]*
- Breast Cancer *[see Warnings and Precautions (5.3)]*
- Anaphylaxis and Anaphylactoid Reactions *[see Warnings and Precautions (5.5)]*
- Bleeding Irregularities *[see Warnings and Precautions (5.10)]*
- Weight Gain *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the two clinical trials with medroxyprogesterone acetate injectable suspension, over 3,900 women, who were treated for up to 7 years, reported the following adverse reactions, which may or may not be related to the use of medroxyprogesterone acetate injectable suspension. The population studied ranges in age from 15 to 51 years, of which 46% were White, 50% Non-White, and 4.9% Unknown race. The patients received 150 mg medroxyprogesterone acetate injectable suspension every 3-months (90 days). The median study duration was 13 months with a range of 1 to 84 months. Fifty eight percent of patients remained in the study after 13 months and 34% after 24 months.

Table 1 Adverse Reactions that Were Reported by More than 5% of Subjects

Body System*	Adverse Reactions [Incidence (%)]
Body as a Whole	Headache (16.5%) Abdominal pain/discomfort (11.2%)
Metabolic/Nutritional	Increased weight> 10lbs at 24 months (37.7%)
Nervous	Nervousness (10.8%) Dizziness (5.6%) Libido decreased (5.5%)
Urogenital	Menstrual irregularities: (bleeding (57.3% at 12 months, 32.1% at 24 months) amenorrhea (55% at 12 months, 68% at 24 months)

* Body System represented from COSTART medical dictionary.

Table 2 Adverse Reactions that Were Reported by between 1 and 5% of Subjects

Body System*	Adverse Reactions [Incidence (%)]
Body as a Whole	Asthenia/fatigue (4.2%) Backache (2.2%) Dysmenorrhea (1.7%) Hot flashes (1.0%)
Digestive	Nausea (3.3%) Bloating (2.3%)
Metabolic/Nutritional	Edema (2.2%)
Musculoskeletal	Leg cramps (3.7%) Arthralgia (1.0%)
Nervous	Depression (1.5%) Insomnia (1.0%)
Skin and Appendages	Acne (1.2%) No hair growth/alopecia (1.1%) Rash (1.1%)
Urogenital	Leukorrhea (2.9%) Breast pain (2.8%) Vaginitis (1.2%)

* Body System represented from COSTART medical dictionary.

Adverse reactions leading to study discontinuation in ⩾ 2% of subjects: bleeding (8.2%), amenorrhea (2.1%), weight gain (2.0%)

6.2 Postmarketing Experience
The following adverse reactions have been identified during post approval use of medroxyprogesterone acetate injectable suspension. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

There have been cases of osteoporosis including osteoporotic fractures reported post-marketing in patients taking medroxyprogesterone acetate injectable suspension.

Table 3 Adverse Reactions Reported during Post-Marketing Experience

Body System[1]	Adverse Reactions
Body as a Whole	Chest pain, Allergic reactions including angioedema, Fever, Injection site abscess[2], Injection site infection[2], Injection site nodule/lump, Injection site pain/tenderness, Injection site persistent atrophy/indentation/dimpling, Injection-site reaction, Lipodystrophy acquired, Chills, Axillary swelling
Cardiovascular	Syncope, Tachycardia, Thrombophlebitis, Deep vein thrombosis, Pulmonary embolus, Varicose veins
Digestive	Changes in appetite, Gastrointestinal disturbances, Jaundice, Excessive thirst, Rectal bleeding
Hematologic and Lymphatic	Anemia, Blood dyscrasia
Musculoskeletal	Osteoporosis
Neoplasms	Cervical cancer, Breast cancer
Nervous	Paralysis, Facial palsy, Paresthesia, Drowsiness
Respiratory	Dyspnea and asthma, Hoarseness
Skin and Appendages	Hirsutism, Excessive sweating and body odor, Dry skin, Scleroderma
Urogenital	Lack of return to fertility, Unexpected pregnancy, Prevention of lactation, Changes in breast size, Breast lumps or nipple bleeding, Galactorrhea, Melasma, Chloasma, Increased libido, Uterine hyperplasia, Genitourinary infections, Vaginal cysts, Dyspareunia

[1] Body System represented from COSTART medical dictionary.
[2] Injection site abscess and injection site infections have been reported; therefore strict aseptic injection technique should be followed when administering medroxyprogesterone acetate injectable suspension in order to avoid injection site infections *[see Dosage and Administration (2.1)]*.

7 DRUG INTERACTIONS

7.1 Changes in Contraceptive Effectiveness Associated With Co-Administration of Other Products
If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:
- barbiturates
- bosentan
- carbamazepine

- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors: Significant changes (increase or decrease) in the plasma levels of progestin have been noted in some cases of coadministration of HIV protease inhibitors. Significant changes (increase or decrease) in the plasma levels of the progestin have been noted in some cases of co-administration with non-nucleoside reverse transcriptase inhibitors.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Consult the labeling of all concurrently used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations.

