PRODUCT MONOGRAPH

# Pr SEASONIQUE®

levonorgestrel and ethinyl estradiol tablets, USP
0.15 mg and 0.03 mg
and
ethinyl estradiol tablets, USP
0.01 mg

Oral Contraceptive

Teva Women's Health Inc.
425 Privet Road
Horsham , PA USA 19044

Date of Preparation:
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Distributor:

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Montreal, Quebec H4P 2T4

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# Pr SEASONIQUE®

(levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg combination tablets USP
and ethinyl estradiol 0.01 mg tablets USP)

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Clinically Relevant Non Medicinal Ingredients |
|---|---|---|
| Oral | Tablets<br>0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol<br>and<br>0.01 mg ethinyl estradiol | Anhydrous lactose<br>Lactose monohydrate<br><br>*For a complete listing see Dosage Forms, Composition and Packaging section.* |

### INDICATIONS AND CLINICAL USE

Seasonique® (levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg combination tablets and ethinyl estradiol 0.01 mg tablets) is indicated for:

- The prevention of pregnancy.

### CONTRAINDICATIONS

Seasonique® should not be used in women who have the following conditions:

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the product monograph.
- History of or actual thrombophlebitis or thromboembolic disorders.
- History of or actual cerebrovascular disorders.
- History of or actual myocardial infarction or coronary artery disease.
- Valvular heart disease with complications.
- History of/or actual prodromi of a thrombosis (e.g. transient ischemic attack, angina pectoris)
- Active liver disease or history of or actual benign or malignant liver tumours.

- Steroid-dependent jaundice, cholestatic jaundice, history of jaundice in pregnancy
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal vaginal bleeding.
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
- Known or suspected pregnancy.
- Presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
  -diabetes mellitus with vascular involvement
  -severe hypertension (persistent values of ≥160/100mm Hg)
  -severe dyslipoproteinemia
  -hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia (e.g. due to MTHFR C677 T, A1298 mutations), prothrombin mutation G20210A and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
  -major surgery associated with an increased risk of post-operative thromboembolism
  -prolonged immobilization
  -heavy smoking (>15 cigarettes per day) and over age 35
- Current or history of migraine with focal aura.
- History of/or actual pancreatitis if associated with severe hypertriglyceridemia

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in oral contraceptive users older than 35 years of age. Women should be counselled not to smoke (see **Cardiovascular** section below).

Birth control pills **DO NOT PROTECT** against Sexually Transmitted Infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** birth control pills.

Use of Seasonique® provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing similar strength synthetic estrogens and progestins (9 additional weeks of combined estrogen/progestin and 4 additional weeks of unopposed estrogen per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic diseases, studies to date with Seasonique® have not suggested, nor can exclude, this additional risk.

## General

**Discontinue Medication at the Earliest Manifestation of:**

**A. Thromboembolic and cardiovascular disorders** such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis and retinal thrombosis.

**B. Conditions that predispose to venous stasis and vascular thrombosis** (e.g., immobilization after accidents or confinement to bed during long-term illness). Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **Peri-Operative Considerations**, below.

**C. Visual defects - partial or complete**

**D. Papilledema or ophthalmic vascular lesions**

**E. Severe headache of unknown etiology or worsening of pre-existing migraine headache.**

**F. Increase in epileptic seizures**

## Seasonique® Oral Contraceptive

Seasonique® is a 91-day cyclic dosing regimen (84 days with tablets of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol, followed by 7 days with tablets of 0.01 mg ethinyl estradiol). Pregnancy should be ruled out in cases of unanticipated bleeding/spotting, missed withdrawal bleeding/ amenorrhea or signs and symptoms of pregnancy.

The following information is provided from studies of combination oral contraceptives (COCs). The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Other medical conditions which have been associated with adverse circulatory events include systemic lupus erythematosus (1), hemolytic uremic syndrome (2-4), chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) (5), sickle cell disease (6), valvular heart disease and atrial fibrillation (7, 8).

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COCs has not been firmly established: porphyria (9), systemic lupus erythematosus (10), hemolytic uremic syndrome (11), Sydenham's chorea (12, 13), herpes gestationis (14, 15), and otosclerosis-related hearing loss (16).

The information contained in this section is principally from studies carried out in women who used combination oral contraceptives with higher formulations of estrogens and progestogens than those in common use today. The effect of long-term use of combination hormonal contraceptives with lower doses of both estrogen and progestogen administered orally remains to be determined.

## Carcinogenesis and Mutagenesis

### Breast cancer

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity, and late age for first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than eight years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present.

Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended, because, if a breast cancer should develop, drugs that contain estrogen may cause a rapid progression.

### Cervical cancer

The most important risk factor for cervical cancer is persistent human papillomavirus (HPV) infection. Some epidemiological studies have indicated that long term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, eg, cervical screening and sexual behaviour including use of barrier contraceptives.

### Hepatocellular carcinoma

Hepatocellular carcinoma may be associated with oral contraceptives. The risk appears to increase with duration of hormonal contraceptive use. However, the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is extremely small.

See also **Product Monograph Part II, Toxicology**.

## Cardiovascular

See also **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS – Boxed Warning, General, Haematologic.**

Use of Seasonique® provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing similar strength synthetic estrogens and progestins (9 additional weeks of combined estrogen/progestin and 4 additional weeks of unopposed estrogen per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic diseases, studies to date with Seasonique® have not suggested, nor can exclude, this additional risk. Coagulation profile has not been studied with Seasonique®.

There was one case of venous thromboembolism in a woman with Factor V Leiden mutation and one case of non-Q wave myocardial infarction secondary to coronary spasm in another woman treated with Seasonique® in clinical studies. In the post-market period, there have been cases of cerebral thrombosis, cerebrovascular accident, pulmonary embolism and deep vein thrombosis reported in patients using Seasonique®.

Prescribers are advised to carefully assess a patient's baseline and cumulative risk of thromboembolism and discuss the risk of thromboembolism with all patients before prescribing Seasonique®.

**Predisposing Factors for Coronary Artery Disease**
Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, especially with increasing age. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use by women who smoke.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these. Whether oral contraceptives accentuate this risk is unclear.

