Enskyce™
(desogestrel and ethinyl estradiol tablets USP)
0.15 mg/0.03 mg
Rx Only

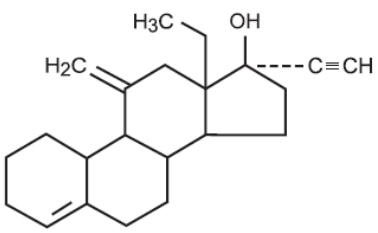
WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH SMOKING
Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including Enskyce™ (desogestrel and ethinyl estradiol tablets USP), 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.

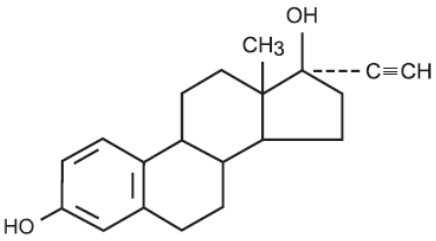
DESCRIPTION

Enskyce™ (desogestrel and ethinyl estradiol tablets USP) provide an oral contraceptive regimen of 21 light orange 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 (19-nor-17 alpha-pregna-1,3,5 (10)-trien-20-yne-3,17,diol). Inactive ingredients include colloidal silicon dioxide, corn starch, hypromellose, iron oxide yellow, iron oxide red, lactose monohydrate, magnesium stearate, polyethylene glycol, povidone, stearic acid, talc, titanium dioxide, and vitamin E. Each green tablet contains the following inactive ingredients: corn starch, D&C Yellow No. 10 Aluminum Lake, FD&C Blue #2/ Indigo Carmine Aluminium Lake, FD&C Yellow #6/ Sunset Yellow FCF Aluminium Lake, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, and titanium dioxide.

desogestrel



ethinyl estradiol



Enskyce 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 Enskyce, 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 Enskyce, the relative bioavailability is approximately 83%.

In the third cycle of use after a single dose of Enskyce, 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

Enskyce 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 Enskyce, 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[1]
Method	**Typical Use[2]**	**Perfect Use[3]**	
(1)	**(2)**	**(3)**	**(4)**
Chance[6]	85	85	
Spermicides[7]	26	6	40
Periodic abstinence	25		63
Calendar		9	
Ovulation Method		3	
Sympto-Thermal[8]		2	
Post-Ovulation		1	
Withdrawal	19	4	
Cap[9]			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm[9]	20	6	56
Condom[10]			
Female (Reality®)	21	5	56
Male	14	3	61
Pill	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T380A	0.8	0.6	78
LNg 20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant® and Norplant-2®	0.05	0.05	88
Female Sterilization	0.5	0.5	100

Male Sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.[4]

Lactation Amenorrhea Method: LAM is a highly effective, temporary method of contraception.[5]

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

2 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.

3 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.

4 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).

5 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.

6 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.

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

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

9 With spermicidal cream or jelly.

10 Without spermicides.

Enskyce has not been studied for and is not indicated for use in emergency contraception.

CONTRAINDICATIONS

Enskyce is contraindicated in females who are known to have or develop 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
- Current diagnosis of, or history of, breast cancer, which may be hormonesensitive
- 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 ombitasvir/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 Enskyce, should not be used by women who are over 35 years of age and smoke.
Contains color additives including FD&C Yellow No. 6.

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.[2,3,19-24] 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 1-2 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.

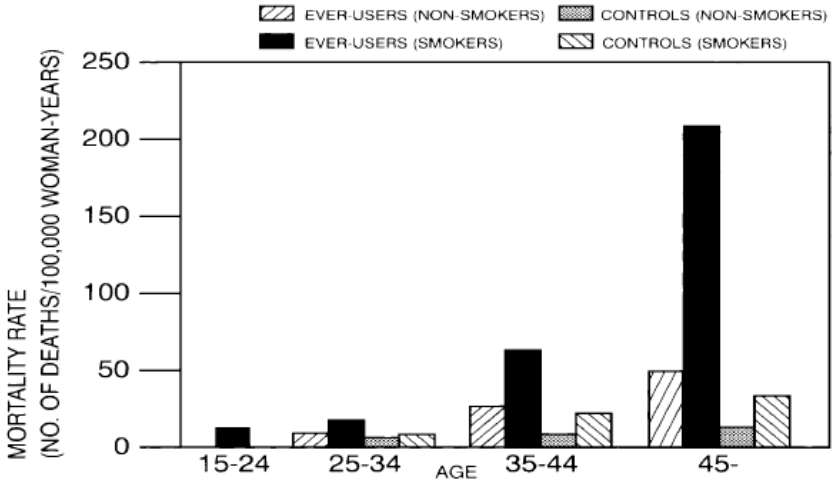
A two- to four-fold increase in relative risk of post-operative thromboembolic complications has been reported with the use of oral contraceptives.[9] The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.[26] If feasible, 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.[4-10] 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.[14-18] 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.[27-29]

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

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

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease.[31-33] A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents.[14-16] A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between doses of estrogen and progestogen and the 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 0.050 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*	7.0	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

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

*****Deaths are birth-related

******Deaths are method-related

3. Malignant Neoplasms

Breast Cancer

Enskyce Tablets is contraindicated in females who currently have or have had breast cancer because breast cancer may be hormonally sensitive *[see CONTRAINDICATIONS]*.

Epidemiology studies have not found a consistent association between use of combined oral contraceptives (COCs) and breast cancer risk. Studies do not show an association between ever (current or past) use of COCs and risk of breast cancer. However, some studies report a small increase in the risk of breast cancer among current or recent users (<6 months since last use) and current users with longer duration of COC use *[see POSTMARKETING EXPERIENCE]*.

