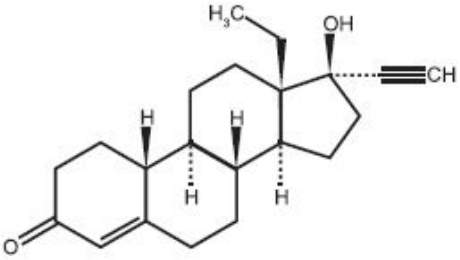
DOLISHALE- levonorgestrel and ethinyl estradiol tablet
Ingenus Pharmaceuticals, LLC

DOLISHALE™
(90 mcg levonorgestrel and 20 mcg ethinyl estradiol) Tablets, USP

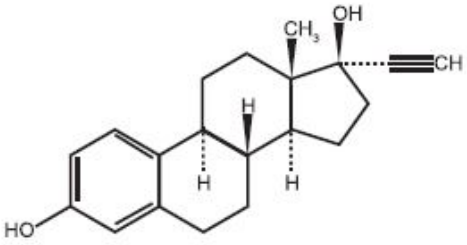
Patients should be counseled that oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases (STDs) such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B, and syphilis.

DESCRIPTION

Twenty-eight (28) green tablets each containing 90 mcg of levonorgestrel (17α)-(–)13-ethyl-17-hydroxy-18, 19-dinorpregn-4-en-20-yn-3-one, a totally synthetic progestogen, and 20 mcg of ethinyl estradiol, (17α)-19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol. The inactive ingredients present are titanium dioxide, macrogol/PEG 3000 NF, talc, polyvinyl alcohol, lecithin (soya), FD&C Blue #2 Aluminum Lake, FD&C Yellow #5 Aluminum Lake, FD&C Red #40 Aluminum Lake, lactose monohydrate, magnesium stearate and pregelatinized starch.



Levonorgestrel
$C_{21}H_{28}O_2$ M.W. 312.45



Ethinyl Estradiol
$C_{20}H_{24}O_2$ M.W. 296.40

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 levonorgestrel and ethinyl estradiol tablets 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%.

A summary of the single dose and multiple dose levonorgestrel and ethinyl estradiol

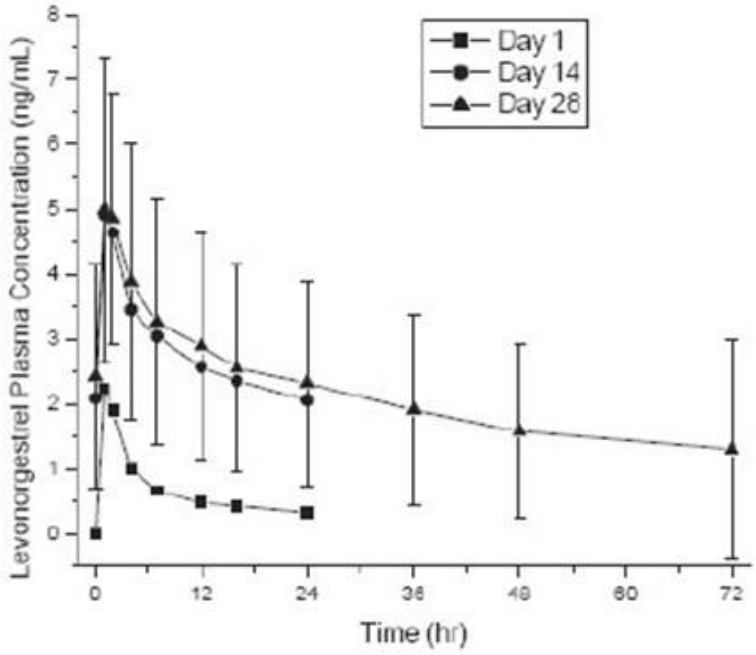
pharmacokinetic parameters for 18 women under fasting conditions is provided in Table 1. The plasma concentrations of levonorgestrel and ethinyl estradiol reached steady-state by approximately day 14. Levonorgestrel and ethinyl estradiol concentrations did not increase from days 14 to 28, but did increase from days 1 to 28.

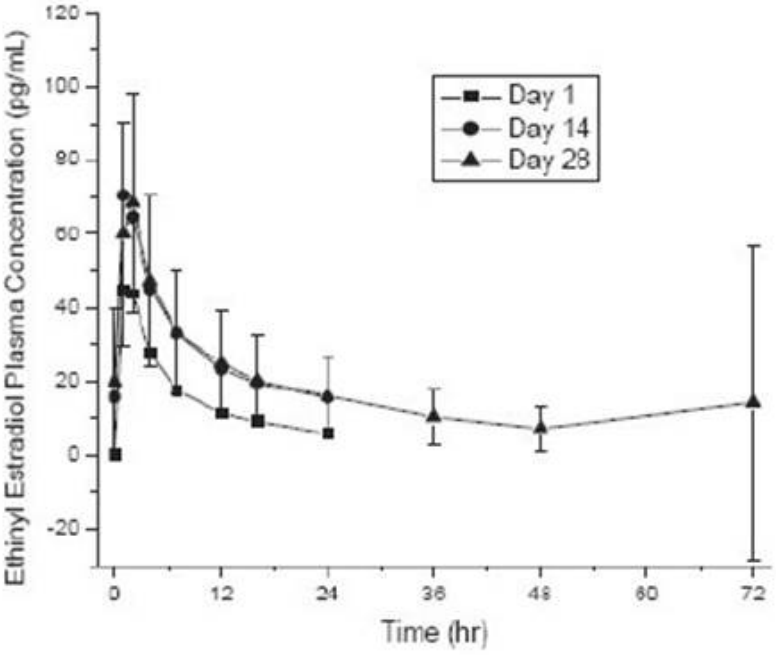
Table 1: Mean (SD) Pharmacokinetic Parameters of Levonorgestrel and Ethinyl Estradiol Tablets Over a 28-Day Dosing Period

		LNG		
Day	**C_{max}** (ng/mL)	**T_{max}** (h)	**$t_{1/2}$** (h)	**AUC_{0-24}** (ng•h/mL)
1	2.4 (0.9)	1.2 (0.4)	-	16 (8)
14	5.4 (2.1)	1.7 (1.4)	-	68 (36)
28	5.7 (2.1)	1.3 (0.8)	36 (19)	74 (41)
		EE		
Day	(pg/mL)	(h)	(h)	(pg h/mL)
1	47.7 (20.1)	1.3 (0.5)	-	378 (140)
14	72.7 (37.2)	1.4 (0.5)	-	695 (361)
28	74.4 (29.7)	1.4 (0.5)	21 (7)	717 (351)

The mean plasma concentrations of levonorgestrel and ethinyl estradiol following single (day 1) and multiple (days 14 and 28) oral administrations of levonorgestrel 90 mcg in combination with ethinyl estradiol 20 mcg to 18 healthy women is provided in Figure 1.

Figure 1: Mean Plasma ± SD[†]Concentrations of Levonorgestrel and Ethinyl Estradiol Following Single (Day 1) and Multiple (Days 14 and 28) Oral Administrations of Levonorgestrel 90 mcg in Combination with Ethinyl Estradiol 20 mcg to Healthy Women





†SD = standard deviation

The effect of food on the rate and the extent of levonorgestrel and ethinyl estradiol absorption following oral administration of DOLISHALE has not been evaluated.

Distribution

Levonorgestrel in serum is primarily bound to sex hormone-binding globulin (SHBG). Ethinyl estradiol is about 97% bound to serum albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis.

