

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LoSeasonique (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets) for oral use

Initial U.S. Approval: 1982

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

See full prescribing information for complete boxed warning.

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

INDICATIONS AND USAGE

LoSeasonique is an estrogen/progestin COC indicated for use by women to prevent pregnancy. (1)

DOSAGE AND ADMINISTRATION

Take one tablet daily by mouth at the same time every day for 91 days. (2)

DOSAGE FORMS AND STRENGTHS

LoSeasonique consists of 84 orange tablets containing 0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol, and 7 yellow tablets containing 0.01 mg ethinyl estradiol. (3)

CONTRAINDICATIONS

- A high risk of arterial or venous thrombotic diseases (4)
- Breast cancer or other estrogen- or progestin-sensitive cancer (4)
- Liver tumors or liver disease (4)
- Pregnancy (4)

WARNINGS AND PRECAUTIONS

- Vascular risks: Stop LoSeasonique if a thrombotic event occurs. Stop LoSeasonique at least 4 weeks before and through 2 weeks after major surgery. Start LoSeasonique no earlier than 4 weeks after delivery, in women who are not breastfeeding. (5.1)
- Liver disease: Discontinue LoSeasonique if jaundice occurs. (5.3)
- High blood pressure: Do not prescribe LoSeasonique for women with uncontrolled hypertension or hypertension with vascular disease. (5.4)
- Carbohydrate and lipid metabolic effects: Monitor prediabetic and diabetic women taking LoSeasonique. Consider an alternate contraceptive method for women with uncontrolled dyslipidemias. (5.6)
- Headache: Evaluate significant change in headaches and discontinue LoSeasonique if indicated. (5.7)
- Uterine bleeding: Evaluate irregular bleeding or amenorrhea. (5.8)

ADVERSE REACTIONS

The most common adverse reactions for COCs are irregular uterine bleeding, nausea, breast tenderness, and headaches. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Duramed Pharmaceuticals Inc. at 1-800-222-0190 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Drugs or herbal products that induce certain enzymes, including CYP3A4, may decrease the effectiveness of COCs or increase breakthrough bleeding. Counsel patients to use a back-up method or alternative method of contraception when enzyme inducers are used with COCs. (7)

USE IN SPECIFIC POPULATIONS

- Nursing: Not recommended for nursing mothers; can decrease milk production (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.

Revised: 10/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Vascular Events

5.2 Carcinoma of the Breast and Cervix

5.3 Liver Disease

5.4 High Blood Pressure

5.5 Gallbladder Disease

5.6 Carbohydrate and Lipid Metabolic Effects

5.7 Headache

5.8 Bleeding Irregularities

5.9 Interference with Laboratory Tests

5.10 Monitoring

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

7 DRUG INTERACTIONS

7.1 Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products

7.2 Increase in Plasma Levels of Estradiol Associated with Co-Administered Drugs

7.3 Changes in Plasma Levels of Co-Administered Drugs

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

17.2 FDA-Approved Patient Labeling

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

FULL PRESCRIBING INFORMATION

WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS

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

1 INDICATIONS AND USAGE

LoSeasonique™ (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets) is indicated for use by women to prevent pregnancy.

2 DOSAGE AND ADMINISTRATION

Take one tablet by mouth at the same time every day. The dosage of LoSeasonique is one orange tablet containing levonorgestrel and ethinyl estradiol daily for 84 consecutive days, followed by one yellow ethinyl estradiol tablet for 7 days. To achieve maximum contraceptive effectiveness, LoSeasonique must be taken exactly as directed and at intervals not exceeding 24 hours.

Instruct the patient to begin taking LoSeasonique on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first orange tablet is taken that day. One orange tablet should be taken daily for 84 consecutive days, followed by one yellow tablet for 7 consecutive days. A non-hormonal back-up method of contraception (such as condoms or spermicide) should be used until an orange tablet has been taken daily for 7 consecutive days. A scheduled period should occur during the 7 days that the yellow tablets are taken.