7.2 Laboratory Test Interactions
The pathologist should be advised of progestin therapy when relevant specimens are submitted.

The following laboratory tests may be affected by progestins including medroxyprogesterone acetate injectable suspension:
(a) Plasma and urinary steroid levels are decreased (e.g., progesterone, estradiol, pregnanediol, testosterone, cortisol).
(b) Gonadotropin levels are decreased.
(c) Sex-hormone-binding-globulin concentrations are decreased.
(d) Protein-bound iodine and butanol extractable protein-bound iodine may increase. T3-uptake values may decrease.
(e) Coagulation test values for prothrombin (Factor II), and Factors VII, VIII, IX, and X may increase.
(f) Sulfobromophthalein and other liver function test values may be increased.
(g) The effects of medroxyprogesterone acetate on lipid metabolism are inconsistent. Both increases and decreases in total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol have been observed in studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Medroxyprogesterone acetate injectable suspension should not be administered during pregnancy. [*See Contraindications and Warnings and Precautions (5.17).]*

8.3 Nursing Mothers
Detectable amounts of drug have been identified in the milk of mothers receiving medroxyprogesterone acetate injectable suspension. [*See Warnings and Precautions (5.13)*.]

8.4 Pediatric Use
Medroxyprogesterone acetate injectable suspension is not indicated before menarche. Use of medroxyprogesterone acetate injectable suspension is associated with significant loss of BMD. This loss of BMD is of particular concern during adolescence and early adulthood, a critical period of bone accretion. In adolescents, interpretation of BMD results should take into account patient age and skeletal maturity. It is unknown if use of medroxyprogesterone acetate injectable suspension by younger women will reduce peak bone mass and increase the risk of osteoporotic fractures in later life. Other than concerns about loss of BMD, the safety and effectiveness are expected to be the same for postmenarchal adolescents and adult women.

8.5 Geriatric Use
This product has not been studied in post-menopausal women and is not indicated in this population.

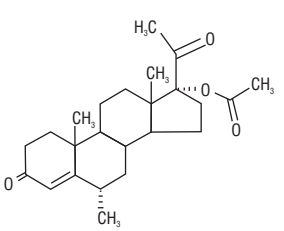
8.6 Renal Impairment
The effect of renal impairment on medroxyprogesterone acetate injectable suspension pharmacokinetics has not been studied.

8.7 Hepatic Impairment
The effect of hepatic impairment on medroxyprogesterone acetate injectable suspension pharmacokinetics has not been studied. Medroxyprogesterone acetate injectable suspension should not be used by women with significant liver disease and should be discontinued if jaundice or disturbances of liver function occur. [*See Contraindications (4) and Warnings and Precautions (5.7)*.]

11 DESCRIPTION
Medroxyprogesterone acetate injectable suspension, USP, a contraceptive injection, contains medroxyprogesterone acetate, USP a derivative of progesterone, as its active ingredient. Medroxyprogesterone acetate is active by the parenteral and oral routes of administration. It is a white or almost white, crystalline powder that is stable in air and that melts between 205°C and 209°C. It is freely soluble in chloroform, soluble in acetone and dioxane, sparingly soluble in alcohol and methanol, slightly soluble in ether, and insoluble in water.

The chemical name for medroxyprogesterone acetate is pregn-4-ene-3, 20-dione, 17-(acetyloxy)-6-methyl-, (6α-).

The structural formula is as follows:



Medroxyprogesterone acetate injectable suspension, USP for IM injection is available in prefilled syringe containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL.

For Medroxyprogesterone acetate injectable suspension prefilled syringe, each mL of sterile aqueous suspension contains:

Medroxyprogesterone acetate	150 mg
Polyethylene glycol 3350	28.90 mg
Polysorbate 80	2.41 mg
Sodium chloride	8.68 mg
Methylparaben	1.37 mg
Propylparaben	0.15 mg
Water for injection	quantity sufficient

When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Medroxyprogesterone acetate injectable suspension, inhibits the secretion of gonadotropins which primarily prevents follicular maturation and ovulation and causes thickening of cervical mucus. These actions contribute to its contraceptive effect.

12.2 Pharmacodynamics
No specific pharmacodynamic studies were conducted with medroxyprogesterone acetate injectable suspension.

12.3 Pharmacokinetics
Absorption
Following a single 150 mg IM dose of medroxyprogesterone acetate injectable suspension in eight women between the ages of 28 and 36 years old, medroxyprogesterone acetate concentrations, measured by an extracted radioimmunoassay procedure, increase for approximately 3 weeks to reach peak plasma concentrations of 1 to 7 ng/mL.