Metabolism

Levonorgestrel: The most important metabolic pathways are reduction of the Δ4-3-oxo group and hydroxylation at positions 2α, 1β, and 16β, followed by conjugation. Most of the circulating metabolites 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, sulfation, and glucuronidation prior to urinary and fecal excretion. Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinyl estradiol 2-hydroxylation.

Excretion

The terminal elimination half-life for levonorgestrel in levonorgestrel and ethinyl estradiol tablets is about 36 hours. Levonorgestrel and its metabolites are excreted in the urine (40% to 68%) and in feces (16% to 48%). The terminal elimination half-life of ethinyl estradiol in levonorgestrel and ethinyl estradiol tablets is about 21 hours.

Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates and undergoes enterohepatic recirculation.

Special Populations

Race

No formal studies on the effect of race on the pharmacokinetic parameters of levonorgestrel and ethinyl estradiol tablets were conducted.

Hepatic Insufficiency

No formal studies have evaluated the effect of hepatic disease on the disposition of levonorgestrel and ethinyl estradiol tablets. 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 levonorgestrel and ethinyl estradiol tablets.

Drug-Drug Interactions

See **PRECAUTIONS**section - **Drug Interactions.**

INDICATIONS AND USAGE

DOLISHALE 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 for pregnancy prevention. Table 2 lists the typical unintended pregnancy rates for users of combination oral contraceptives and other methods of contraception. The efficacy of these contraceptive methods, except sterilization, the IUD, and implants, depend upon the reliability with which they are used. Correct and consistent use of methods can result in lower failure rates.

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	
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.

Clinical Studies

The efficacy and safety of levonorgestrel and ethinyl estradiol tablets were studied in 2 one-year clinical trials of subjects age 18 to 49. There were no exclusions for body mass index (BMI), weight, or bleeding history.

The primary efficacy and safety study (313-NA) was a one-year open-label clinical trial that treated 2,134 subjects in North America. Of these subjects 1,213 (56.8%) discontinued prematurely, including 102 (4.8%) discontinued by the Sponsor for early study closure. The mean weight of subjects in this study was 70.38 kg. The efficacy of levonorgestrel and ethinyl estradiol tablets was assessed by the number of pregnancies that occurred after the onset of treatment and within 14 days of the last dose. Among subjects 35 years or less, there were 23 pregnancies (4 of these occurred during the interval 1 to 14 days after the last day of pill use) during 12,572 28-day pill packs of use. The resulting total Pearl Index was 2.38 (95% CI: 1.51, 3.57) and the one-year life table pregnancy rate was 2.39 (95% CI: 1.57, 3.62). Pill pack cycles during which subjects used back-up contraception or were not sexually active were not included in these calculations. Among women 35 years or less who took the pills completely as directed, there were 15 pregnancies (method failures) resulting in a Pearl Index of 1.55 (95% CI: 0.87, 2.56) and the one-year life table pregnancy rate was 1.59 (95% CI: 0.95 to 2.67).

In a second supportive study conducted in Europe (315-EU), 641 subjects were randomized to levonorgestrel and ethinyl estradiol tablets (n=323) or the cyclic comparator of 100 mcg levonorgestrel and 20 mcg ethinyl estradiol (n=318). The mean weight of subjects in this study was 63.86 kg. The efficacy analysis among women 35 years or less included 2,756 levonorgestrel and ethinyl estradiol tablet pill packs and 2,886 cyclic comparator pill packs. There was one pregnancy in the levonorgestrel and ethinyl estradiol group that occurred within 14 days following the last dose. There were three pregnancies in the cyclic comparator group.

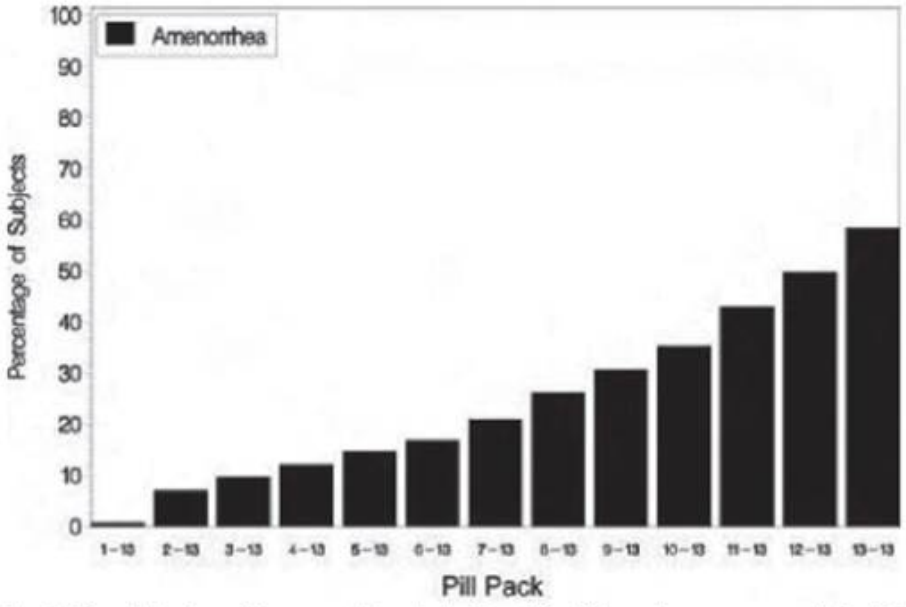
Inhibition of Menses (Bleeding Profile)

The bleeding profile for subjects in Study 313-NA also was assessed. Women with a

history of unscheduled bleeding and/or spotting were not excluded from the study.

In those subjects who provided complete bleeding data, the percentage of patients who were amenorrheic in a given cycle and remained amenorrheic through cycle 13 (cumulative amenorrhea rate) was determined (Figure 2).

Figure 2: Percentage of Subjects with Cumulative Amenorrhea for Each Pill Pack through Pill Pack 13



The 779 subjects with complete data for 13 pill packs were used in this cumulative analysis.

Subjects were to begin pill pack 1 on the first day of menses.

When prescribing DOLISHALE, the convenience of having no scheduled menstrual bleeding should be weighed against the inconvenience of unscheduled bleeding and spotting (see **WARNINGS, 12**).

CONTRAINDICATIONS

Combination oral contraceptives should not be used in women with any of the following conditions:

- Thrombophlebitis or thromboembolic disorders
- 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 such as aura
- Uncontrolled hypertension

• Current diagnosis of, or history of, breast cancer, which may be hormone-sensitive

• 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 DOLISHALE

• 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, stroke, and transient ischemic attack), 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

DOLISHALE is a non-cyclic oral contraceptive that provides a low daily dose of estrogen and progestin; however, DOLISHALE provides women with more hormonal exposure on

a yearly basis (13 additional weeks of hormone intake per year) than conventional cyclic oral contraceptives containing the same strength of synthetic estrogens and similar strength of progestins.

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 3) among women who use oral contraceptives.

Figure 3: Circulatory Disease Mortality Rates per 100,000 Woman Years by Age, SmokingStatus and Oral Contraceptive Use

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 **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.

b. Venous Thrombosis and Thromboembolism

An increased risk of venous thromboembolic and thrombotic disease associated with the use of oral contraceptives is well established. The risk of venous thrombotic and thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism. 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 (<0.05 mg 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 post-marketing observational study evaluated the risk of venous thromboembolism with levonorgestrel and ethinyl estradiol tablets use in two large US automated healthcare claims databases. The study was not completed as planned due to low accrual of levonorgestrel and ethinyl estradiol tablets users in these databases and discontinuation of the product from the market due to low usage. At study discontinuation, the crude incidence rate of venous thromboembolism among levonorgestrel and ethinyl estradiol tablets users (n=12,281) was 17.6 per 10,000 person- years, compared to 8.8 per 10,000 person-years among the users of cyclic oral contraceptives containing 20 mcg of ethinyl estradiol and a progestogen, and 5.1 per 10,000 person-years among the users of cyclic oral contraceptives containing the progestin levonorgestrel and 20 mcg of ethinyl estradiol. Adjustment for important risk factors or confounders (such as obesity, cardiovascular disease and other diseases) for venous thromboembolism could not be performed due to the small sample size. Although the study results suggest an elevated risk of venous thromboembolism with current levonorgestrel and ethinyl estradiol tablets use compared to cyclic oral hormonal contraceptive use, reliable interpretation of the results is significantly limited due to the small sample size and concerns over unmeasured and uncontrolled confounding, as well as questions about the suitability of the comparator selection and the validity of the venous thromboembolism definition.