Begin the next and all subsequent 91-day cycles without interruption on the same day of the week (Sunday) on which the patient began her first dose of LoSeasonique, following the same schedule: 84 days taking an orange tablet followed by 7 days taking a yellow tablet. If the patient does not immediately start her next pill pack, she should protect herself from pregnancy by using a non-hormonal back-up method of contraception until she has taken an orange tablet daily for 7 consecutive days.

If unscheduled spotting or bleeding occurs, instruct the patient to continue on the same regimen. If the bleeding is persistent or prolonged, advise the patient to consult her healthcare provider.

For patient instructions regarding missed pills, see *PATIENT COUNSELING INFORMATION (17.2)*.

For postpartum women who are not breastfeeding, start LoSeasonique no earlier than four to six weeks postpartum. If the patient starts on LoSeasonique postpartum and has not yet had a period, evaluate for possible pregnancy, and instruct her to use an additional method of contraception until she has taken an orange tablet for 7 consecutive days.

3 DOSAGE FORMS AND STRENGTHS

LoSeasonique tablets are available in Extended-Cycle Tablet Dispensers, each containing a 13-week supply of tablets: 84 orange tablets, each containing 0.1 mg of levonorgestrel and 0.02 mg ethinyl estradiol, and 7 yellow tablets each containing 0.01 mg of ethinyl estradiol. The orange tablets are round, film-coated, unscored tablets with a debossed stylized **b** on one side and **28** on the other side. The yellow tablets are round, film-coated, unscored tablet with a debossed stylized **b** on one side and **56** on the other side.

4 CONTRAINDICATIONS

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

- A high risk of arterial or venous thrombotic diseases. Examples include women who are known to:
 - Smoke, if over age 35
 - Have deep vein thrombosis or pulmonary embolism, now or in the past
 - Have cerebrovascular disease
 - Have coronary artery disease

- Have thrombotic valvular or thrombotic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
- Have hypercoagulopathies
- Have uncontrolled hypertension
- Have diabetes with vascular disease
- Have headaches with focal neurological symptoms or have migraine headaches with or without aura if over age 35

- Breast cancer or other estrogen- or progestin-sensitive cancer, now or in the past
- Liver tumors, benign or malignant, or liver disease
- Pregnancy, because there is no reason to use OCs during pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Vascular Events

Stop COCs if an arterial or deep venous thrombotic event occurs. Although use of COCs increases the risk of venous thromboembolism, pregnancy increases the risk of venous thromboembolism as much or more than the use of COCs. The risk of venous thromboembolism in women using COCs is 3 to 9 per 10,000 woman-years. Use of COCs also increases the risk of arterial thromboses such as strokes and myocardial infarctions, especially in women with other risk factors for these events.

Use of LoSeasonique provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing the same strength synthetic estrogens and progestins (an additional 9 and 13 weeks of exposure to progestin and estrogen, respectively, per year.)

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

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

Stop COCs if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions. Evaluate for retinal vein thrombosis immediately.

5.2 Carcinoma of the Breast and Cervix

Women who currently have or have had breast cancer should not use COCs because breast cancer may be hormonally sensitive.

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

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

5.3 Liver Disease

Discontinue COCs if jaundice develops. Steroid hormones may be poorly metabolized in patients with impaired liver function.

Hepatic adenomas are associated with COC use. An estimate of the attributable risk is 3.3 cases/100,000 COC users. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

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

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

5.4 High Blood Pressure

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

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

5.5 Gallbladder Disease

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

5.6 Carbohydrate and Lipid Metabolic Effects

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

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

5.7 Headache

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

5.8 Bleeding Irregularities

Unscheduled (breakthrough) bleeding and spotting sometimes occur in patients on COCs, especially during the first 3 months of use. If bleeding persists, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC product.

When prescribing LoSeasonique, the convenience of fewer planned menses (4 per year instead of 13 per year) should be weighed against the inconvenience of increased unscheduled bleeding and/or spotting. The clinical trial that evaluated the efficacy of LoSeasonique also assessed unscheduled bleeding. The participants in this 12-month clinical trial (N=2,185) completed the equivalent of over 20,000 28-day cycles of exposure and were composed primarily of women who had used OCs previously (89%), as opposed to new users (11%). A total of 209 subjects (9.6%) discontinued LoSeasonique, at least in part, due to bleeding and/or spotting.

Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over time, with an average of 2-3 days of bleeding and/or spotting per each 91-day cycle. Unscheduled bleeding and unscheduled spotting decreased over successive 91-day cycles. Table 1 below presents the number of days with unscheduled bleeding in treatment cycles 1 and 4. Table 2 presents the number of days with unscheduled spotting in treatment cycles 1 and 4.

Table 1: Total Number of Days with Unscheduled Bleeding

91-Day Treatment Cycle	Days per 84-Day Interval				Days per 28-Day Interval
	Q1	Median	Q3	Mean	Mean
1st	0	5	11	7.5	2.5
4th	0	0	5	3.5	1.2

Q1=Quartile 1: 25% of women had this number of days of unscheduled bleeding
 Median: 50% of women had ≤ this number of days of unscheduled bleeding
 Q3=Quartile 3: 75% of women had ≤ this number of days of unscheduled bleeding

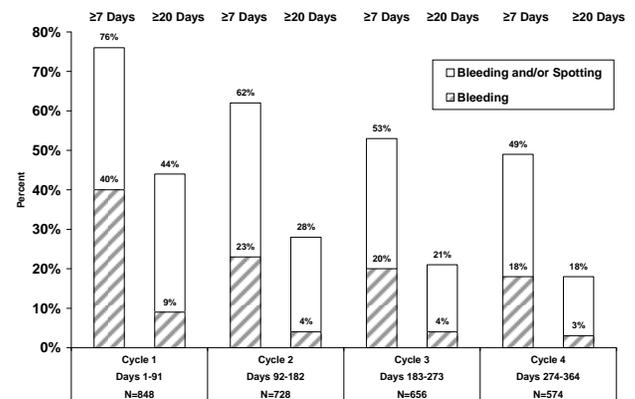
Table 2: Total Number of Days with Unscheduled Spotting

91-Day Treatment Cycle	Days per 84-Day Interval				Days per 28-Day Interval
	Q1	Median	Q3	Mean	Mean
1st	3	10	19	14.0	4.7
4th	0	3	10	6.5	2.2

Q1=Quartile 1: 25% of women had ≤ this number of days of unscheduled spotting
 Median: 50% of women had ≤ this number of days of unscheduled spotting
 Q3=Quartile 3: 75% of women had ≤ this number of days of unscheduled spotting

Figure 1 shows the percentage of LoSeasonique subjects participating in the primary clinical trial with ≥ 7 days or ≥ 20 days of unscheduled bleeding and/or spotting, or just unscheduled bleeding, during each 91-day treatment cycle.

Figure 1. Percent of Women Taking LoSeasonique who Reported Unscheduled Bleeding and/or Spotting (Based on Daily Diaries)



Amenorrhea sometimes occurs in women who are using COCs. Pregnancy should be ruled out in the event of amenorrhea. Some women may encounter amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was pre-existent.

5.9 Interference with Laboratory Tests

The use of COCs may change the results of some laboratory tests, such as coagulation factors, lipids, glucose tolerance, and binding proteins. Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid binding globulin increase with use of COCs.

5.10 Monitoring

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

6 ADVERSE REACTIONS

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

- Serious cardiovascular events and smoking [see **BOXED WARNING**]
- Vascular events [see **WARNINGS AND PRECAUTIONS (5.1)**]
- Liver disease [see **WARNINGS AND PRECAUTIONS (5.3)**]

Adverse reactions commonly reported by COC users are:

- Irregular uterine bleeding
- Nausea
- Breast tenderness
- Headache

6.1 Clinical Trial Experience

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

The clinical trial that evaluated the safety and efficacy of LoSeasonique was a 12-month, multicenter, non-comparative open-label study, which enrolled women aged 18-41, of whom 2,185 took at least one dose of LoSeasonique.

Adverse Reactions Leading to Study Discontinuation: 11% of the women discontinued from the clinical trial due to an adverse reaction; the most common adverse reactions leading to discontinuation were irregular and/or heavy uterine bleeding, headache, mood changes, nausea, acne, and weight gain.