Distribution
Plasma protein binding of MPA averages 86%. MPA binding occurs primarily to serum albumin. No binding of MPA occurs with sex-hormone-binding globulin (SHBG).

Metabolism
MPA is extensively metabolized in the liver by P450 enzymes. Its metabolism primarily involves ring A and/or side-chain reduction, loss of the acetyl group, hydroxylation in the 2-, 6-, and 21-positions or a combination of these positions, resulting in more than 10 metabolites.

Excretion
The concentrations of medroxyprogesterone acetate decrease exponentially until they become undetectable (<100 pg/mL) between 120 to 200 days following injection. Using an unextracted radioimmunoassay procedure for the assay of medroxyprogesterone acetate in serum, the apparent half-life for medroxyprogesterone acetate following IM administration of medroxyprogesterone acetate injectable suspension is approximately 50 days. Most medroxyprogesterone acetate metabolites are excreted in the urine as glucuronide conjugates with only minor amounts excreted as sulfates.

Specific Populations
The effect of hepatic and/or renal impairment on the pharmacokinetics of medroxyprogesterone acetate injectable suspension is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
[See Warnings and Precautions, (5.3, 5.15, and 5.17).]

14 CLINICAL STUDIES

14.1 Contraception
In five clinical studies using medroxyprogesterone acetate injectable suspension, the 12-month failure rate for the group of women treated with medroxyprogesterone acetate injectable suspension was zero (no pregnancies reported) to 0.7 by Life-Table method. The effectiveness of medroxyprogesterone acetate injectable suspension is dependent on the patient returning every 3 months (13 weeks) for reinjection.

14.2 Bone Mineral Density Changes in Adult Women Treated with Medroxyprogesterone Acetate Injectable Suspension
In a controlled, clinical study, adult women using medroxyprogesterone acetate injectable suspension (150 mg) for up to 5 years showed spine and hip bone mineral density (BMD) mean decreases of 5 to 6%, compared to no significant change in BMD in the control group. The decline in BMD was more pronounced during the first two years of use, with smaller declines in subsequent years. Mean changes in lumbar spine BMD of -2.86%, -4.11%, -4.89%, -4.93% and -5.38% after 1, 2, 3, 4, and 5 years, respectively, were observed. Mean decreases in BMD of the total hip and femoral neck were similar.

After stopping use of medroxyprogesterone acetate injectable suspension, there was partial recovery of BMD toward baseline values during the 2-year post-therapy period. Longer duration of treatment was associated with less complete recovery during this 2-year period following the last injection. Table 4 shows the change in BMD in women after 5 years of treatment with medroxyprogesterone acetate injectable suspension and in women in a control group, as well as the extent of recovery of BMD for the subset of the women for whom 2-year post treatment data were available.

Table 4. Mean Percent Change from Baseline in BMD in Adults by Skeletal Site and Cohort (5 Years of Treatment and 2 Years of Follow-Up)

Time in Study	Spine		Total Hip		Femoral Neck	
	Medroxyprogesterone Acetate Injectable Suspension*	Control**	Medroxyprogesterone Acetate Injectable Suspension*	Control**	Medroxyprogesterone Acetate Injectable Suspension*	Control**
5 years	-5.38% n=33	0.43% n=105	-5.16% n=21	0.19% n=65	-6.12% n=34	-0.27% n=106
7 years	-3.13% n=12	0.53% n=60	-1.34% n=7	0.94% n=39	-5.38% n=13	-0.11% n=63

* The treatment group consisted of women who received medroxyprogesterone acetate injectable suspension for 5 years and were then followed for 2 years post-use (total time in study of 7 years).
** The control group consisted of women who did not use hormonal contraception and were followed for 7 years.

14.3 Bone Mineral Density Changes in Adolescent Females (12 to 18 Years of Age) Treated with Medroxyprogesterone Acetate Injectable Suspension

The impact of medroxyprogesterone acetate injectable suspension (150 mg) use for up to 240 weeks (4.6 years) was evaluated in an open-label non-randomized clinical study in 389 adolescent females (12 to 18 years of age). Use of medroxyprogesterone acetate injectable suspension was associated with a significant decline from baseline in BMD.

Partway through the trial, drug administration was stopped (at 120 weeks). The mean number of injections per medroxyprogesterone acetate injectable suspension user was 9.3. Table 5 summarizes the study findings. The decline in BMD at total hip and femoral neck was greater with longer duration of use. The mean decrease in BMD at 240 weeks was more pronounced at total hip (-6.4%) and femoral neck (-5.4%) compared to lumbar spine (-2.1%).

Adolescents in the untreated cohort had an increase in BMD during the period of growth following menarche. However, the two cohorts were not matched at baseline for age, gynecologic age, race, BMD and other factors that influence the rate of acquisition of BMD.