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 post-partum 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 (>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. Transient ischemic attacks have also been associated with oral contraceptive use.

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 such as aura) who take combination oral contraceptives may be at an increased risk of stroke. (See **CONTRAINDICATIONS**.)

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 persisted 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 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 3). 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 3: 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 to 63, 1983.

3. Malignant Neoplasms

Breast Cancer
DOLISHALE 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 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.

Endometrial biopsies performed in a subset of subjects (Study 1; n = 93) ages 18 to 49 years, after 6 to 12 months of use of levonorgestrel and ethinyl estradiol, did not reveal any hyperplasias or malignancies. Endometrial malignancy is rare in this age group, so change in the risk is unlikely to be detected with a study of this size.

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 (>8 years) oral contraceptive user. 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 DOLISHALE prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ ritonavir, with or without dasabuvir *[see Contraindications (4)]*. DOLISHALE 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 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.

7. 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.

The possibility of pregnancy should be considered in any patient who may be experiencing symptoms of pregnancy, especially if she has not adhered to the prescribed schedule. Oral-contraceptive use must be discontinued if pregnancy is confirmed.

8. 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.

9. 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 0.075 mg 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.

10. 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.

11. Headache

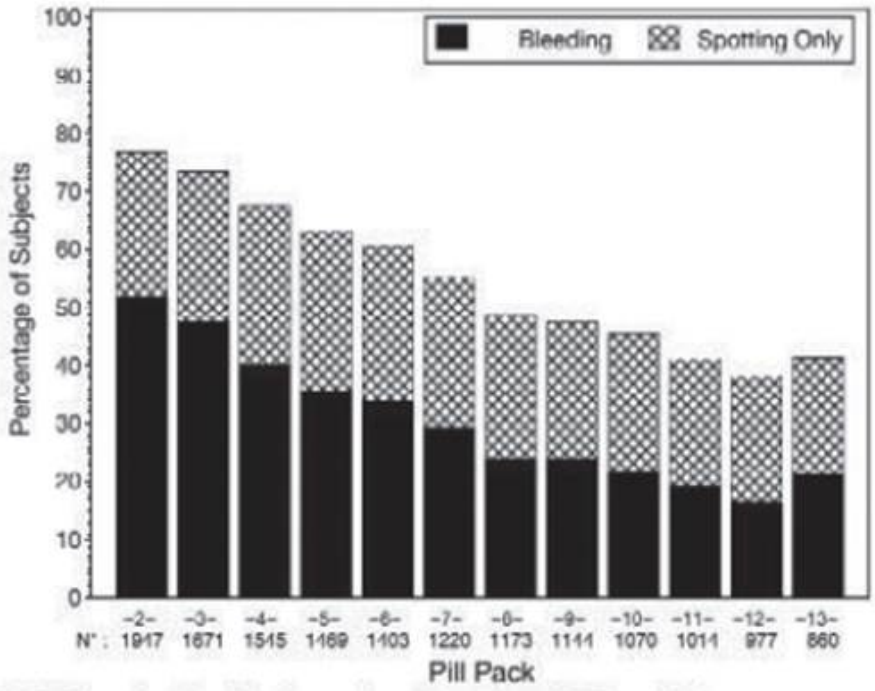
The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent, or severe requires discontinuation of oral contraceptives and evaluation of the cause. (See **WARNINGS**, 1c. and **CONTRAINDICATIONS**.)

12. Bleeding Irregularities

When prescribing DOLISHALE, the convenience of having no scheduled menstrual bleeding should be weighed against the inconvenience of unscheduled breakthrough bleeding and spotting. In Study 313-NA, 385/2,134 (18%) of women discontinued prematurely due to bleeding that was reported either as an adverse event or where bleeding was given as one of the reasons for discontinuation (see **INDICATIONS AND USAGE, Clinical Studies**).

Figure 4 shows the percentage of levonorgestrel and ethinyl estradiol subjects in study 313-NA by pill pack who experienced unscheduled bleeding or spotting only (Defined as "No sanitary protection required").

Figure 4: Percentage of Subjects Reporting Bleeding or Spotting Only per Pill Pack

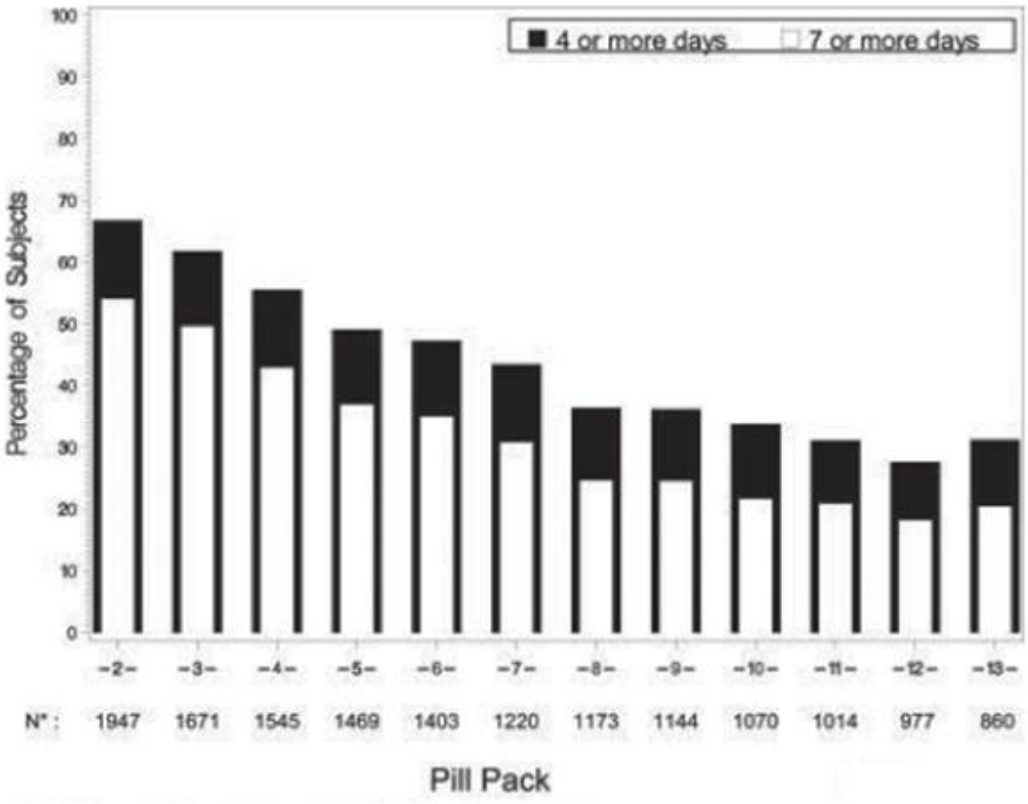


*:The N for each pill pack is the number of subjects with 28 days of data.

Bleeding required sanitary protection; spotting only did not require sanitary protection.