Common Treatment-Emergent Adverse Reactions (≥ 5% of women): headaches (33%); irregular and/or heavy uterine bleeding (13%), dysmenorrhea (11%), nausea and/or vomiting (11%), back pain (8%).

7 DRUG INTERACTIONS

No formal drug-drug interaction studies were conducted with LoSeasonique.

7.1 Changes in Contraceptive Effectiveness Associated with Co-Administration of Other Products

If a woman on hormonal contraceptives takes a drug or herbal product that induces enzymes, including CYP3A4, that metabolize contraceptive hormones, counsel her to use additional contraception or a different method of contraception. Drugs or herbal products that induce such enzymes may decrease the plasma concentrations of contraceptive hormones, and may decrease the effectiveness of hormonal contraceptives or increase breakthrough bleeding. Some drugs or herbal products that may decrease the effectiveness of hormonal contraceptives include:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

HIV protease inhibitors: Significant changes (increase or decrease) in the plasma levels of the estrogen and progestin have been noted in some cases of co-administration of HIV protease inhibitors.

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

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

7.2 Increase in Plasma Levels of Estradiol Associated with Co-Administered Drugs

Co-administration of atorvastatin and certain COCs containing ethinyl estradiol increase AUC values for ethinyl estradiol by approximately 20%. Ascorbic acid and acetaminophen may increase plasma ethinyl estradiol levels, possibly by inhibition of conjugation. CYP3A4 inhibitors such as itraconazole or ketoconazole may increase plasma hormone levels.

7.3 Changes in Plasma Levels of Co-Administered Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

The administration of COCs to induce withdrawal bleeding should not be used as a test for pregnancy. Combination OCs should not be used during pregnancy to treat threatened or habitual abortion.

Women who do not breastfeed may start COCs no earlier than four to six weeks postpartum.

8.3 Nursing Mothers

When possible, advise the nursing mother to use other forms of contraception until she has weaned her child. Estrogen-containing OCs can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well established; however, it can occur at any time in some women. Small amounts of estrogen and progestin from low dose COCs are present in breast milk, but these doses have not produced adverse effects in breastfeeding infants.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

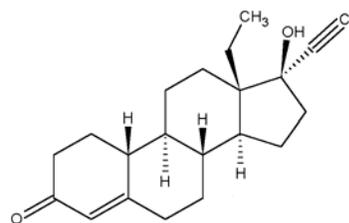
10 OVERDOSAGE

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

11 DESCRIPTION

LoSeasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol) tablets provide an oral contraceptive regimen of 84 orange tablets each containing 0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol, followed by 7 yellow tablets each containing 0.01 mg ethinyl estradiol.

The structural formulas for the active components are:

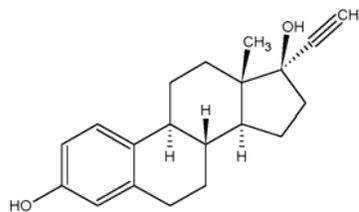


Levonorgestrel

$C_{21}H_{28}O_2$

MW: 312.4

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



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

Ethinyl Estradiol is 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol, (17 α)-.

Inactive ingredients for the orange tablets include FD&C Yellow # 6 (Sunset Yellow) aluminum lake, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, corn starch, titanium dioxide and triacetin.

Inactive ingredients for the yellow tablets include anhydrous lactose, FD&C Yellow # 10 aluminum lake, FD&C Yellow # 6 (Sunset Yellow) aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polacrillin potassium, polyethylene glycol, polysorbate 80 and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of LoSeasonique in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability nearly 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 systemic bioavailability of ethinyl estradiol is approximately 43%.

The mean plasma pharmacokinetic parameters of LoSeasonique following a single oral dose of three levonorgestrel/ethinyl estradiol combination tablets in normal healthy women under fasting conditions are reported in Table 3.