Table 5. BMD Mean Percent Change from Baseline in Adolescents Receiving ⩾ 4 Injections per 60-week Period, by Skeletal Site and Cohort

Duration of Treatment	Medroxyprogesterone Acetate Injectable Suspension (150 mg IM)		Unmatched, Untreated Cohort	
	N	Mean % Change	N	Mean % Change
Total Hip BMD Week 60 (1.2 years) Week 120 (2.3 years) Week 240 (4.6 years)	 113 73 28	 -2.75 -5.40 -6.40	 166 109 84	 1.22 2.19 1.71
Femoral Neck BMD Week 60 Week 120 Week 240	 113 73 28	 -2.96 -5.30 -5.40	 166 108 84	 1.75 2.83 1.94
Lumbar Spine BMD Week 60 Week 120 Week 240	 114 73 27	 -2.47 -2.74 -2.11	 167 109 84	 3.39 5.28 6.40

BMD Recovery Post-Treatment in Adolescents

Longer duration of treatment and smoking were associated with less recovery of BMD following the last injection of medroxyprogesterone acetate injectable suspension. Table 6 shows the extent of recovery of BMD up to 60 months post-treatment for adolescents who received medroxyprogesterone acetate injectable suspension for two years or less compared to more than two years. Post-treatment follow-up showed that, in women treated for more than two years, only lumbar spine BMD recovered to baseline levels after treatment was discontinued. Adolescents treated with medroxyprogesterone acetate injectable suspension for more than two years did not recover to their baseline BMD level at femoral neck and total hip even up to 60 months post-treatment. Adolescents in the untreated cohort gained BMD throughout the trial period (data not shown) *[see Warnings and Precautions (5.1)]*.

Table 6: BMD Recovery (Months Post-Treatment) in Adolescents by Years of Medroxyprogesterone Acetate Injectable Suspension Use (2 Years or Less vs. More than 2 Years)

Duration of Treatment	2 years or less		More than 2 years	
	N	Mean % Change from baseline	N	Mean % Change from baseline
Total Hip BMD				
End of Treatment	49	-1.5%	49	-6.2%
12 M post-treatment	33	-1.4%	24	-4.6%
24 M post-treatment	18	0.3%	17	-3.6%
36 M post-treatment	12	2.1%	11	-4.6%
48 M post-treatment	10	1.3%	9	-2.5%
60 M post-treatment	3	0.2%	2	-1.0%
Femoral Neck BMD				
End of Treatment	49	-1.6%	49	-5.8%
12 M post-treatment	33	-1.4%	24	-4.3%
24 M post-treatment	18	0.5%	17	-3.8%
36 M post-treatment	12	1.2%	11	-3.8%
48 M post-treatment	10	2.0%	9	-1.7%
60 M post-treatment	3	1.0%	2	-1.9%
Lumbar Spine BMD				
End of Treatment	49	-0.9%	49	-3.5%
12 M post-treatment	33	0.4%	23	-1.1%
24 M post-treatment	18	2.6%	17	1.9%
36 M post-treatment	12	2.4%	11	0.6%
48 M post-treatment	10	6.5%	9	3.5%
60 M post-treatment	3	6.2%	2	5.7%

14.4 Bone Fracture Incidence in Women Treated with Medroxyprogesterone Acetate Injectable Suspension

A retrospective cohort study to assess the association between medroxyprogesterone acetate injectable suspension and the incidence of bone fractures was conducted in 312,395 female contraceptive users in the U.K. The incidence rates of fracture were compared between medroxyprogesterone acetate injectable suspension users and contraceptive users who had no recorded use of medroxyprogesterone acetate injectable suspension . The Incident Rate Ratio (IRR) for any fracture during the follow-up period (mean = 5.5 years) was 1.41 (95% CI 1.35, 1.47). It is not known if this is due to medroxyprogesterone acetate injectable suspension use or to other related lifestyle factors that have a bearing on fracture rate.

In the study, when cumulative exposure to medroxyprogesterone acetate injectable suspension was calculated, the fracture rate in users who received fewer than 8 injections was higher than that in women who received 8 or more injections. However, it is not clear that cumulative exposure, which may include periods of intermittent use separated by periods of non-use, is a useful measure of risk, as compared to exposure measures based on continuous use.

There were very few osteoporotic fractures (fracture sites known to be related to low BMD) in the study overall, and the incidence of osteoporotic fractures was not found to be higher in medroxyprogesterone acetate injectable suspension users compared to non-users. Importantly, this study could not determine whether use of medroxyprogesterone acetate injectable suspension has an effect on fracture rate later in life.

15 REFERENCES

1. Li CI, Beaber EF, Tang, MCT et al. Effect of Depo-Medroxyprogesterone Acetate on Breast Cancer Risk among Women 20 to 44 years of Age. Cancer Research 2012;72:2028-2035.
2. Paul C, Skegg DCG, Spears GFS. Depot medroxyprogesterone (Depo-Provera) and risk of breast cancer. Br Med J 1989; 299:759-62.