Figure 5 shows the percentage of levonorgestrel and ethinyl estradiol tablet subjects with complete bleeding data in Study 313-NA who had 4 or more and 7 or more days of bleeding and/or spotting during each pill pack cycle. During pill pack 2, 67% of subjects experienced 4 or more days of bleeding and/or spotting and 54% of these subjects experienced 7 or more days of bleeding and/or spotting. During the final cycle of use of levonorgestrel and ethinyl estradiol (pill pack 13), these percentages were 31% and 20%, respectively.

Figure 5: Percentage of Subjects Reporting Greater Than or Equal to 4 or 7 Days of Bleeding and/or Spotting per Pill Pack (Study 313-NA)



*: The N for each pill pack is the number of subjects with 28 days of data.

As in any case of bleeding irregularities, nonhormonal causes should be considered and adequate diagnostic measures may be indicated to rule out pregnancy, infection, malignancy, or other conditions.

Some women may encounter post-pill amenorrhea or oligomenorrhea (possibly with anovulation), especially when such a condition was preexistent.

13. Ectopic Pregnancy

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

PRECAUTIONS

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

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.

Scheduled withdrawal bleeding does not occur with the use of DOLISHALE, therefore, the absence of withdrawal bleeding cannot be used as a sign of an unexpected

pregnancy and as such, unexpected pregnancy may be difficult to recognize. Although pregnancy is unlikely if DOLISHALE is taken as directed, if for any reason, pregnancy is suspected in a woman using DOLISHALE, a pregnancy test should be performed.

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 9.)

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 unscheduled bleeding. Examples include rifampin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, carbamazepine, felbamate, oxcarbazepine, topiramate, griseofulvin, and modafinil. In such cases a nonhormonal back-up method of birth control should be considered.

Several cases of contraceptive failure and unscheduled 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. Enterohepatic recirculation of estrogens may also be decreased by substances that reduce gut transit time.

Several of the anti-HIV protease inhibitors have been studied with coadministration 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. Health care professionals should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

Concomitant Use with HCV Combination Therapy – Liver Enzyme Elevation Do not co-administer DOLISHALE 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**).

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 unscheduled bleeding.

Increase in Plasma Levels Associated with Coadministered Drugs:

Coadministration 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 Coadministered Drugs:

Combination hormonal contraceptives containing some synthetic estrogens (eg, 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 lamotrigine, 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.

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), 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 ie, 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 levonorgestrel and ethinyl estradiol 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.

15. Geriatric Use

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

16. Information for the Patient

See **DETAILED PATIENT LABELING**printed below.

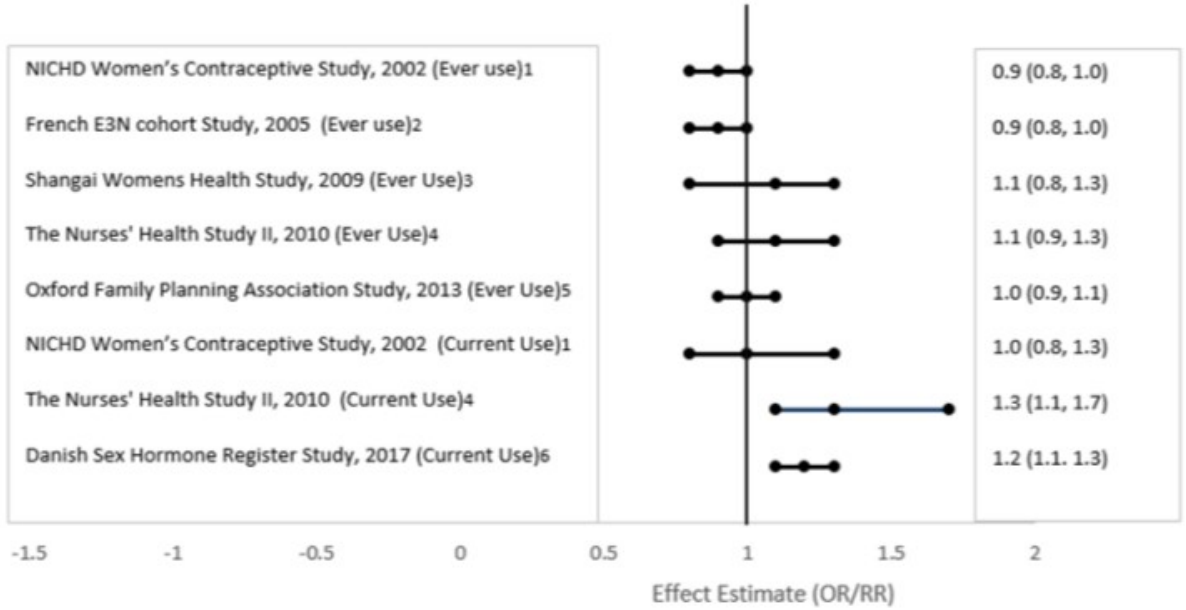
ADVERSE REACTIONS

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 6).

Three studies compared breast cancer risk between current or recent COC users (<6 months since last use) and never users of COCs (Figure 6). 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 6. 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 (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, transient ischemic attack), carcinoma of the reproductive organs and breasts, hepatic neoplasia/liver disease (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
- Focal nodular hyperplasia
- 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

To report SUSPECTED ADVERSE REACTIONS, contact Ingenus

Pharmaceuticals, LLC Toll-Free at 1-877-748-1970 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

OVERDOSAGE

Symptoms of oral contraceptive overdosage in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, 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:

May decrease blood loss and may decrease the incidence of iron-deficiency anemia

May decrease incidence of dysmenorrhea

Effects related to inhibition of ovulation:

May decrease incidence of functional ovarian cysts

May decrease incidence of ectopic pregnancies

Effects from long-term use:

May decrease incidence of fibroadenomas and fibrocystic disease of the breast

May decrease incidence of acute pelvic inflammatory disease

May decrease incidence of endometrial cancer

May decrease incidence of ovarian cancer

DOSAGE AND ADMINISTRATION

To achieve maximum contraceptive effectiveness, DOLISHALE (levonorgestrel and ethinyl estradiol tablets) must be taken exactly as directed and at intervals not exceeding 24 hours. The possibility of ovulation and conception prior to initiation of medication should be considered. Women who do not wish to become pregnant after discontinuation should be advised to immediately use another method of birth control. The dosage of DOLISHALE is one green tablet daily without any tablet-free interval.

It is recommended that DOLISHALE tablets be taken at the **same time** each day.

Initiation of Therapy

Instructions for beginning DOLISHALE are provided in Table 4 below.

Table 4

Current contraceptive therapy	DOLISHALE start day	Nonhormonal back-up method of birth control needed when correctly starting DOLISHALE?
None	Day 1 of patient's menstrual cycle (during the first 24 hours of her period)	No
21-day COC	Day 1 of patient's withdrawal	No

regimen OR 28-day COC regimen	bleed, at the latest 7 days after her last active tablet.	
Progestin-only pill	Day after taking a progestin-only pill	Yes, for the first 7 days of DOLISHALE tablet taking
Implant	Day of implant removal	Yes, for the first 7 days of DOLISHALE tablet taking
Injection	Day the next injection is due	Yes, for the first 7 days of DOLISHALE tablet taking

If spotting or unscheduled bleeding occurs, 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 health care professional. The possibility of ovulation increases with each successive day that scheduled green tablets are missed. 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. Hormonal contraception must be discontinued if pregnancy is confirmed.

The risk of pregnancy increases with each 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.

DOLISHALE 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. However, if intercourse has already occurred, pregnancy should be excluded before the start of combined oral contraceptive use or the patient must wait for her first menstrual period.