Table 3: Mean (SD) Pharmacokinetic Parameters Following a Single Dose Administration of Three Tablets of LoSeasonique in 30 Healthy Women under Fasting Conditions

	$AUC_{0-\infty}$	C_{max}	T_{max}	$T_{1/2}$
Levonorgestrel	76.5 \pm 24.9 ng*hr/mL	6.0 \pm 1.6 ng/mL	1.6 \pm 0.6 hours	28.5 \pm 8.7 hours
Ethinyl estradiol	1335.8 \pm 365.3 pg*hr/mL	122.8 \pm 39.5 pg/mL	1.8 \pm 0.7 hours	17.5 \pm 7.4 hours

$AUC_{0-\infty}$ = area under the drug concentration curve from time 0 to infinity

C_{max} = maximum concentration

T_{max} = time to maximum concentration

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

Distribution

The apparent volume of distribution of levonorgestrel and ethinyl estradiol is reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively. Levonorgestrel is about 97.5 to 99% protein-bound, principally to sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. Ethinyl estradiol is about 95 to 97% bound to serum albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis, which leads to decreased levonorgestrel clearance. Following repeated daily dosing of combination levonorgestrel/ethinyl estradiol OCs, levonorgestrel plasma

concentrations accumulate more than predicted based on single-dose pharmacokinetics, due in part, to increased SHBG levels that are induced by ethinyl estradiol, and a possible reduction in hepatic metabolic capacity.

Metabolism

Following absorption, levonorgestrel is conjugated at the 17 β -OH position to form sulfate conjugates and, to a lesser extent, glucuronide conjugates in plasma. Significant amounts of conjugated and unconjugated 3 α , 5 β -tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3 α , 5 α -tetrahydrolevonorgestrel and 16 β -hydroxylevonorgestrel. Levonorgestrel and its phase I metabolites are excreted primarily as glucuronide conjugates. 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.

First-pass metabolism of ethinyl estradiol involves formation of ethinyl estradiol-3-sulfate in the gut wall, followed by 2-hydroxylation of a portion of the remaining untransformed ethinyl estradiol by hepatic cytochrome P-450 3A4 (CYP3A4). Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinyl estradiol hydroxylation. Hydroxylation at the 4-, 6-, and 16- positions may also occur, although to a much lesser extent than 2-hydroxylation. The various hydroxylated metabolites are subject to further methylation and/or conjugation.

Excretion

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates, and then undergoes enterohepatic recirculation.

Race

The effect of race on the pharmacokinetics of LoSeasonique has not been evaluated.

Renal and Hepatic Impairment

No formal studies were conducted to evaluate the effect of hepatic or renal disease on the disposition of LoSeasonique. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

[See **WARNINGS AND PRECAUTIONS** (5.2, 5.3).]

14 CLINICAL STUDIES

In a 12-month multicenter open-label clinical trial, 2,185 women aged 18-41 were studied to assess the safety and efficacy of LoSeasonique, completing the equivalent of 20,937 28-day cycles of exposure. The racial demographic of those enrolled was: Caucasian (75%), African-American (12%), Hispanic (10%), Asian (2%), and Other (2%). There were no exclusions for body mass index (BMI) or weight. The weight range for those women treated was 87 to 381 lbs., with a mean weight of 159 lbs. Among the women in the trial, 59% were current or recent hormonal contraceptive users, 30% were prior users (had used hormonal contraceptives in the past but not in the 6 months prior to enrollment) and 11% were new starts. Of treated women, 14.2% were lost to follow-up, 11.6% discontinued due to an adverse event, and 10.3% discontinued by withdrawing their consent.

The pregnancy rate (Pearl Index [PI]) in women aged 18 to 35 years was 2.74 pregnancies per 100 women-years of use (95% confidence interval 1.92 – 3.78), based on 36 pregnancies that occurred after the onset of treatment and within 14 days after the last combination pill. Cycles in which conception did not occur, but which included the use of backup contraception, were not included in the calculation of the PI. The PI includes patients who did not take the drug correctly.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lo Seasonique (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets) are available in an Extended-Cycle Tablet Dispenser that contains 84 round, orange tablets and 7 round, yellow tablets. Each orange tablet (debossed stylized **b** on one side and **28** on the other side) contains 0.1 mg levonorgestrel and 0.02 mg ethinyl estradiol. Each yellow tablet (debossed stylized **b** on one side and **556** on the other side) contains 0.01 mg ethinyl estradiol. The tablets should not be removed from the protective blister packaging and outer plastic dispenser to avoid damage to the product.