Cervical Cancer

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

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 Enskyce prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir, with or without dasabuvir (see **CONTRAINDICATIONS**). Enskyce 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.[56-57] 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.[62-64] 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 Enskyce 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
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 Enskyce 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.

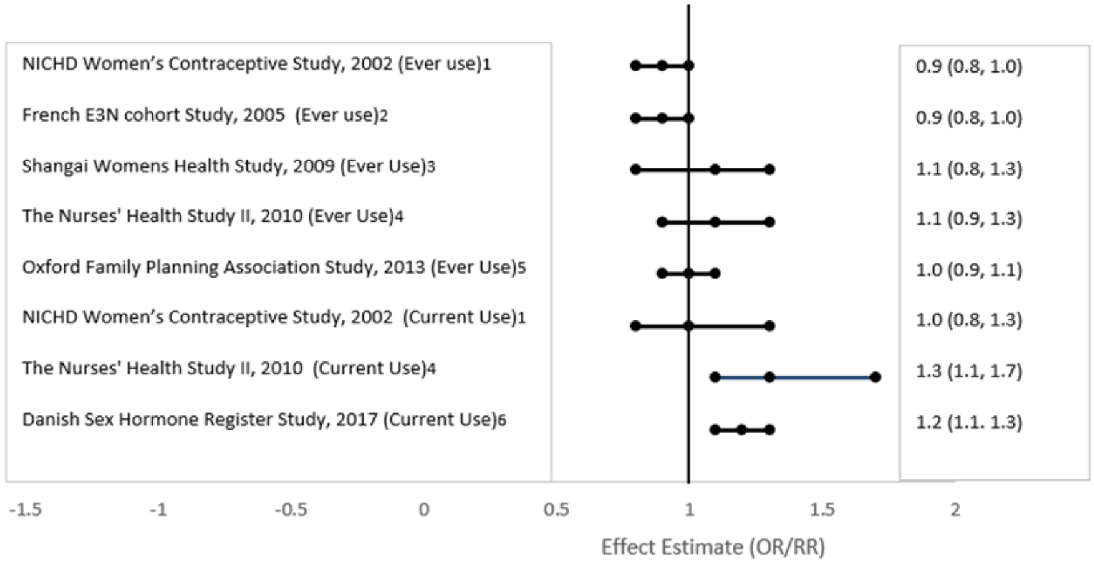
14. Geriatric Use
This product has not been studied in women over 65 years of age and is not indicated in this population.

INFORMATION FOR THE PATIENT
See Patient Labeling printed below.

ADVERSE REACTIONS
Post Marketing Experience
Five studies that compared breast cancer risk between ever-users (current or past use) of COCs and never-users of COCs reported no association between ever use of COCs and breast cancer risk, with effect estimates ranging from 0.90 - 1.12 (Figure 2).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure 1). One of these studies reported no association between breast cancer risk and COC use. The other two studies found an increased relative risk of 1.19 - 1.33 with current or recent use. Both of these studies found an increased risk of breast cancer with current use of longer duration, with relative risks ranging from 1.03 with less than one year of COC use to approximately 1.4 with more than 8-10 years of COC use.

Figure 2: Risk of Breast Cancer with Combined Oral Contraceptive Use



RR = relative risk; OR = odds ratio; HR = hazard ratio. "ever COC" are females with current or past COC use; "never COC use" are females that never used COCs.

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.[73-78]
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, Enskyce must be taken exactly as directed and at intervals not exceeding 24 hours. Enskyce is available in the blister which is preset for a Sunday Start. Day 1 Start is also provided.

Day 1 Start

The dosage of Enskyce for the initial cycle of therapy is one light orange "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 light orange "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 light orange "active" tablet is taken the next day.

The use of Enskyce 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 Enskyce postpartum, and has not yet had a period, she should be instructed to use another method of contraception until a light orange "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) light orange "active" tablet in Weeks 1, 2, or 3, the light orange "active" tablet should be taken as soon as she remembers. If the patient misses two (2) light orange "active" tablets in Week 1 or Week 2, the patient should take two (2) light orange "active" tablets the day she remembers and two (2) light orange "active" tablets the next day; and then continue taking one (1) light orange "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) light orange "active" tablets in the third week or misses three (3) or more

light orange "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 Enskyce, the first light orange "active" tablet should be taken on the first Sunday after menstruation begins. If the period begins on Sunday, the first light orange "active" tablet is taken on that day. If switching directly from another oral contraceptive, the first light orange "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 light orange "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 light orange "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 Enskyce 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 Enskyce postpartum, and has not yet had a period, she should be instructed to use another method of contraception until a light orange "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) light orange active tablet in Weeks 1, 2, or 3, the light orange "active" tablet should be taken as soon as she remembers. If the patient misses two (2) light orange "active" tablets in Week 1 or Week 2, the patient should take two (2) light orange "active" tablets the day she remembers and two (2) light orange "active" tablets the next day; and then continue taking one (1) light orange "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) light orange "active" tablets in the third week or misses three (3) or more light orange "active" tablets in a row, the patient should continue taking one light orange "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

Enskyce Tablets are available in a blister (NDC 68180-891-71) containing 28 tablets packed in a pouch (NDC 68180-891-71). Such three pouches are packaged in a carton (NDC 68180-891-73).

Each blister contains 28 film-coated tablets in the following order:

- Each of the 21 light orange, round, biconvex, film-coated tablet contains 0.15 mg of desogestrel and 0.03 mg of ethinyl estradiol USP and is debossed with "L" on one side and "J7" on the other side.
- Each of the 7 green coloured, round, biconvex, film-coated tablet contains inert ingredients and is debossed with "LU" on one side and "L22" on the other side.

STORAGE: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

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