In the case of first-trimester abortion, if the patient starts DOLISHALE immediately, additional contraceptive measures are not needed.

HOW SUPPLIED

DOLISHALE(90 mcg levonorgestrel and 20 mcg ethinyl estradiol) tablets are available in a blister pack, arranged in 4 rows of 7 active tablets as follows:

28 round, green biconvex tablets debossed with "H1" on one side.

DOLISHALE Tablets are available in the following packaging configurations:

Carton of 1	Blister Card of 28 Tablets	NDC 50742-659-28
Carton of 3	Blister Cards of 28 Tablets Each	NDC 50742-659-84
Carton of 6	Blister Cards of 28 Tablets Each	NDC 50742-659-68

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

References available upon request.

Rx Only

Iss: 12/2024

I0154

Rev B

Manufactured for:

Ingenus Pharmaceuticals, LLC

Orlando, FL 32839-6408

Product of China

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 to 2% per year (1 to 2 pregnancies 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. However, forgetting to take pills considerably increases the chances of pregnancy.

DOLISHALE is a birth-control pill that is taken every day. When you take DOLISHALE, the lining of your uterus does not undergo the changes needed for menstruation, and therefore you do not have regular menstrual periods. You are likely to have unscheduled or unplanned bleeding or spotting when you start to use DOLISHALE. The number of days each month with unscheduled bleeding and spotting usually decreases over time for the majority of women. When using DOLISHALE , the convenience of having no regular menstrual periods should be weighed against the inconvenience of unscheduled or unplanned breakthrough bleeding and spotting.

For the majority of women, oral contraceptives can be taken safely. However, 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, or are obese

• 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 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.

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.

Most side effects of the pill are not serious. The most common such effects are nausea, vomiting, unscheduled bleeding, 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), lungs (pulmonary embolism), stoppage or rupture of a blood vessel in the brain (stroke), blockage of blood vessels in the heart (heart attack and angina pectoris) or other organs of the body. As mentioned above, smoking increases the risk of heart attacks and strokes and subsequent serious medical consequences. 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.

There may be slight increases in the risk of breast cancer among current users of hormonal birth control pills with longer duration of use of 8 years or more.

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, 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.

What You Should Know About Your Menstrual Cycle When You Use DOLISHALE

You are likely to have unscheduled or unplanned bleeding or spotting when you start to

use DOLISHALE. The number of days each month with bleeding or spotting usually decreases over time in the majority of women. In a study of levonorgestrel and ethinyl estradiol, about 5 out of 10 women had 7 or more days of bleeding or spotting while using their third 28-day pill pack of levonorgestrel and ethinyl estradiol tablets. The number of women with 7 or more days of bleeding or spotting decreased to 3 out of 10 women during the use of their seventh pill pack. Among women who continued to use levonorgestrel and ethinyl estradiol tablets for one year, about 6 out of 10 women had no bleeding or spotting during their last month of use.

Do not stop taking DOLISHALE because of bleeding or spotting as this will increase your chance of getting pregnant. If the spotting or bleeding continues for more than 7 consecutive days or if the bleeding is heavy, call your health care provider.

Can I Get Pregnant While Taking DOLISHALE?

You are not likely to get pregnant if you take DOLISHALE at the same time everyday as directed by your health care provider. Because regular monthly bleeding does not occur on DOLISHALE, it may be difficult to recognize if you get pregnant. If you suspect that you may be pregnant, or if you have symptoms of pregnancy such as nausea/vomiting or unusual breast tenderness, you should have a pregnancy test and you should contact your health care professional. Stop taking DOLISHALE if you are pregnant.

Instructions for the Patient

HOW TO TAKE *DOLISHALE*

Important Points to Remember

Before You Start Taking DOLISHALE:

1. BE SURE TO READ THESE DIRECTIONS:

Before you start taking DOLISHALE.

And

Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE *DOLISHALE* 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 DOLISHALE. This will usually go away. If it doesn't go away, check with your health care professional.

4. MOST WOMEN HAVE SPOTTING OR BLEEDING DURING THE FIRST FEW MONTHS OF TAKING *DOLISHALE*. Do not stop taking your pills even if you are having bleeding or spotting. If the bleeding or spotting lasts for more than 7 consecutive days, talk to your health care provider.

5. 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.

6. IF YOU VOMIT (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 and/or spermicide) until you check with your health care professional.

7. IF YOU HAVE TROUBLE REMEMBERING TO TAKE *DOLISHALE*, talk to your health care professional about how to make pill-taking easier or about using another method of birth control.

8. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your health care professional.

BEFORE YOU START TAKING *DOLISHALE*

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL. It is important to take your pill at the SAME TIME every day.

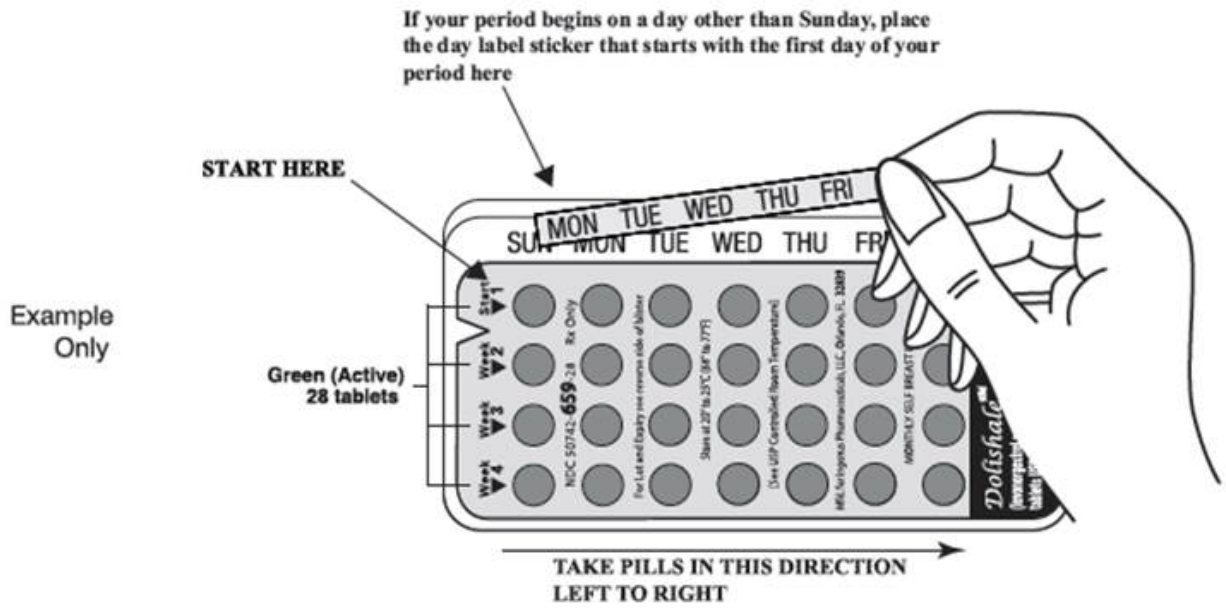
2. LOOK AT YOUR *DOLISHALE* BLISTER CARD. The pill pack has 28 "active" green pills (with hormones).

3. ALSO FIND:

1) where on the pack to start taking pills,

2) in what order to take the pills (follow the arrows),

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 NONHORMONAL BIRTH CONTROL (such as condoms and/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 *DOLISHALE*

Day 1 Start

1. If 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) is Sunday, then follow the days of the week imprinted on the plastic compact. You do not need to use the Day Label Stickers.

2. If 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) is on a day other than Sunday, then pick the day label sticker that starts with that day of the week.

3. Place this chosen day label sticker over the area that has the days of the week (starting with Sunday) imprinted on the plastic compact as shown in the graphic above.