The plastic dispenser should be kept in the foil pouch until dispensed to the patient.

Box of 2 Extended-Cycle Tablet Dispensers NDC 51285-092-87

Storage

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

17 PATIENT COUNSELING INFORMATION

See FDA-APPROVED PATIENT LABELING (17.2)

17.1 Information for Patients

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

17.2 FDA Approved Patient Labeling

Guide for Using LoSeasonique

WARNING TO WOMEN WHO SMOKE

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

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

WHAT IS LoSeasonique?

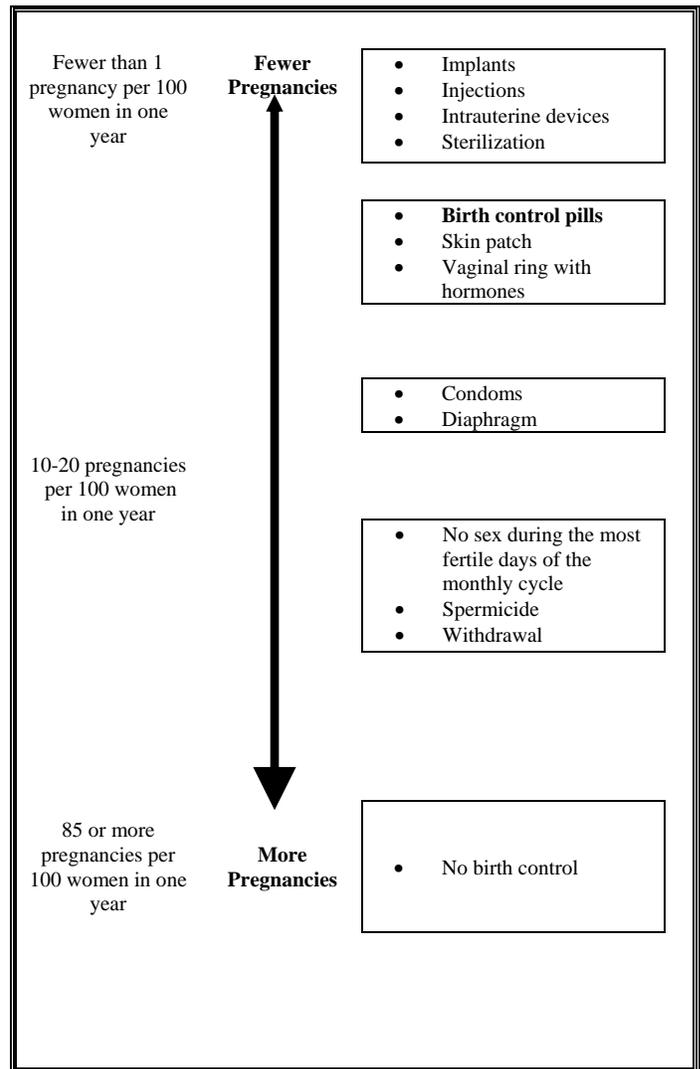
LoSeasonique is a birth control pill. It contains two female hormones, an estrogen called ethinyl estradiol, and a progestin called levonorgestrel.

HOW WELL DOES LoSeasonique WORK?

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

Based on the results of a single clinical study lasting 12 months, 2 to 4 women, out of 100 women, may get pregnant during the first year they use LoSeasonique.