In low-risk, non-smoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low-dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

**Thromboembolism**
See **Haematologic** section.

**Hypertension**
Patients with essential hypertension whose blood pressure is well-controlled may be given hormonal contraceptives but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary.

## Endocrine and Metabolism

**Diabetes**
Current low-dose oral contraceptives exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives.

**Lipid and other metabolic effects**
A small proportion of women will have adverse lipid changes while on oral contraceptives. Alternative contraception should be used in women with uncontrolled dyslipidemias (see also **CONTRAINDICATIONS)**. Elevations of plasma triglycerides may lead to pancreatitis and other complications.

**Gastrointestinal**

Published epidemiological studies indicate a possible association of COC use and the development of Crohn's disease and ulcerative colitis, although this has not been firmly established (17-22).

**Genitourinary**

**Vaginal Bleeding and Bleeding Irregularities**
In the pivotal trial for Seasonique®, intermenstrual bleeding and menorrhagia were the most commonly reported treatment-emergent adverse events leading to study discontinuation, with 2.98% of patients treated with Seasonique® discontinuing due to intermenstrual bleeding and 2.78% of patients discontinuing due to menorrhagia. See also **Clinical trial adverse drug reactions** section.

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

**Fibroids**
Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness requires discontinuation of the use of oral contraceptives.

**Hematologic**

Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in users of oral contraceptives with low estrogen content (<50 µg ethinyl estradiol) ranges from about 20 to 40 cases per 100,000 women-years, but this risk estimate varies according to the progestogen. This compares with 5 to 10 cases per 100,000 women-years for non-users.

The use of any combined oral contraceptive (COC) carries an increased risk of VTE compared

with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1-2% of cases. (23)

**Other risk factors for venous thromboembolism**
Other generalized risk factors for venous thromboembolism include but are not limited to a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index $\geq$30 kg/m$^2$) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking. The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. Also, patients with varicose veins and leg cast should be closely supervised.

If a hereditary or acquired predisposition to venous thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any COC use.

**Hepatic/Biliary/Pancreatic**

**Jaundice**
Patients who have had jaundice should be given oral contraceptives only with great care and under close observation. Oral contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. Women with a history of cholestasis may have the condition recur with subsequent hormonal contraceptive use.

The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved.

If a patient develops jaundice that proves to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

**Hepatic nodules**
Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are extremely rare, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

**Gallbladder disease**
Users of oral contraceptives have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

## Immune

### Angioedema
Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema (24-26).

## Neurologic

### Migraine and headache
The onset or exacerbation of migraine or the development of headaches with a new pattern that is recurrent, persistent or severe, requires discontinuation of hormonal contraceptives and evaluation of the cause. Women with migraine who take combination oral contraceptives may be at an increased risk of stroke (see **CONTRAINDICATIONS**).

### Epilepsy/seizures
Patients with epilepsy or other seizure disorders who are being treated with anticonvulsants should be monitored closely while using hormonal contraceptives. In some patients being treated with anticonvulsants, a method of contraception other than hormonal contraceptives may be recommended (see **DRUG INTERACTIONS: Drug-Drug Interactions**). If a woman experiences new onset or exacerbation of seizures while using Seasonique®, the use of Seasonique® should be re-evaluated.

## Ophthalmologic

Patients who are pregnant or are taking oral contraceptives may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type. Soft contact lenses usually do not cause disturbances. If visual changes or alterations in tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised.

## Peri-Operative Considerations

There is an increased risk of thromboembolic complications in oral contraceptive users after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least one month prior to **MAJOR** elective surgery. Oral contraceptive use should not be resumed until the first menstrual period after hospital discharge following surgery.

## Psychiatric

### Emotional Disorders
Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In case of a serious recurrence, an alternate method of contraception should be used temporarily in order to help clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

## Renal

### Fluid retention
Hormonal 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.

## Sexual Function/Reproduction

### Return to Fertility
After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least one normal spontaneous menstrual cycle has occurred in order to date the pregnancy. An alternative contraceptive method should be used during this time.

### Amenorrhea
Seasonique® is a 91-day cyclic dosing regimen (84 days with tablets of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol, followed by 7 days with tablets of 0.01 mg ethinyl estradiol). In the case of unanticipated bleeding/spotting, missed withdrawal bleeding or amenorrhea, the possibility of pregnancy must be considered.

Women with a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy.

Amenorrhea, especially if associated with breast secretion, which continues for six months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

### Reduced Efficacy
The efficacy of COCs may be reduced in the event of missed tablets, gastro-intestinal disturbances or concomitant medication (see **DRUG INTERACTIONS**).

## Special Populations

### Pregnant Women
Oral contraceptive use should be discontinued if pregnancy is confirmed. Oral contraceptives should not be taken by pregnant women. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child.

### Nursing Women
In breast-feeding women, the use of hormonal contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. Published studies have indicated that during lactation, 0.1% of the daily maternal dose of levonorgestrel (27) and 0.02% of the daily maternal dose of ethinyl estradiol (28) could be transferred to the newborn via milk. Adverse effects on the child have been reported, including

jaundice and breast enlargement (29). 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. There have been no formal studies of Seasonique® in nursing women.

**Pediatrics**
The safety and efficacy of Seasonique® has not been established in women under the age of 18 years.

Use of this product before menarche is not indicated.

**Geriatrics**
Seasonique® is not indicated for use in post-menopausal women.

**Monitoring and Laboratory Tests**

**Physical Examination and Follow-up**
Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination and the family case history carefully noted. In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (eg, deep vein thrombosis, stroke, myocardial infarction) at a young age. Breasts, liver, extremities and pelvic organs should be examined and a Papanicolaou (PAP) smear should be taken if the patient has been sexually active.

The first follow-up visit should be three months after the initiation of hormonal contraceptive therapy. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. Women with a strong family history of breast cancer or who have breast nodules should be monitored with particular care. At each annual visit, examination should include those procedures that were done at the initial visit, as outlined above or as per the recommendations of the Canadian Task Force on the Periodic Health Examination.