4. Take the first "active" green pill of the first pack during the *first 24 hours of your period*.

5. 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.

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 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 pill. **Do not wait any days between packs.**

IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS:

When switching from a 21 pill pack: Start DOLISHALE on the first day of your period (withdrawal bleed). Be sure that no more than 7 days pass between the last day of your 21-day pack and your first DOLISHALE pill.

When switching from a 28 pill pack (21 active and 7 inactive pills, or 24 active and 4 inactive pills): Start DOLISHALE on the first day of your period (withdrawal bleed). Be sure that no more than 7 days pass after the last active pill and your first DOLISHALE pill.

IF YOU SWITCH FROM ANOTHER TYPE OF BIRTH CONTROL

When switching from other types of birth control such as pills containing only a progestin (progestin only pill or POP), an injection, or an implant, your health care professional will provide you with instructions for when to start DOLISHALE.

WHAT TO DO IF YOU MISS PILLS

Combination oral contraceptives may not be as effective if you miss pills. Instructions for what to do if you miss pills are provided in the following table.

# of pills missed in a row	**What to do when you miss a pill(s)**
1 missed pill	• Take the missed pill as soon as you remember. THEN • Take the next pill at your regular time. This means you may take 2 pills in 1 day. • You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms and/or spermicide) as a back-up for those 7 days.
2 missed pills and remembered on the day of the second missed pill	• Take 2 missed pills on the day you remember. The following day you are back on schedule to take 1 pill a day. For example, you take your pills in the morning and you missed 1 pill on Monday and 1 on Tuesday. On Tuesday evening you remembered that you missed your Monday and Tuesday pills. You take the 2 missed pills on Tuesday evening and on Wednesday morning you're back on schedule and you take 1 pill.

	• You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms and/or spermicide) as a back-up for those 7 days.
2 missed pills and remembered on the day after the second pill is missed	• Take 2 missed pills on the day you remember. The next day you take 2 pills. The following day you are back on schedule to take your pills. For example, you take your pills in the morning and you missed 1 pill on Monday and 1 on Tuesday. On Wednesday morning you remembered that you missed your Monday and Tuesday pills. You take the 2 missed pills on Wednesday morning and 2 pills on Thursday morning. On Friday morning you're back on schedule and you take 1 pill. • You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms and/or spermicide) as a back-up for those 7 days.
3 or more missed pills	• Contact your health care professional for further advice. Keep taking one pill every day until you reach your health care professional. Do not take the missed pills. • You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms and/or spermicide) as a back-up for those 7 days.

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.

PREGNANCY AFTER STOPPING THE PILL

If you do not desire pregnancy, you should use another method of birth-control immediately after stopping DOLISHALE. You can get pregnant within days after stopping DOLISHALE.

For additional information see "Detailed Patient Labeling."

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

DOLISHALE is a birth-control pill that is taken every day. When you take DOLISHALE, the lining of your uterus does not undergo the changes needed for menstruation, and therefore you do not have regular menstrual periods. You are likely to have unscheduled or unplanned bleeding or spotting when you start to use DOLISHALE. The number of days each month with unscheduled bleeding and spotting usually decreases over time

for the majority of women. When using DOLISHALE, the convenience of having no regular menstrual periods should be weighed against the inconvenience of unscheduled or unplanned breakthrough bleeding and spotting.

EFFECTIVENESS OF ORAL CONTRACEPTIVES

Oral contraceptives or "birth-control pills" or "the pill" are used to prevent pregnancy and are more effective than other nonsurgical methods of birth control. When they are taken correctly, without missing any pills the chance of becoming pregnant is approximately 1 to 2% per year (1 to 2 pregnancies per 100 women per year of use). Average 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.

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

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.

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.

• History of blood clots in the deep veins of your legs.

• Hereditary or acquired blood clotting disorders

• 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 professional).

• Liver tumor (benign or cancerous) or active liver disease.

• 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.

• 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 such as aura.

• Uncontrolled high blood pressure.

• Allergy or hypersensitivity to any of the components of DOLISHALE (levonorgestrel and ethinyl estradiol tablets).

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

OTHER CONSIDERATIONS BEFORE TAKING ORAL CONTRACEPTIVES

Tell your health care professional 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 professional if they choose to use oral contraceptives. Also, be sure to inform your health care professional if you smoke or are on any medications.

RISKS OF TAKING ORAL CONTRACEPTIVES

DOLISHALE is a non-cyclic oral contraceptive that provides a low daily dose of estrogen and progestin; however, DOLISHALE provides women with more hormonal exposure on a yearly basis (13 additional weeks of hormone intake per year) than conventional cyclic oral contraceptives containing the same strength of synthetic estrogens and similar strength of progestins.

1. Risk 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 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 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 0.05 mg 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 bedrest. 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 such as aura) 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 Tumor

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. Risk of Cancer

It is not known if hormonal birth control pills causes breast cancer. Some studies, but not all, suggest that there could be a slight increase in the risk of breast cancer among current users with longer duration of use.

If you have breast cancer now, or have had it in the past, do not use hormonal birth control because some breast cancers are sensitive to hormones.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 is 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 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 health care 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).

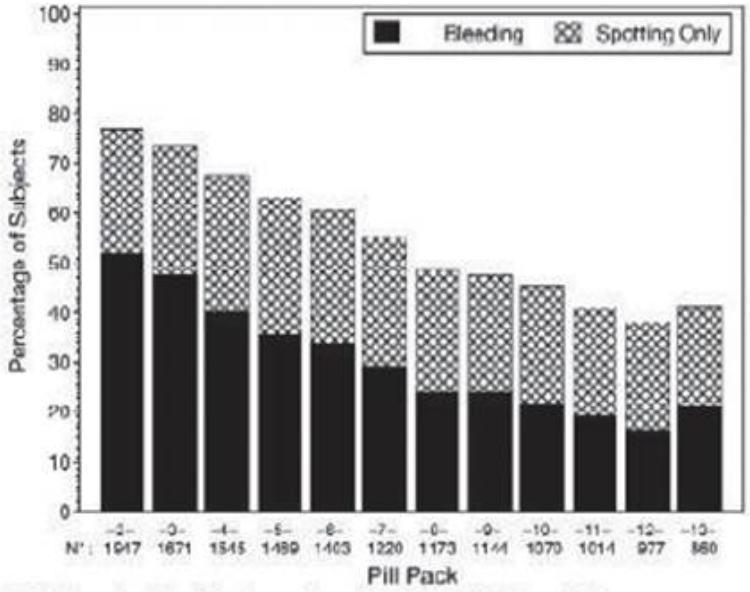
SIDE EFFECTS OF ORAL CONTRACEPTIVES

1. Unscheduled Bleeding and Spotting

Unscheduled bleeding or spotting is likely to occur while you are taking DOLISHALE. Unscheduled bleeding or spotting occurs most often during the first seven pill packs of DOLISHALE use. It tends to decrease with subsequent pill packs of use, but may occur after you have been taking DOLISHALE for some time. In a study of levonorgestrel and ethinyl estradiol tablets, 60% of women had bleeding and/or spotting during the sixth pill pack of use. Bleeding and/or spotting decreased to 48% during pill pack 9, and to 41% during pill pack 13. In this study, the percentage of women who discontinued treatment, at least in part, due to unscheduled bleeding or spotting was 18%.

The following figure shows by pill pack, the percentage of women using levonorgestrel and ethinyl estradiol tablets in a North American study, who experienced unscheduled bleeding or spotting only.