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

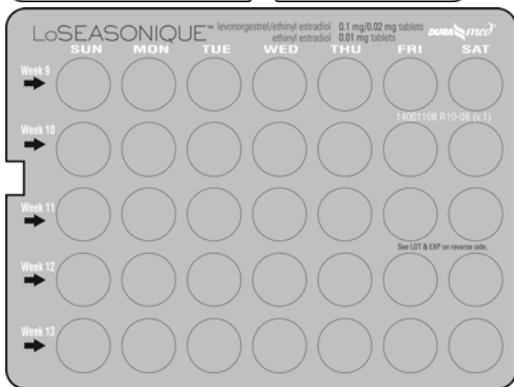
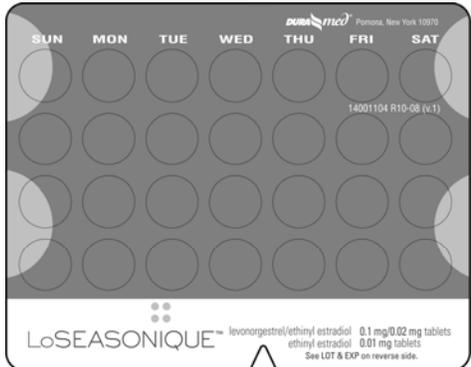
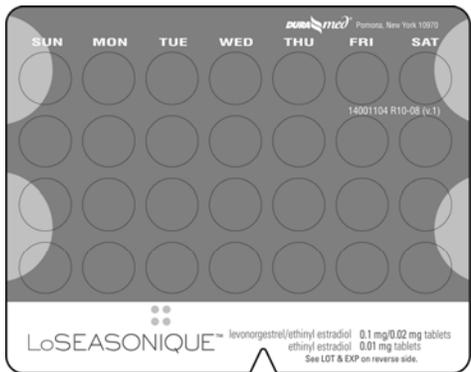


HOW DO I TAKE LoSeasonique?

1. 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.
2. Many women have spotting or light bleeding, or may feel sick to their stomach during the first few months of taking LoSeasonique. If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your healthcare provider.
3. Missing pills can also cause spotting or light bleeding, even when you take the missed pills later. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.
4. If you have trouble remembering to take LoSeasonique, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

Before you start taking LoSeasonique

1. Decide what time of day you want to take your pill. It is important to take it at about the same time every day.
2. Look at your Extended-Cycle Tablet Dispenser. Your Tablet Dispenser consists of 3 trays with cards that hold 91 individually sealed pills (a 13-week or 91-day cycle). The 91 pills consist of 84 orange and 7 yellow pills. Trays 1 and 2 each contain 28 orange pills (4 rows of 7 pills). Tray 3 contains 35 pills consisting of 28 orange pills (4 rows of 7 pills) and 7 yellow pills (1 row of 7 pills).



3. Also find:

- Where on the first tray in the pack to start taking pills (upper left corner at the start arrow) and
- In what order to take the pills (follow the weeks and arrow).

4. Be sure you have ready at all times another kind of birth control (such as condoms or spermicides), to use as a back-up in case you miss pills.

When to Start LoSeasonique

1. Take the first orange pill on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the first orange pill that same day.
2. Use another method of birth control (such as condoms or spermicides) as a back-up method if you have sex anytime from the Sunday you start your first orange pill until the next Sunday (first 7 days). If you have been using a different hormonal method of birth control (such as a different pill, the “patch,” or the “vaginal ring”), you need to use another method of birth control (such as condoms or spermicides) each time you have sex after stopping your old method of birth control until you have taken LoSeasonique for 7 days.

How to Take LoSeasonique

1. Take one pill at the same time every day until you have taken the last pill in the tablet dispenser.
 - Do not skip pills even if you are experiencing 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 tablet dispenser

- After taking the last yellow pill, start taking the first orange pill from a new Extended-Cycle Tablet Dispenser the very next day (this should be on a Sunday) regardless of when your period started.

3. If you miss your scheduled period when you are taking the yellow pills, contact your healthcare provider because you may be pregnant. If you are pregnant, you should stop taking LoSeasonique.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** orange pill:

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

If you **MISS 2** orange pills in a row:

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

If you **MISS 3 OR MORE** orange pills in a row:

1. Do not take the missed pills. Keep taking 1 pill every day as indicated on the pack until you have completed all of the remaining pills in the pack. For example: If you resume taking the pill on Thursday, take the pill under “Thursday” and do not take the missed pills. You may experience bleeding during the week following the missed pills.
2. You could become pregnant if you have sex during the days of missed pills or during the first **7 days** after restarting your pills.
3. You **MUST** use a non-hormonal birth control method (such as condoms or spermicide) as a back-up when you miss pills and for the first 7 days after you restart your pills. If you do not have your period when you are taking the yellow pills, call your healthcare provider because you may be pregnant.