## ADVERSE REACTIONS

**Adverse Drug Reaction Overview**

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives:

- benign hepatic tumours
- cerebral hemorrhage
- cerebral thrombosis
- congenital anomalies
- gallbladder disease
- hypertension
- mesenteric thrombosis

- myocardial infarction
- neuro-ocular lesions (e.g., retinal thrombosis)
- pulmonary embolism
- thrombophlebitis

The following adverse reactions also have been reported in patients receiving oral contraceptives: nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10 % or fewer of patients during the first cycle. The following other reactions, as a general rule, are seen less frequently or only occasionally:

- abdominal pain
- amenorrhea during and after treatment
- auditory disturbances
- breakthrough bleeding
- breast changes (tenderness, enlargement, secretion)
- cataracts
- changes in appetite
- change in corneal curvature (steepening)
- change in menstrual flow
- changes in libido
- change in weight (increase or decrease)
- chloasma or melasma which may persist
- cholestatic jaundice
- chorea
- cystitis-like syndrome
- diarrhea
- dizziness
- dysmenorrhea
- edema
- endocervical hyperplasia
- erythema multiforme
- erythema nodosum
- gastrointestinal symptoms (such as abdominal cramps and bloating)
- headache
- hemolytic uremic syndrome
- hemorrhagic eruption
- hirsutism
- hypersensitivity
- impaired renal function
- increase in size of uterine leiomyomata
- intolerance to contact lenses
- loss of scalp hair
- mental depression
- migraine
- nervousness

- optic neuritis
- pancreatitis
- premenstrual like syndrome
- porphyria
- possible diminution in lactation when given immediately postpartum
- rash (including allergic rash)
- Raynaud's phenomenon
- reduced tolerance to carbohydrates
- retinal thrombosis
- rhinitis
- spotting
- temporary infertility after discontinuation of treatment
- urticaria
- vaginal candidiasis
- vaginal discharge
- vaginitis

## Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The safety data set [intention-to-treat (ITT) cohort] for Seasonique® includes 4035 91-day cycles (13,293 28-day cycles) from studies PSE-301, PSE-302 and PSE-304 combined. The ITT cohort includes patients with at least one complete cycle on treatment.

Pivotal study PSE-301 was a Phase III, randomized, multicenter clinical trial conducted to evaluate the efficacy and safety of Seasonique® and another 91-day oral contraceptive regimen for one year (4 91-day cycles). The second 91-day regimen is identical to Seasonique®, except that higher dose of ethinyl estradiol-alone is administered during the last 7 days of each 91-day cycle. This second higher dose-regimen is investigational and is not approved for use in Canada.

Supportive study PSE-302 was a Phase III, randomized, multicenter, clinical trial conducted to evaluate the efficacy and safety of Seasonique, an investigational 91-day regimen (see above), a third investigational 28-day regimen, and a fourth 28-day oral contraceptive in which 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol were taken for 21 days followed by placebo for 7 days (21/7 regimen). The duration of study PSE-302 was one year (4 91-day cycles or 13-28 day cycles, depending on the regimen). Neither of the investigational regimens are approved for use in Canada.

Study PSE-304 was an extension safety study in which subjects who completed the one-year PSE-301 or PSE-302 studies were eligible to receive either Seasonique or the investigational higher dose 91-day regimen for up to an additional three years, following their one-year exposure to any of the regimens in the PSE-301/302 studies. Over the course of PSE-304, all patients initially assigned to receive the higher dose investigational 91-day regimen were ultimately switched over to receive Seasonique. Despite the switch, all subjects were analyzed in the group to which they were originally assigned.

Safety data with an oral contraceptive containing a similar strength of levonorgestrel (0.15 mg) and ethinyl estradiol (0.03 mg) but taken in a conventional monthly (21/7) regimen is available for one year only from study PSE-302.

Tables 1 and 2 show the adverse events reported by at least 1% or more of treated patients in pivotal study PSE-301, supportive study PSE-302 and extension safety study PSE-304.

Table 1: Treatment-emergent adverse events reported at a frequency of ≥ 1 % of subjects in studies PSE-301 and PSE-302

| | **Pivotal Study PSE-301** | | **Supportive Study PSE-302** | | | |
|---|---|---|---|---|---|---|
| **MedDRA System Organ Class and Preferred Term** | **Seasonique® (N=1006)** | | **Seasonique® (N=95)** | | **21/7 Regimen[a] (N=93)** | |
| | **N** | **%** | **N** | **%** | **N** | **%** |
| **Blood and Lymphatic System Disorders** | | | | | | |
| Anemia NOS | 1 | 0.10 | 1 | 1.05 | 0 | 0.00 |
| **Ear and Labyrinth Disorders** | | | | | | |
| Vertigo | 2 | 0.20 | 1 | 1.05 | 0 | 0.00 |
| Ear pain | 1 | 0.10 | 2 | 2.11 | 0 | 0.00 |
| Labyrinthitis NOS | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| **Eye Disorders** | | | | | | |
| Conjunctivitis | 5 | 0.50 | 1 | 1.05 | 0 | 0.00 |
| **Gastrointestinal Disorders** | | | | | | |
| Nausea | 45 | 4.47 | 3 | 3.16 | 7 | 7.53 |
| Abdominal distension | 25 | 2.49 | 2 | 2.11 | 2 | 2.15 |
| Diarrhoea NOS | 19 | 1.89 | 1 | 1.05 | 0 | 0.00 |
| Vomiting NOS | 18 | 1.79 | 1 | 1.05 | 3 | 3.23 |
| Abdominal pain NOS | 17 | 1.69 | 4 | 4.21 | 1 | 1.08 |
| Dental discomfort | 12 | 1.19 | 1 | 1.05 | 2 | 2.15 |
| Dyspepsia | 12 | 1.19 | 1 | 1.05 | 1 | 1.08 |
| Abdominal pain upper | 9 | 0.89 | 1 | 1.05 | 0 | 0.00 |
| Abdominal pain lower | 5 | 0.50 | 1 | 1.05 | 0 | 0.00 |
| Food poisoning | 1 | 0.10 | 1 | 1.05 | 0 | 0.00 |