Percentage of Subjects Reporting Bleeding or Spotting Only per Pill Pack

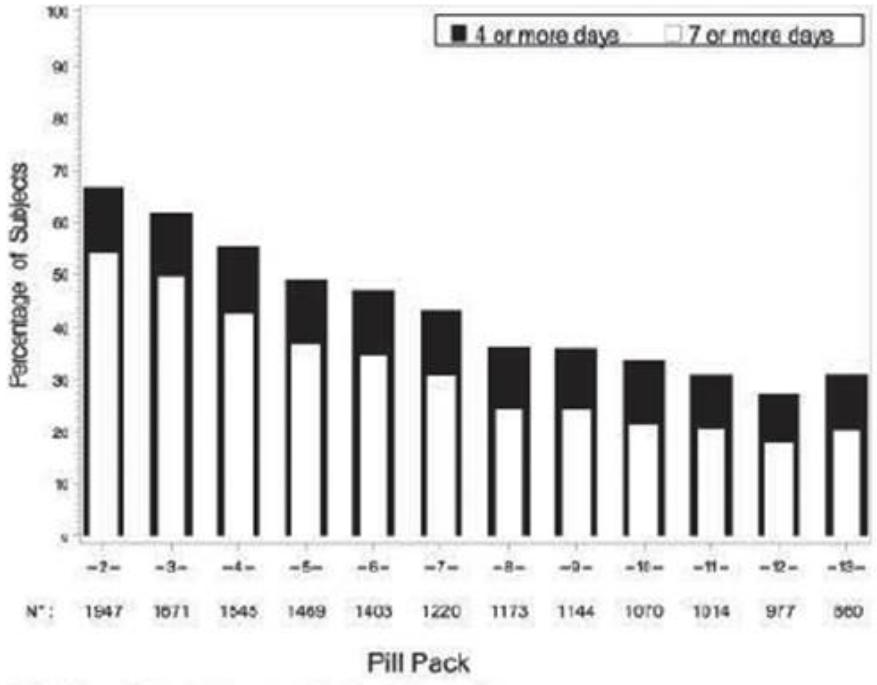


*:The N for each pill pack is the number of subjects with 28 days of data.

Bleeding required sanitary protection; spotting only did not require sanitary protection.

The following figure shows the percentage of women using levonorgestrel and ethinyl estradiol tablets in a North American study who had 4 or more and 7 or more days of bleeding and/or spotting during each pill pack. During pill pack 2, 67% of women experienced 4 or more days of bleeding and/or spotting and 54% of these women experienced 7 or more days of bleeding and/or spotting. During the final pill pack of use of levonorgestrel and ethinyl estradiol tablets (pill pack 13), these percentages were 31% and 20%, respectively.

Percentage of Subjects Reporting Greater Than or Equal to 4 or 7 Days of Bleeding and/or Spotting per Pill Pack (Study 313-NA)



*: The N for each pill pack is the number of subjects with 28 days of data.

It is important to continue taking your pills at the same time each day according to your daily routine, even if you are having unscheduled bleeding or spotting. If the unscheduled bleeding and/or spotting continue for an extended period of time (for example, 7 consecutive days) or if the bleeding is heavy, contact your health care professional.

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 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 health care professional.

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 these or any other side effects bother you, contact your health care professional.

GENERAL PRECAUTIONS

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the

overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

1. Use of Oral Contraceptives Before or During Early Pregnancy

Because regular monthly bleeding does not occur on DOLISHALE, an unexpected pregnancy may be difficult to recognize. If you suspect you may be pregnant, or if you have symptoms of pregnancy such as nausea/vomiting or unusual breast tenderness, a pregnancy test should be performed and you should contact your health care professional. Stop taking DOLISHALE if you are pregnant. Pregnancy is unlikely if the pill is taken as directed.

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 professional 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 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 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 health care professional 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 unscheduled 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 pill pack in which you take drugs that can make oral contraceptives less effective.

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

You should inform your health care professional 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.

What You Should Know About Your Menstrual Cycle When You Use DOLISHALE

You are likely to have unscheduled or unplanned bleeding or spotting when you start to use DOLISHALE. The number of days each month with bleeding or spotting usually decreases over time in the majority of women. In a study of levonorgestrel and ethinyl estradiol tablets, about 5 out of 10 women had 7 or more days of bleeding or spotting while using their third 28-day pill pack of levonorgestrel and ethinyl estradiol. The number of women with 7 or more days of bleeding or spotting decreased to 3 out of 10 women during the use of their seventh pill pack. Among women who continued to use levonorgestrel and ethinyl estradiol tablets for one year, about 6 out of 10 women had no bleeding or spotting during their last month of use.

Do not stop taking DOLISHALE because of bleeding or spotting as this will increase your chance of getting pregnant. If the spotting or bleeding continues for more than 7 consecutive days or if the bleeding is heavy, call your health care provider.

Can I Get Pregnant While Taking DOLISHALE?

You are not likely to get pregnant if you take DOLISHALE at the same time everyday as directed by your health care provider. Because regular monthly bleeding does not occur on DOLISHALE, it may be difficult to recognize if you get pregnant. If you suspect that you may be pregnant, or if you have symptoms of pregnancy such as nausea/vomiting or unusual breast tenderness, you should have a pregnancy test and you should contact your health care professional. Stop taking DOLISHALE if you are pregnant.

HOW TO TAKE *DOLISHALE*

Important Points to Remember

Before You Start Taking DOLISHALE:

1. BE SURE TO READ THESE DIRECTIONS:

Before you start taking DOLISHALE.

And

Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE *DOLISHALE* 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 DOLISHALE. This will usually go away. If it doesn't go away, check with your health care professional.

4. MOST WOMEN HAVE SPOTTING OR BLEEDING DURING THE FIRST FEW MONTHS OF TAKING *DOLISHALE*. Do not stop taking your pills even if you are having bleeding or spotting. If the bleeding or spotting lasts for more than 7 consecutive days, talk to your health care provider.

5. 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.

6. IF YOU VOMIT (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 and/or spermicide) until you

check with your health care professional.

7. IF YOU HAVE TROUBLE REMEMBERING TO TAKE *DOLISHALE*, talk to your health care professional about how to make pill-taking easier or about using another method of birth control.

8. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your health care professional.

BEFORE YOU START TAKING *DOLISHALE*

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL. It is important to take your pill at the SAME TIME every day.

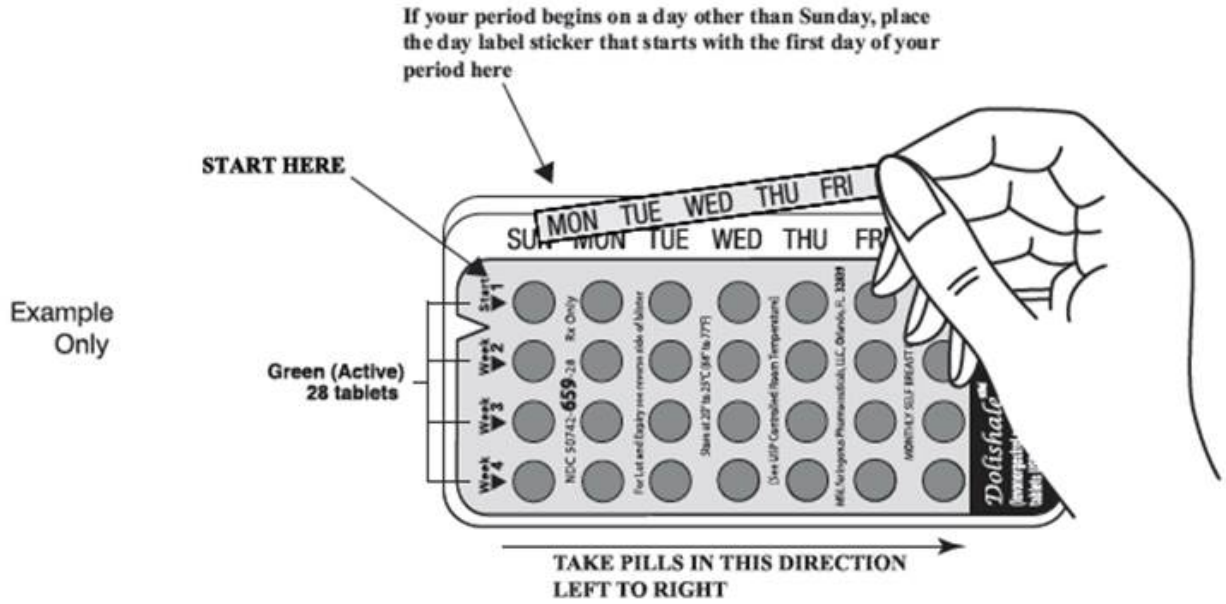
2. LOOK AT YOUR *DOLISHALE* BLISTER CARD. The pill pack has 28 "active" green pills (with hormones).