16 HOW SUPPLIED/STORAGE AND HANDLING

Medroxyprogesterone acetate injectable suspension, USP is supplied as follows:

Package Configuration	Strength	NDC
Medroxyprogesterone acetate injectable suspension, USP, 150 mg/mL, 1 mL Prefilled Syringe packed with 22 gauge x 1 1/2 inch Terumo SurGuard® Needles		
1 mL prefilled syringe	150 mg/mL	NDC 50102-591-40

Stored at controlled room temperature 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

"See FDA-approved patient labeling (Patient Information)."

- Advise patients at the beginning of treatment that their menstrual cycle may be disrupted and that irregular and unpredictable bleeding or spotting results, and that this usually decreases to the point of amenorrhea as treatment with medroxyprogesterone acetate injectable suspension continues, without other therapy being required.
- Counsel patients about the possible increased risk of breast cancer in women who use medroxyprogesterone acetate injectable suspension [*see Warnings and Precautions (5.3)]*.
- Counsel patients that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.
- Counsel patients on Warnings and Precautions associated with use of medroxyprogesterone acetate injectable suspension.
- Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with medroxyprogesterone acetate injectable suspension.

Patient Information

Medroxyprogesterone Acetate (med ROX ee proe JES ter one AS e tate) Injectable Suspension, USP

Read this Patient Information carefully before you decide if medroxyprogesterone acetate injectable suspension is right for you. This information does not take the place of talking with your gynecologist or other healthcare provider who specializes in women's health. If you have any questions about medroxyprogesterone acetate injectable suspension, ask your healthcare provider. You should also learn about other birth control methods to choose the one that is best for you.

What is the most important information I should know about medroxyprogesterone acetate injectable suspension?

Medroxyprogesterone acetate injectable suspension can cause serious side effects, including:

- **Use of medroxyprogesterone acetate injectable suspension may cause you to lose calcium stored in your bone and decrease your bone mass. The longer you use medroxyprogesterone acetate injectable suspension, the greater your loss of calcium from your bones. Your bones may not recover completely when you stop using medroxyprogesterone acetate injectable suspension.**
- **If you use medroxyprogesterone acetate injectable suspension continuously for a long time (for more than 2 years), it may increase the risk of weak, porous bones (osteoporosis) that could increase the risk of broken bones, especially after menopause.**
- **You should not use medroxyprogesterone acetate injectable suspension for more than two years unless you cannot use other birth control methods.**
- **It is not known if your risk of developing osteoporosis is greater if you are a teenager or young adult when you start to use medroxyprogesterone acetate injectable suspension (see "What are the possible side effects of medroxyprogesterone acetate injectable suspension?").**

Medroxyprogesterone acetate injectable suspension is intended to prevent pregnancy. Medroxyprogesterone acetate injectable suspension does not protect against HIV infection (AIDS) and other sexually transmitted diseases (STDs).

What is medroxyprogesterone acetate injectable suspension?

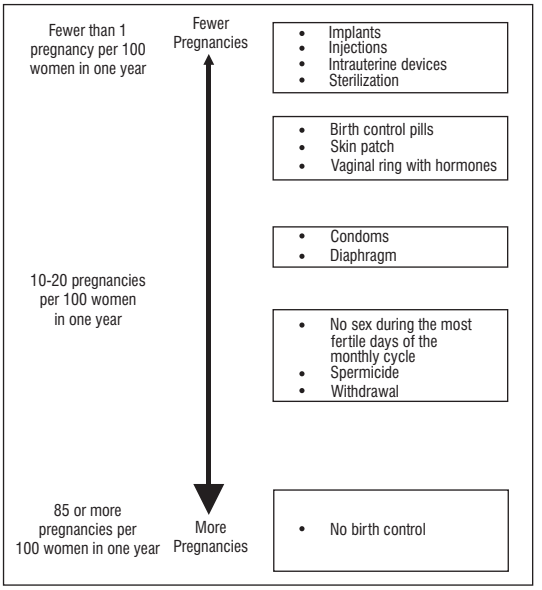
Medroxyprogesterone acetate injectable suspension is a progestin hormone birth control method that is given by injection (a shot) to prevent pregnancy.

How well does medroxyprogesterone acetate injectable suspension work?

Your chance of getting pregnant depends on how well you follow the directions for taking your medroxyprogesterone acetate injectable suspension. The more carefully you follow the directions (such as returning every 3 months for your next injection), the less chance you have of getting pregnant.

In clinical studies, about 1 out of 100 women got pregnant during the first year that they used medroxyprogesterone acetate injectable suspension.

The following chart shows the chance of getting pregnant for women who use different methods of birth control. Each box on the chart contains a list of birth control methods that are similar in effectiveness. The most effective methods are at the top of the chart. The box on the bottom of the chart shows the chance of getting pregnant for women who do not use birth control and are trying to get pregnant.