| MedDRA System Organ Class and Preferred Term | Pivotal Study PSE-301 Seasonique® (N=1006) | | Supportive Study PSE-302 Seasonique® (N=95) | | 21/7 Regimen[a] (N=93) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Aphthous stomatitis | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fatigue | 29 | 2.88 | 0 | 0.00 | 1 | 1.08 |
| Influenza like illness | 5 | 0.50 | 2 | 2.11 | 4 | 4.30 |
| Pyrexia | 4 | 0.40 | 1 | 1.05 | 1 | 1.08 |
| **Immune System Disorders** | | | | | | |
| Hypersensitivity NOS | 10 | 0.99 | 1 | 1.05 | 1 | 1.08 |
| Seasonal allergy | 8 | 0.80 | 2 | 2.11 | 0 | 0.00 |
| **Infections And Infestations** | | | | | | |
| Nasopharyngitis | 72 | 7.16 | 8 | 8.42 | 12 | 12.90 |
| Sinusitis NOS | 65 | 6.46 | 7 | 7.37 | 3 | 3.23 |
| Upper respiratory tract infection NOS | 49 | 4.87 | 4 | 4.21 | 1 | 1.08 |
| Urinary tract infection NOS | 45 | 4.47 | 4 | 4.21 | 7 | 7.53 |
| Pharyngitis streptococcal | 31 | 3.08 | 5 | 5.26 | 2 | 2.15 |
| Fungal infection NOS | 26 | 2.58 | 1 | 1.05 | 4 | 4.30 |
| Bronchitis NOS | 25 | 2.49 | 3 | 3.16 | 1 | 1.08 |
| Vaginosis fungal NOS | 20 | 1.99 | 0 | 0.00 | 0 | 0.00 |
| Influenza | 18 | 1.79 | 3 | 3.16 | 3 | 3.23 |
| Vaginitis bacterial NOS | 13 | 1.29 | 3 | 3.16 | 3 | 3.23 |
| Gastroenteritis viral NOS | 12 | 1.19 | 0 | 0.00 | 0 | 0.00 |
| Ear infection NOS | 10 | 0.99 | 2 | 2.11 | 1 | 1.08 |
| Herpes simplex | 9 | 0.89 | 2 | 2.11 | 0 | 0.00 |
| Vaginal candidiasis | 6 | 0.60 | 2 | 2.11 | 2 | 2.15 |
| Gastroenteritis NOS | 5 | 0.50 | 2 | 2.11 | 4 | 4.30 |
| Pneumonia NOS | 3 | 0.30 | 1 | 1.05 | 1 | 1.08 |
| Vaginitis | 2 | 0.20 | 2 | 2.11 | 0 | 0.00 |
| Cystitis NOS | 1 | 0.10 | 1 | 1.05 | 0 | 0.00 |
| Infected insect bite | 1 | 0.10 | 1 | 1.05 | 1 | 1.08 |
| Respiratory tract infection NOS | 1 | 0.10 | 1 | 1.05 | 0 | 0.00 |
| Body tinea | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| Breast infection NOS | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| Endometritis NOS | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |

| MedDRA System Organ Class and Preferred Term | Pivotal Study PSE-301 | | Supportive Study PSE-302 | | | |
|---|---|---|---|---|---|---|
| | Seasonique® (N=1006) | | Seasonique® (N=95) | | 21/7 Regimen[a] (N=93) | |
| | N | % | N | % | N | % |
| **Injury, Poisoning and procedural complications** | | | | | | |
| Post procedural pain | 6 | 0.60 | 2 | 2.11 | 1 | 1.08 |
| Foot fracture | 2 | 0.20 | 1 | 1.05 | 0 | 0.00 |
| Limb injury NOS | 2 | 0.20 | 1 | 1.05 | 0 | 0.00 |
| Muscle strain | 2 | 0.20 | 1 | 1.05 | 0 | 0.00 |
| Rib fracture | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| **Investigations** | | | | | | |
| Weight increased | 53 | 5.27 | 0 | 0.00 | 1 | 1.08 |
| Blood pressure increased | 4 | 0.40 | 2 | 2.11 | 0 | 0.00 |
| Blood triglycerides increased | 1 | 0.10 | 1 | 1.05 | 0 | 0.00 |
| Blood glucose increased | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| **Metabolism and Nutrition Disorders** | | | | | | |
| Appetite increased NOS | 6 | 0.60 | 1 | 1.05 | 0 | 0.00 |
| Fluid retention | 1 | 0.10 | 1 | 1.05 | 0 | 0.00 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | | | |
| Back pain | 21 | 2.09 | 1 | 1.05 | 2 | 2.15 |
| Arthralgia | 17 | 1.69 | 0 | 0.00 | 0 | 0.00 |
| Peripheral swelling | 11 | 1.09 | 1 | 1.05 | 1 | 1.08 |
| Muscle cramp | 5 | 0.50 | 1 | 1.05 | 0 | 0.00 |
| Myalgia | 5 | 0.50 | 1 | 1.05 | 0 | 0.00 |
| Neck pain | 4 | 0.40 | 1 | 1.05 | 1 | 1.08 |
| Tendonitis | 3 | 0.30 | 1 | 1.05 | 0 | 0.00 |
| Osteoarthritis NOS | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| Pain in limb | 0 | 0.00 | 2 | 2.11 | 0 | 0.00 |
| **Nervous System Disorders** | | | | | | |
| Headache NOS | 39 | 3.88 | 3 | 3.16 | 3 | 3.23 |
| Migraine NOS | 18 | 1.79 | 1 | 1.05 | 1 | 1.08 |
| Headache NOS aggravated | 11 | 1.09 | 1 | 1.05 | 0 | 0.00 |
| Dizziness | 8 | 0.80 | 2 | 2.11 | 0 | 0.00 |
| Syncope | 3 | 0.30 | 1 | 1.05 | 1 | 1.08 |