If you **MISS ANY** of the 7 yellow pills:

1. Throw away the missed pills.
2. Keep taking the scheduled pills until the pack is finished.
3. You do not need a back-up method of birth control.

Finally, if you are still not sure what to do about the pills you have missed

1. Use a back-up method anytime you have sex.
2. Keep taking one pill each day until you contact your healthcare provider.

WHO SHOULD NOT TAKE LOSEASONIQUE?

Your healthcare provider will not give you LoSeasonique if you have:

- Ever had breast cancer or any cancer that is sensitive to female hormones
- Liver disease, including liver tumors
- Ever had blood clots in your arms, legs, or lungs
- Ever had a stroke
- Ever had a heart attack
- Certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
- An inherited problem with your blood that makes it clot more than normal
- High blood pressure that medicine can't control
- Diabetes with kidney, eye, or blood vessel damage
- Certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision

Also, do not take birth control pills if you:

- Smoke and are over 35 years old
- Are pregnant

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

WHAT ELSE SHOULD I KNOW ABOUT TAKING LoSeasonique?

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

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

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

If you are breastfeeding, consider another birth control method until you are ready to stop breastfeeding. Birth control pills that contain estrogen, like LoSeasonique, may decrease the amount of milk you make. A small amount of the pill's hormones pass into breast milk, but this has not caused harmful effects in breastfeeding infants.

Tell your health care provider about all medicines and herbal products that you take. Some medicines and herbal products may make birth control pills less effective, including:

- barbiturates
- bosentan
- carbamazepine
- felbamate
- griseofulvin
- oxcarbazepine
- phenytoin
- rifampin
- St. John's wort
- topiramate

Consider using another birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your physician may need to adjust the dose of lamotrigine.

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

WHAT ARE THE MOST SERIOUS RISKS OF TAKING BIRTH CONTROL PILLS?

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age > 35. It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious blood clots are blood clots in the:

- Legs (thrombophlebitis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

A few women who take birth control pills may get:

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

All of these events are uncommon in healthy women.

Call your health care provider right away if you have:

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

WHAT ARE COMMON SIDE EFFECTS OF BIRTH CONTROL PILLS?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat levels in the blood.
- Depression, especially if you have had depression in the past. Call your health care provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

This is not a complete list of possible side effects. Talk to your health care provider if you develop any side effects that concern you.

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

DO BIRTH CONTROL PILLS CAUSE CANCER?

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

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

WHAT SHOULD I KNOW ABOUT MY PERIOD WHEN TAKING LoSeasonique?

When you take LoSeasonique, which has a 91-day extended dosing cycle, you should expect to have 4 scheduled periods per year (bleeding when you are taking the 7 yellow pills). Each period is likely to last about 2 to 3 days. However, you will probably have more bleeding or spotting between your scheduled periods than if you were using a birth control pill with a 28-day dosing cycle. This bleeding or spotting tends to decrease with time. Do not stop taking LoSeasonique because of this bleeding or spotting. If the spotting continues for more than 7 consecutive days or if the bleeding is heavy, call your healthcare provider.

WHAT IF I MISS MY SCHEDULED PERIOD WHEN TAKING LoSeasonique?

You should consider the possibility that you are pregnant if you miss your scheduled period (no bleeding on the days that you are taking yellow tablets). Since scheduled periods are less frequent when you are taking LoSeasonique, notify your healthcare provider that you have missed your period and that you are taking LoSeasonique. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider evaluates you to determine if you are pregnant. Stop taking LoSeasonique if it is determined that you are pregnant.

WHAT IF I WANT TO BECOME PREGNANT?

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

Rx only

DURAMED PHARMACEUTICALS, INC.
Subsidiary of Barr Pharmaceuticals, Inc. Pomona, New York 10970

Issued October 2008
11001294
Revised 10/24/2008