3. ALSO FIND:

1) where on the pack to start taking pills,

2) in what order to take the pills (follow the arrows),

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 NONHORMONAL BIRTH CONTROL (such as condoms and/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 *DOLISHALE*

Day 1 Start

1. If 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) is Sunday, then follow the days of the week imprinted on the plastic compact. You do not need to use the Day Label Stickers.

2. If 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) is on a day other than Sunday, then pick

the day label sticker that starts with that day of the week.

3. Place this chosen day label sticker over the area that has the days of the week (starting with Sunday) imprinted on the plastic compact as shown in the graphic above.

4. Take the first "active" green pill of the first pack during the *first 24 hours of your period*.

5. 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.

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 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 pill. **Do not wait any days between packs.**

IF YOU SWITCH FROM ANOTHER BRAND OF COMBINATION PILLS:

When switching from a 21 pill pack: Start DOLISHALE on the first day of your period (withdrawal bleed). Be sure that no more than 7 days pass between the last day of your 21-day pack and your first DOLISHALE pill.

When switching from a 28 pill pack (21 active and 7 inactive pills, or 24 active and 4 inactive pills): Start DOLISHALE on the first day of your period (withdrawal bleed). Be sure that no more than 7 days pass after the last active pill and your first DOLISHALE pill.

IF YOU SWITCH FROM ANOTHER TYPE OF BIRTH CONTROL

When switching from other types of birth control such as pills containing only a progestin (progestin only pill or POP), an injection, or an implant, your health care professional will provide you with instructions for when to start DOLISHALE.

WHAT TO DO IF YOU MISS PILLS

Combination oral contraceptives may not be as effective if you miss pills. Instructions for what to do if you miss pills are provided in the following table.

# of pills missed in a row	**What to do when you miss a pill(s)**
1 missed pill	• Take the missed pill as soon as you remember. THEN • Take the next pill at your regular time. This means you may take 2 pills in 1 day. • You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms and/or spermicide) as a back-up for those 7 days.
2 missed pills and remembered on the day of the second missed pill	• Take 2 missed pills on the day you remember. The following day you are back on schedule to take 1 pill a day. For example, you take your pills in the morning and you missed 1 pill on Monday and 1 on Tuesday. On Tuesday evening you remembered that you missed your Monday and Tuesday pills. You take the 2 missed pills on Tuesday evening and on Wednesday morning you're back on schedule and you take 1 pill. • You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms and/or spermicide) as a back-up for those 7 days.

2 missed pills and remembered on the day after the second pill is missed	• Take 2 missed pills on the day you remember. The next day you take 2 pills. The following day you are back on schedule to take your pills. For example, you take your pills in the morning and you missed 1 pill on Monday and 1 on Tuesday. On Wednesday morning you remembered that you missed your Monday and Tuesday pills. You take the 2 missed pills on Wednesday morning and 2 pills on Thursday morning. On Friday morning you're back on schedule and you take 1 pill. • You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms and/or spermicide) as a back-up for those 7 days.
3 or more missed pills	• Contact your health care professional for further advice. Keep taking one pill every day until you reach your health care professional. Do not take the missed pills. • You COULD BECOME PREGNANT if you have sex during the 7 days after you restart your pills. You MUST use a nonhormonal birth-control method (such as condoms and/or spermicide) as a back-up for those 7 days.

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 professional.

PREGNANCY DUE TO PILL FAILURE

The incidence of pill failure resulting in pregnancy is approximately 1 to 2% per year (1 to 2 pregnancies per 100 women per year of use) if taken every day as directed, but the average 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 professional.

PREGNANCY AFTER STOPPING THE PILL

If you do not desire pregnancy, you should use another method of birth-control immediately after stopping DOLISHALE. A pregnancy can occur within days after stopping DOLISHALE.

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

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 professional or pharmacist.

OTHER INFORMATION

Your health care 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 health care professional believes that it is appropriate to postpone it. You should be reexamined at least once a year. Be sure to inform your health care 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 health care 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, some information suggests that the use of oral contraceptives provide certain other benefits. The benefits are:

• Decreased blood loss, and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur.

• Pain or other cycle-related symptoms may occur 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 professional or pharmacist. They have a more technical leaflet called the Professional Labeling which you may wish to read.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Rx Only

Iss: 12/2024

Rev B

Manufactured for:

Ingenus Pharmaceuticals, LLC

Orlando, FL 32839-6408

Product of China

PRINCIPAL DISPLAY PANEL 1-cycle carton

PRINCIPAL DISPLAY PANEL 3-cycle carton

DOLISHALE

levonorgestrel and ethinyl estradiol tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50742-659
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
LEVONORGESTREL (UNII: 5W7SIA7YZW) (LEVONORGESTREL - UNII:5W7SIA7YZW)	LEVONORGESTREL	90 ug
ETHINYL ESTRADIOL (UNII: 423D2T571U) (ETHINYL ESTRADIOL - UNII:423D2T571U)	ETHINYL ESTRADIOL	20 ug

Inactive Ingredients	
Ingredient Name	**Strength**
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
POLYETHYLENE GLYCOL 3000 (UNII: SA1B764746)	
TALC (UNII: 7SEV7J4R1U)	
POLYVINYL ALCOHOL, UNSPECIFIED (UNII: 532B59J990)	
LECITHIN, SOYBEAN (UNII: 1DI56QDM62)	
FD&C BLUE NO. 2--ALUMINUM LAKE (UNII: 4AQJ3LG584)	
FD&C YELLOW NO. 5 (UNII: I753WB2F1M)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	

Product Characteristics			
Color	GREEN	**Score**	no score
Shape	ROUND (biconvex)	**Size**	5mm
Flavor		**Imprint Code**	H1
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50742-659-28	1 in 1 CARTON	01/03/2021	
1		28 in 1 BLISTER PACK; Type 0: Not a Combination Product		
2	NDC:50742-659-84	3 in 1 CARTON	01/03/2021	
2		28 in 1 BLISTER PACK; Type 0: Not a Combination Product		
3	NDC:50742-659-68	6 in 1 CARTON	01/03/2021	
3		28 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA091692	01/03/2021	

Labeler - Ingenus Pharmaceuticals, LLC (833250017)

Registrant - Novast Laboratories, Ltd. (527695995)

Establishment

Name	Address	ID/FEI	Business Operations
Novast Laboratories, Ltd.		527695995	ANALYSIS(50742-659) , LABEL(50742-659) , MANUFACTURE(50742-659) , PACK(50742-659)

Revised: 4/2025 Ingenus Pharmaceuticals, LLC