| MedDRA System Organ Class and Preferred Term | Pivotal Study PSE-301 Seasonique® (N=1006) | | Supportive Study PSE-302 Seasonique® (N=95) | | 21/7 Regimen[a] (N=93) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| **Pregnancy, Puerperium and Perinatal Conditions** | | | | | | |
| Pregnancy NOS | 3 | 0.3 | 1 | 1.05 | 2 | 2.15 |
| **Psychiatric Disorders** | | | | | | |
| Mood swings | 35 | 3.48 | 2 | 2.11 | 2 | 2.15 |
| Depression | 30 | 2.98 | 4 | 4.21 | 1 | 1.08 |
| Libido decreased | 14 | 1.39 | 2 | 2.11 | 1 | 1.08 |
| Anxiety | 11 | 1.09 | 0 | 0.00 | 0 | 0.00 |
| Irritability | 10 | 0.99 | 1 | 1.05 | 0 | 0.00 |
| Major depressive disorder NOS | 1 | 0.10 | 1 | 1.05 | 0 | 0.00 |
| Anxiety aggravated | 1 | 0.10 | 1 | 1.05 | 1 | 1.08 |
| Mood alteration NOS | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| **Renal and Urinary Disorders** | | | | | | |
| Calculus renal NOS | 2 | 0.20 | 1 | 1.05 | 0 | 0.00 |
| **Reproductive system and Breast Disorders** | | | | | | |
| Intermenstrual bleeding | 116 | 11.53 | 10 | 10.53 | 2 | 2.15 |
| Menorrhagia | 58 | 5.77 | 4 | 4.21 | 2 | 2.15 |
| Dysmenorrhoea | 36 | 3.58 | 2 | 2.11 | 4 | 4.30 |
| Breast tenderness | 29 | 2.88 | 1 | 1.05 | 1 | 1.08 |
| Cervical dysplasia | 6 | 0.60 | 3 | 3.16 | 1 | 1.08 |
| Dyspareunia NOS | 3 | 0.30 | 1 | 1.05 | 0 | 0.00 |
| Vaginal discharge | 3 | 0.30 | 1 | 1.05 | 1 | 1.08 |
| Genital pruritus female | 2 | 0.20 | 1 | 1.05 | 0 | 0.00 |
| Pelvic pain NOS | 2 | 0.20 | 1 | 1.05 | 2 | 2.15 |
| Post coital bleeding | 2 | 0.20 | 1 | 1.05 | 1 | 1.08 |
| Mastitis | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| Nipple pain | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| Ovarian cyst ruptured | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | | | |
| Pharyngitis | 20 | 1.99 | 1 | 1.05 | 3 | 3.23 |
| Sinus congestion | 18 | 1.79 | 1 | 1.05 | 1 | 1.08 |
| Cough | 9 | 0.89 | 2 | 2.11 | 0 | 0.00 |
| Rhinitis allergic NOS | 4 | 0.40 | 1 | 1.05 | 1 | 1.08 |

| MedDRA System Organ Class and Preferred Term | Pivotal Study PSE-301 | | Supportive Study PSE-302 | | | |
|---|---|---|---|---|---|---|
| | Seasonique® (N=1006) | | Seasonique® (N=95) | | 21/7 Regimen[a] (N=93) | |
| | N | % | N | % | N | % |
| **Skin And Subcutaneous Tissue Disorders** | | | | | | |
| Acne NOS | 52 | 5.17 | 8 | 8.42 | 1 | 1.08 |
| Acne aggravated | 4 | 0.40 | 1 | 1.05 | 1 | 1.08 |
| Dermatitis exfoliative NOS | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| Epidermal cyst | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| Seborrhoea | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |
| Skin lesion NOS | 0 | 0.00 | 1 | 1.05 | 0 | 0.00 |

[a] LNG 0.150 mg/ EE 0.03 mg for 21 days followed by 7 days of placebo

Treatment-emergent adverse events were similar with the 91-day higher dose supplemental EE regimen.

Table 2: Treatment-emergent adverse events reported at a frequency of ≥ 1 % of subjects in extension safety study PSE-304

| MedDRA System Organ Class and Preferred Term | Study PSE-304 | |
|---|---|---|
| | Seasonique® (N=173) | |
| | N | % |
| **Blood and Lymphatic System Disorders** | | |
| Lymphadenopathy | 2 | 1.16 |
| **Ear and Labyrinth Disorders** | | |
| Motion sickness | 3 | 1.73 |
| **Eye Disorders** | | |
| Conjunctivitis | 2 | 1.16 |
| **Gastrointestinal Disorders** | | |
| Abdominal pain upper | 7 | 4.05 |
| Diarrhoea | 7 | 4.05 |
| Dyspepsia | 6 | 3.47 |
| Nausea | 5 | 2.89 |
| Constipation | 4 | 2.31 |
| Stomach discomfort | 4 | 2.31 |
| Abdominal distension | 3 | 1.73 |
| Toothache | 3 | 1.73 |
| Vomiting | 3 | 1.73 |
| Abdominal pain lower | 2 | 1.16 |
| Flatulence | 2 | 1.16 |

| MedDRA System Organ Class and Preferred Term | Study PSE-304 Seasonique® (N=173) | |
|---|---|---|
| | N | % |
| Food poisoning | 2 | 1.16 |
| Gastrooesophageal reflux disease | 2 | 1.16 |
| Irritable bowel syndrome | 2 | 1.16 |
| **General Disorders and Administration Site Conditions** | | |
| Fatigue | 4 | 2.31 |
| Chest discomfort | 3 | 1.73 |
| Pyrexia | 3 | 1.73 |
| **Immune System Disorders** | | |
| Hypersensitivity | 3 | 1.73 |
| Seasonal allergy | 3 | 1.73 |
| **Infections and Infestations** | | |
| Upper respiratory tract infection | 34 | 19.65 |
| Nasopharyngitis | 26 | 15.03 |
| Vaginitis bacterial | 19 | 10.98 |
| Influenza | 18 | 10.40 |
| Sinusitis | 18 | 10.40 |
| Urinary tract infection | 16 | 9.25 |
| Bronchitis | 13 | 7.51 |
| Vulvovaginal mycotic infection | 13 | 7.51 |
| Fungal infection | 7 | 4.05 |
| Gastroenteritis | 7 | 4.05 |
| Pharyngitis streptococcal | 6 | 3.47 |
| Gastroenteritis viral | 5 | 2.89 |
| Herpex simplex | 5 | 2.89 |
| Ear infection | 3 | 1.73 |
| Pneumonia | 3 | 1.73 |
| Tooth abscess | 3 | 1.73 |
| Vaginal candidiasis | 3 | 1.73 |
| Candidiasis | 2 | 1.16 |
| Condyloma acuminatum | 2 | 1.16 |
| Cystitis | 2 | 1.16 |
| Pharyngitis | 2 | 1.16 |
| Tonsillitis | 2 | 1.16 |
| Tooth infection | 2 | 1.16 |
| Viral infection | 2 | 1.16 |
| **Injury, Poisoning and Procedural Complications** | | |
| Procedural pain | 5 | 2.89 |
| Arthropod sting | 3 | 1.73 |