How should I take medroxyprogesterone acetate injectable suspension?

- Medroxyprogesterone acetate injectable suspension is given by your healthcare provider as a shot into your muscle (intramuscular injection). The shot is given in your buttock or upper arm 1 time every 3 months. At the end of the 3 months, you will need to return to your healthcare provider for your next injection in order to continue your protection against pregnancy.
- **To make sure that you are not pregnant before you take medroxyprogesterone acetate injectable suspension, the first injection should be given only:**
  - during the first 5 days of a normal menstrual period, or
  - within the first 5 days after giving birth, **if you are not breastfeeding**, or
  - at the 6th week after giving birth, **if you are feeding your baby only breastmilk.**
- Medroxyprogesterone acetate injectable suspension may be given at other times than those listed above, but you will likely need to have a pregnancy test first to show that you are not pregnant.
- During treatment with medroxyprogesterone acetate injectable suspension, you should see your healthcare provider every year for a blood pressure check and other healthcare needs.

Who should not use medroxyprogesterone acetate injectable suspension?

Do not use medroxyprogesterone acetate injectable suspension if you:

- are pregnant or think you might be pregnant
- have bleeding from your vagina that has not been explained
- have breast cancer now or in the past, or think you have breast cancer
- have had a stroke
- ever had blood clots in your arms, legs or lungs
- have problems with your liver or liver disease
- are allergic to medroxyprogesterone acetate or any of the other ingredients in medroxyprogesterone acetate injectable suspension. See the end of this leaflet for a complete list of ingredients in medroxyprogesterone acetate injectable suspension.

What should I tell my healthcare provider before taking medroxyprogesterone acetate injectable suspension?

Before taking medroxyprogesterone acetate injectable suspension, tell your healthcare provider if you have:

- risk factors for weak bones (osteoporosis) such as bone disease, use alcohol or smoke regularly, anorexia nervosa, or a strong family history of osteoporosis
- irregular or lighter than usual menstrual periods
- breast cancer now or in the past, or think you have breast cancer
- a family history of breast cancer
- an abnormal mammogram (breast X-ray), lumps in your breasts, or bleeding from your nipples
- kidney problems
- high blood pressure
- had a stroke
- had blood clots in your arms, legs or lungs
- migraine headaches
- asthma
- epilepsy (convulsions or seizures)
- diabetes
- depression or a history of depression
- any other medical conditions

If you are breastfeeding or plan to breastfeed, medroxyprogesterone acetate can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take medroxyprogesterone acetate injectable suspension.

Tell your healthcare provider about all of the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Medroxyprogesterone acetate injectable suspension and certain other medicines may affect each other, causing serious side effects. Sometimes the doses of other medicines may need to be changed while you are taking medroxyprogesterone acetate injectable suspension.

Some medicines may make medroxyprogesterone acetate injectable suspension less effective at preventing pregnancy, including those listed below.

Especially tell your healthcare provider if you take:

- medicine to help you sleep
- bosentan
- medicine for seizures
- griseofulvin
- an antibiotic
- medicine for HIV (AIDS)
- St. John's wort

Know the medicines you take. Keep a list of your medicines with you to show your healthcare provider or pharmacist before you first start taking medroxyprogesterone acetate injectable suspension or when you get a new medicine.

Follow your healthcare provider's instructions about using a back-up method of birth control if you are taking medicines that may make medroxyprogesterone acetate injectable suspension less effective.

What are the possible side effects of medroxyprogesterone acetate injectable suspension?

Medroxyprogesterone acetate injectable suspension can cause serious side effects, including:

- Effect on the bones: See "What is the most important information I should know about medroxyprogesterone acetate injectable suspension?" Teenage years are the most important years to gain bone strength. The decrease in calcium in your bones is of most concern if you are a teenager or have the following problems:
- bone disease
- an eating disorder (anorexia nervosa)
- a strong family history of osteoporosis
- you take a drug that can lower the amount of calcium in your bones (drugs for epilepsy or steroid drugs)
- you drink a lot of alcohol (more than 2 drinks a day)
- you smoke

If you need a birth control method for more than 2 years, your healthcare provider may switch you to another birth control method instead of using medroxyprogesterone acetate injectable suspension. If you continue using medroxyprogesterone acetate injectable suspension, your healthcare provider may ask you to have a bone test, especially if you have other risks for weak bones.

When medroxyprogesterone acetate injectable suspension is stopped, your bones may start to regain calcium. However, in a study of teenage girls who used medroxyprogesterone acetate injectable suspension for more than 2 years, their hip bones did not completely recover by 5 years after they stopped using medroxyprogesterone acetate injectable suspension. Taking calcium and Vitamin D and exercising daily may lessen the loss of calcium from your bones.