| MedDRA System Organ Class and Preferred Term | Study PSE-304 Seasonique® (N=173) | |
|---|---|---|
| | N | % |
| Contusion | 3 | 1.73 |
| Road traffic accident | 3 | 1.73 |
| Joint sprain | 2 | 1.16 |
| Muscle strain | 2 | 1.16 |
| Tendon injury | 2 | 1.16 |
| **Investigations** | | |
| Weight Increased | 16 | 9.25 |
| Blood pressure increased | 8 | 4.62 |
| Smear cervix abnormal | 2 | 1.16 |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Back pain | 21 | 12.14 |
| Arthralgia | 7 | 4.05 |
| Myalgia | 6 | 3.47 |
| Muscle spasms | 5 | 2.89 |
| Intervertebral disc protrusion | 3 | 1.73 |
| Shoulder pain | 3 | 1.73 |
| Musculoskeletal pain | 2 | 1.16 |
| **Nervous System Disorders** | | |
| Headache | 38 | 21.97 |
| Migraine | 8 | 4.62 |
| Sinus headache | 6 | 3.47 |
| Dizziness | 3 | 1.73 |
| **Psychiatric Disorders** | | |
| Insomnia | 13 | 7.51 |
| Anxiety | 10 | 5.78 |
| Depression | 10 | 5.78 |
| Libido decreased | 3 | 1.73 |
| Bipolar disorder | 2 | 1.16 |
| **Reproductive system and Breast Disorders** | | |
| Metrorrhagia | 16 | 9.25 |
| Dysmenorrhoea | 15 | 8.67 |
| Cervical dysplasia | 11 | 6.36 |
| Breast mass | 4 | 2.31 |
| Cervix erythema | 3 | 1.73 |
| Vaginal haemorrhage | 3 | 1.73 |
| Breast tenderness | 2 | 1.16 |
| Cervical cyst | 2 | 1.16 |
| Menorrhagia | 2 | 1.16 |

| MedDRA System Organ Class and Preferred Term | Study PSE-304 Seasonique® (N=173) | |
|---|---|---|
| | N | % |
| Vaginal discharge | 2 | 1.16 |
| **Respiratory, Thoracic and Mediastinal disorders** | | |
| Pharyngolaryngeal pain | 8 | 4.62 |
| Sinus congestion | 7 | 4.05 |
| Cough | 5 | 2.89 |
| Nasal congestion | 5 | 2.89 |
| Respiratory tract congestion | 2 | 1.16 |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Rash | 5 | 2.89 |
| Dermatitis contact | 4 | 2.31 |
| Acne | 3 | 1.73 |
| **Surgical and Medicinal Procedures** | | |
| Tooth extraction | 3 | 1.73 |
| Wisdom teeth removal | 2 | 1.16 |
| **Vascular Disorders** | | |
| Hot flush | 3 | 1.73 |
| Hypertension | 2 | 1.16 |

**Note:** all subjects in the higher dose 91-day treatment group were eventually switched over to Seasonique but were analyzed separately. Adverse events observed in subjects originally assigned to the higher dose group were generally similar to those observed with Seasonique.

## Less Common Clinical Trial Adverse Drug Reactions (< 1%)

The following adverse events were reported in the Seasonique® treatment arm at a frequency <1% in studies PSE-301, PSE-302 and PSE-304:

Cardiac disorders: mitral valve prolapse, palpitations, tachycardia.

Ear and labyrinth disorders: ear congestion.

Endocrine disorders: acquired hypothyroidism, goitre, thyroid nodule.

Eye disorders: dry eye, optic neuritis.

Gastrointestinal disorders: appendicitis, gastritis, haematemesis, haematochezia, haemorrhoids, hiatus hernia, loose stools, nausea aggravated, oesophageal reflux aggravated, pancreatitis, salivary gland calculus, small intestinal obstruction, tooth impacted.

General disorders and administration site conditions: chest pain, feeling hot, hangover, malaise, mass, oedema, oedema peripheral, pain, thirst, ulcer, weakness.

Hepatobiliary disorders: cholelithiasis, cholecystitis.

Immune systems disorders: drug hypersensitivity.

Infections and infestations: abscess, bacterial infection, bladder infection, breast cellulitis, candidial infection, cervicitis, dermatophytosis, dry socket, eye infection, gastroenteritis salmonella, gastroenteritis shigella, genitourinary chlamydia infection, gingivitis infection, helicobacter infection, herpes zoster, hordeolum, infectious mononucleosis, kidney infection, laryngitis chronic, localised infection, otitis media, pelvic inflammatory disease, periodontitis, post procedural site wound infection, sialoadenitis, skin and subcutaneous tissue abscess, skin infection, tooth caries, vaginal infection, vulvovaginitis trichomonal.

Injury, poisoning and procedural complications: abrasion NOS, animal bite, arthropod bite, arthropod sting, back injury NOS, clavicle fracture, foot fracture, hand fracture, joint sprain, laceration, ligament injury NOS, limb injury NOS, muscle strain, post procedural haemorrhage, radius fracture, rib fracture, road traffic accident, tooth injury, thermal burn, wrist fracture.

Investigations: blood pressure diastolic increased, blood testosterone decreased, blood testosterone increased, heart rate increased, lipids increased, liver function tests abnormal, weight decreased.

Metabolism and nutrition disorders: anorexia, appetite decreased, diabetes mellitus, hypercholesterolaemia, insulin resistance.

Musculoskeletal and connective tissue disorders: arthritis, axillary mass, chondritis, costochondritis, intervertebral disc degeneration, intervertebral disc herniation, joint swelling, joint stiffness, neck pain, neck stiffness, osteopenia, pain in extremity, pain in jaw, rheumatoid arthritis aggravated, temporomandibular joint disorder.

Neoplasms benign, malignant and unspecified (including cyst and polyps): cyst, fibrocystic breast disease, malignant melanoma, uterine fibroids, uterine fibroids aggravated.

Nervous system disorders: carpal tunnel syndrome, cervical root pain, convulsions, facial palsy, hyperaesthesia, hypoasthesia, increased activity, migraine aggravated, migraine with aura, nerve compression, paraesthesia, sciatica, tension headaches, vasovagal attack, visual field defect.

Psychiatric disorders: affect lability, bruxism, depression aggravated, depressed mood, emotional distress, insomnia exacerbated, orgasm abnormal, panic attack, paranoia, sleep disorder, stress symptoms, suicidal ideation.

Renal and urinary disorders: bladder spasm, urinary frequency, urinary incontinence, urine odour abnormal, urinary retention, urinary tract obstruction, urinary tract pain.

Reproductive systems and breast disorders: breast discharge, breast pain, breast engorgement, breast enlargement, endometriosis, galactorrhoea, genital rash, menstruation irregular, ovarian cyst, polycystic ovaries, uterine spasm, vaginal irritation, vulval disorder, vulvovaginal discomfort, vulvovaginal dryness.

Respiratory, thoracic and mediastinal disorders: asthma, asthma aggravated, dyspnoea, hoarseness, laryngitis, paranasal sinus hypersecretion, pleurisy, rhinitis, rhinorrhoea, upper respiratory tract congestion.

Skin and subcutaneous tissue disorders: contusion, dermatitis, dermatitis allergic, eczema, erythema nodosum, face oedema, folliculitis, hair disorder, hair growth abnormal, hair texture abnormal, hidradenitis, hypotrichosis, ingrowing nail, nail disorder, night sweats, photosensitivity reaction, pityriasis rosea, pruritus generalised, rash pruritic, skin atrophy, skin hyperpigmentation, skin irritation, swelling face, urticaria.

Social circumstances: exposure to communicable disease.

Vascular disorders: hypertension aggravated, orthostatic hypotension.

**Vaginal bleeding**

Intermenstrual bleeding and menorrhagia were the most commonly reported treatment-emergent adverse events leading to study discontinuation in the Seasonique® treatment arm in study PSE-301. See also **WARNINGS AND PRECAUTIONS, Genitourinary.**

As well, in supportive study PSE-302, intermenstrual bleeding and menorrhagia were more commonly reported as treatment-emergent adverse events in the subjects treated with Seasonique® versus the subjects treated with LNG 0.150 mg/EE 0.03 mg for 21 days followed by 7 days placebo. See Table 1, above.

**Unscheduled bleeding and/or spotting per 28-day patient-month**

In pivotal study PSE-301, the median number of days of unscheduled bleeding and/or spotting decreased from 2.8 days per patient-month in the first 91-day cycle to 1.0 day per patient-month in the 4th 91-day cycle.

In supportive study PSE-302, the median number of days of unscheduled bleeding and/or spotting ranged from 2.5 days per patient-month in the first 91-day cycle, decreasing to 1.6 days per patient-month in the 4th 91-day cycle in the Seasonique® treatment arm. Subjects treated with LNG 0.150 mg/EE 0.03 mg for 21 days followed by 7 days placebo experienced a median 0-2 days per month of unscheduled bleeding and/or spotting, depending on the 28-day cycle evaluated.

**Scheduled bleeding and/or spotting per 91-day or 28-day cycle**
In pivotal study PSE-301, the median number of days of scheduled bleeding and/or spotting per 91-day cycle was consistent at 3 days in all four 91-day cycles in the Seasonique® treatment arm.

In supportive study PSE-302, the median number of days of scheduled bleeding and/or spotting in the Seasonique® treatment arm was 4 days per 91-day cycle in the first cycle, decreasing to 2.5 days in the 4th 91-day cycle. The median number of days of scheduled bleeding and/or spotting per 28-day cycle in the subjects treated with LNG 0.150 mg/EE 0.03 mg for 21 days followed by 7 days placebo ranged from 2-3 days from cycles 1 through to 13.

**Total bleeding and/or spotting per 28-day patient- month**
In pivotal study PSE-301, use of Seasonique® was associated with a median 4.3 days total bleeding and/ or spotting per patient month in the first 91-day cycle, decreasing to 2.0 days per patient-month in the 4th 91-day cycle.

In supportive study PSE-302, the median number of total bleeding and/or spotting days in the Seasonique® treatment arm decreased from 4.3 days per patient-month in the first 91-day cycle to 3.1 days per patient-month in the 4$^{th}$ 91-day cycle. The median number of total bleeding and/or spotting days in the subjects treated with LNG 0.150mg/EE 0.03mg for 21 days followed by 7 days placebo ranged from 3-5 days per month over the course of the 13 28-day cycles.

**Endometrial biopsies**

In supportive study PSE-302, endometrial biopsies were conducted in 63 women treated with Seasonique® both at baseline and during the last cycle of treatment. Forty-six (46) of these 63 women completed the full year of study. There were no reports of endometrial hyperplasia or endometrial cancer on end-of-treatment endometrial biopsy in any of the four treatment arms. See also **Post-market adverse drug reactions** section, below.

**Thromboembolic events**
There was one case of venous thromboembolism in a woman with Factor V Leiden mutation treated with Seasonique® in study PSE-301 and one case of non-Q wave myocardial infarction secondary to coronary spasm in another woman treated with Seasonique® in study PSE-304." See also **Post-market adverse drug reactions** section, below.

**Weight**

In PSE-301, median weight gain in the Seasonique group was 2.0 lbs. In supportive study PSE-302, there was a potential for slightly greater weight gain from baseline in the Seasonique® (median 2.0 lbs) treatment arm versus the LNG 0.15 mg/EE 0.03 mg (21/7 regimen) treatment arm (median 1.0 lbs).