- possible increased risk of breast cancer. Women who use medroxyprogesterone acetate injectable suspension may have a slightly increased risk of breast cancer compared to non-users.
- blood clots in your arms, legs, lungs, and eyes
- stroke
- a pregnancy outside of your uterus (ectopic pregnancy). Ectopic pregnancy is a medical emergency that often requires surgery. Ectopic pregnancy can cause internal bleeding, infertility, and even death.
- allergic reactions. Severe allergic reactions have been reported in some women using medroxyprogesterone acetate injectable suspension.
- loss of vision or other eye problems
- migraine headaches
- depression
- convulsions or seizures
- liver problems

Call your healthcare provider right away if you have:

- sharp chest pain, coughing up blood, or sudden shortness of breath (indicating a possible clot in the lung)
- sudden severe headache or vomiting, dizziness or fainting, problems with your eyesight or speech, weakness, or numbness in an arm or leg (indicating a possible stroke)
- severe pain or swelling in the calf (indicating a possible clot in the leg)
- sudden blindness, partial or complete (indicating a possible clot in the blood vessels of the eye)
- unusually heavy vaginal bleeding
- severe pain or tenderness in the lower abdominal area
- persistent pain, pus, or bleeding at the injection site
- yellowing of the eyes or skin
- hives
- difficulty breathing
- swelling of the face, mouth, tongue or neck

The most common side effects of medroxyprogesterone acetate injectable suspension include:

- irregular vaginal bleeding, such as lighter or heavier menstrual bleeding, or continued spotting
- weight gain. You may experience weight gain while you are using medroxyprogesterone acetate injectable suspension. About two-thirds of the women who used medroxyprogesterone acetate injectable suspension in the clinical trials reported a weight gain of about 5 pounds during the first year of use. You may continue to gain weight after the first year. Women who used medroxyprogesterone acetate injectable suspension for 2 years gained an average of 8 pounds over those 2 years.
- abdominal pain
- headache
- weakness
- tiredness
- nervousness
- dizziness

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

These are not all the possible side effects of medroxyprogesterone acetate injectable suspension. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

What other information should I know before choosing medroxyprogesterone acetate injectable suspension?

- **Pregnancy**. When you take medroxyprogesterone acetate injectable suspension every 3 months, your chance of getting pregnant is very low. You could miss a period or have a light period and not be pregnant. If you miss 1 or 2 periods and think you might be pregnant, see your healthcare provider as soon as possible. You should not use medroxyprogesterone acetate injectable suspension if you are pregnant. However, medroxyprogesterone acetate injectable suspension taken by accident during pregnancy does not seem to cause birth defects.
- **Nursing Mothers**. Although Medroxyprogesterone acetate injectable suspension can be passed to the nursing baby in the breast milk, no harmful effects on babies have been found. Medroxyprogesterone acetate injectable suspension does not stop the breasts from producing milk, so it can be used by nursing mothers. However, to minimize the amount of medroxyprogesterone acetate injectable suspension that is passed to the baby in the first weeks after birth, you should wait until your baby is 6 weeks old before you start using medroxyprogesterone acetate injectable suspension for birth control.

How will medroxyprogesterone acetate injectable suspension change my periods?

- **Change in normal menstrual cycle**. The side effect reported most frequently by women who use medroxyprogesterone acetate injectable suspension for birth controls is a change in their normal menstrual cycle. During the first year of using medroxyprogesterone acetate injectable suspension, you might have one or more of the following changes:
  - irregular or unpredictable bleeding or spotting
  - an increase or decrease in menstrual bleeding
  - **no bleeding at all**. In clinical studies of medroxyprogesterone acetate injectable suspension, 55% of women reported no menstrual bleeding (amenorrhea) after one year of use and 68% of women reported no menstrual bleeding after two years of use.

- **Missed period**. During the time you are using medroxyprogesterone acetate injectable suspension for birth controls, you may skip a period, or your periods may stop completely. If you have been receiving your shot of medroxyprogesterone acetate injectable suspension regularly every 3 months, then you are probably not pregnant. However, if you think that you may be pregnant, see your healthcare provider.

Unusually heavy or continuous bleeding is not a usual effect of medroxyprogesterone acetate injectable suspension and if this happens you should see your healthcare provider right away.

With continued use of medroxyprogesterone acetate injectable suspension, bleeding usually decreases and many women stop having periods completely. When you stop using medroxyprogesterone acetate injectable suspension your menstrual period will usually, in time, return to its normal cycle.

What if I want to become pregnant?
Because medroxyprogesterone acetate injectable suspension is a long-acting birth control method, it takes some time after your last shot for its effect to wear off. Most women who try to get pregnant after using Medroxyprogesterone acetate injectable suspension get pregnant within 18 months after their last shot. The length of time you use medroxyprogesterone acetate injectable suspension has no effect on how long it takes you to become pregnant after you stop using it.

General Information about medroxyprogesterone acetate injectable suspension
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. This leaflet summarizes the most important information about medroxyprogesterone acetate injectable suspension. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider for information about medroxyprogesterone acetate injectable suspension that is written for healthcare providers.

What are the ingredients in medroxyprogesterone acetate injectable suspension?
Active ingredient: medroxyprogesterone acetate
Inactive ingredients: polyethylene glycol 3350, polysorbate 80, sodium chloride, methylparaben, propylparaben, and water for injection. When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or both.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Distributed by:
Afaxys Pharma, LLC.
Charleston, SC, 29403, USA.

Manufactured by:
Sun Pharmaceutical Industries Limited
Halol-Baroda Highway,
Halol-389 350, Gujarat, India.

ISS. 01/2021
PJPI0665B

EContra One-Step®

(Levonorgestrel) Tablet, 1.5 mg
Emergency Contraceptive
One Tablet. One Step.
What You Need to Know

What is EContra One-Step®?

EContra One-Step® is emergency contraception that helps prevent pregnancy after birth control failure or unprotected sex. It is a **backup** method of preventing pregnancy and should not be used as regular birth control.

What EContra One-Step® is not.

EContra One-Step® will not work if you are already pregnant and will not affect an existing pregnancy. EContra One-Step® will not protect you from HIV infection (the virus that causes AIDS) and other sexually transmitted diseases (STDs).

When should I use EContra One-Step®?

The sooner you take emergency contraception, the better it works. You should use EContra One-Step® within 72 hours (3 days) **after you have had unprotected sex.**

EContra One-Step® is a backup or emergency method of birth control you can use when:

- your regular birth control was used incorrectly or failed
- you did not use any birth control method

When not to use EContra One-Step®.

EContra One-Step® should not be used:

- as a regular birth control method, because it's not as effective as regular birth control.
- if you are already pregnant, because it will not work.
- if you are allergic to levonorgestrel or any other ingredients in EContra One-Step®.

When should I talk to a doctor or pharmacist?

Ask a doctor or pharmacist before use if you are taking efavirenz (HIV medication) or rifampin (tuberculosis treatment) or medication for seizures (epilepsy). These medications may reduce the effectiveness of EContra One-Step® and increase your chance of becoming pregnant. Your doctor may prescribe another form of emergency contraception that may not be affected by these medications.

How does EContra One-Step® work?

EContra One-Step® is one tablet with levonorgestrel, a hormone that has been used in many birth control pills for several decades. EContra One-Step® contains a higher dose of levonorgestrel than birth control pills, but works in a similar way to prevent pregnancy. It works mainly by stopping the release of an egg from the ovary. It is possible that EContra One-Step® may also work by preventing fertilization of an egg (the uniting of sperm with the egg) or by preventing attachment (implantation) to the uterus (womb).

How can I get the best results from EContra One-Step®?

You have 72 hours (3 days) to try to prevent pregnancy after birth control failure or unprotected sex. **The sooner you take EContra One-Step®, the better it works.**

How effective is EContra One-Step®?

If EContra One-Step® is taken as directed, it can significantly decrease the chance that you will get pregnant. About 7 out of every 8 women who would have gotten pregnant will not become pregnant.

How will I know EContra One-Step® worked?

You will know EContra One-Step® has been effective when you get your next period, which should come at the expected time, or within a week of the expected time. If your period is delayed beyond 1 week, it is possible you may be pregnant. You should get a pregnancy test and follow up with your healthcare professional.

Will I experience any side effects?

- some women may have changes in their period, such as a period that is heavier or lighter or a period that is early or late. **If your period is more than a week late, you may be pregnant.**
- if you have severe abdominal pain, you may have an ectopic pregnancy, and should get immediate medical attention.
- when used as directed, EContra One-Step® is safe and effective. Side effects may include changes in your period, nausea, lower stomach (abdominal) pain, tiredness, headache, dizziness, and breast tenderness.
- if you vomit within 2 hours of taking the medication, call a healthcare professional to find out if you should repeat the dose.

What if I still have questions about EContra One-Step®?

If you have questions or need more information, call our toll-free number Afaxys Pharma, LLC at 1-855-888-2467.

Other Information

Keep out of reach of children:

In case of overdose, get medical help or contact a Poison Control Center right away at 1-800-222-1222.

Do not use if the blister seal is opened.

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

Active ingredient: levonorgestrel 1.5 mg

Inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, potato starch, and talc.

If you are sexually active, you should see a healthcare provider for routine checkups. Your healthcare provider will talk to you about and, if necessary, test you for sexually transmitted diseases, teach you about effective methods of routine birth control, and answer any other questions you may have.

Manufactured for:
Afaxys Pharma, LLC
Charleston, SC, 29403, USA.

Made in India

Code: TS/DRUGS/22/2009

Revised: 11/2019

P1522818