**Abnormal Haematologic and Clinical Chemistry Findings**

Laboratory data with an oral contraceptive containing a similar strength of levonorgestrel (0.15 mg) and ethinyl estradiol (0.03 mg) but taken in a conventional 21/7 monthly regimen (21 days of combination estrogen/progestin therapy followed by 7 days of placebo) is available for one year only from study PSE-302.

In study PSE-302, 11.9% of subjects in the treatment arm versus 7.8% in the LNG 0.15 mg/EE 0.03 mg (21/7 regimen) treatment arm who had normal triglycerides at baseline had values at the end of treatment that exceeded the upper limit of normal. No subjects in either of these two treatment arms had a shift in LDL cholesterol from normal at baseline to above upper limit of normal at the end-of-treatment. No notable differences were observed between treatment groups for shifts to low HDL cholesterol at end of treatment. In PSE-301, 13.2 % of subjects in the Seasonique® treatment arm who had normal triglycerides at baseline had values at the end of treatment that exceeded the upper limit of normal, 5.8% had a shift in LDL cholesterol from normal at baseline to above the upper limit of normal at the end-of-treatment and 2.3% had a shift to low HDL cholesterol at the end of treatment.

In study PSE-302, 6.3% of subjects in the Seasonique® treatment arm versus 4.8% of subjects in the LNG 0.15 mg/EE 0.03 mg (21/7 regimen) treatment arm with normal serum glucose at baseline had values at end of treatment that exceeded the upper limit of normal. In PSE-301 2.1% of subjects on Seasonique with normal serum glucose levels at baseline had values at end of treatment that exceeded the upper limit of normal.

In study PSE-302, 6.1% of subjects in the Seasonique® treatment arm versus 0% of subjects in the LNG 0.15mg/EE 0.03mg (21/7 regimen) treatment arm with normal ALT at baseline had values at end of treatment that exceeded the upper limit of normal. As well, in study PSE-302, 4.5% of subjects in the Seasonique® treatment arm versus 0% of subjects in the LNG 0.15 mg/EE 0.03 mg (21/7 regimen) treatment arm with normal AST at baseline had values at end of treatment that exceeded the upper limit of normal. In PSE-301, 8.2% of subjects on Seasonique with normal ALT levels at baseline had values at end of treatment that exceeded the upper limit of normal, and 5.3% with normal AST levels at baseline had values at end of treatment that exceeded the upper limit of normal.

The clinical significance of the laboratory results (median change from baseline) as noted above is unknown, however, as there was a large range of both decreases and increases in serum lipids, glucose and liver enzymes in all treatment arms in studies PSE-301 and PSE-302. See also **CONTRAINDICATIONS** and **WARNINGS and PRECAUTIONS** for information regarding lipids, glucose metabolism and liver disease as related to use of hormonal contraceptives in general.

## Post-Market Adverse Drug Reactions

The following other serious and unexpected adverse events have been reported in users of Seasonique® in the post marketing period. These adverse events are compiled from spontaneous reports and are listed regardless of frequency and whether or not a causal relationship with

Seasonique® has been established.

Gastrointestinal Disorders: rectal spasm.

Infections and Infestations: Appendicitis.

Investigations: Blood lactate dehydrogenase increased.

Nervous System Disorders: Brain oedema, cerebral thrombosis, cerebrovascular accident, intracranial pressure increased, loss of consciousness.

Neoplasm: Uterine leiomyoma.

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary embolism.

Reproductive System and Breast Disorders: Endometrial hyperplasia, haemorrhagic ovarian cyst, uterine enlargement, menometrorrhagia.

Vascular Disorders: Deep vein thrombosis, thrombosis.

## DRUG INTERACTIONS

### Overview

The concurrent administration of oral contraceptives with other drugs may lead to breakthrough bleeding and/or may result in an altered response to either agent (see Tables 3 and 4). Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low-dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before oral contraceptives are prescribed.

## Drug-Drug Interactions

| Table 3: Drugs Which May Decrease the Efficacy of Oral Contraceptives | | | |
|---|---|---|---|
| **Class of Compound** | **Drug** | **Proposed Mechanism** | **Suggested Management** |
| Antacids | | Decreased intestinal absorption of progestins. | Dose two hours apart. |
| Antibiotics | Ampicillin<br>Cotrimoxazole<br>Penicillin | Enterohepatic circulation disturbance, intestinal hurry. | For short course, use additional method or use another drug. For long course, use another method. |
| | Rifabutin<br>Rifampin (30) | Increased metabolism of progestins. Suspected acceleration of estrogen metabolism. | Use another method. |
| | Chloramphenicol<br>Metronidazole<br>Neomycin<br>Nitrofurantoin<br>Sulfonamides<br>Tetracyclines | Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation. | For short course, use additional method or use another drug. For long course, use another method. |
| | Troleandomycin | May retard metabolism of oral contraceptives, increasing the risk of cholestatic jaundice. | |
| Anticonvulsants (31-33) | Carbamazepine<br>Ethosuximide<br>Felbamate<br>Lamotrigine<br>Oxcarbazepine<br>Phenobarbital<br>Phenytoin<br>Primidone<br>Topiramate | Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG. | Use higher dose oral contraceptives (50 µg ethinyl estradiol), another drug or another method. |
| Antifungals | Griseofulvin | Stimulation of hepatic metabolism of contraceptive steroids may occur. | Use another method. |
| Cholesterol Lowering Agents | Clofibrate | Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy. | Use another method. |
| HIV protease inhibitors (34) | Ritonavir | Induction of hepatic microsomal enzymes. | Use another drug or another method. |
| Non-nucleoside reverse transcriptase inhibitors (29, 35) | Nevirapine | Induction of hepatic microsomal enzymes. | Use another drug or another method. |

| Table 3: Drugs Which May Decrease the Efficacy of Oral Contraceptives | | | |
|---|---|---|---|
| **Class of Compound** | **Drug** | **Proposed Mechanism** | **Suggested Management** |
| Sedatives and Hypnotics | Barbiturates<br>Benzodiazepines<br>Chloral hydrate<br>Glutethimide<br>Meprobamate | Induction of hepatic microsomal enzymes. | For short course, use additional method or another drug. For long course, use another method or higher dose oral contraceptives. |
| Other Drugs | Analgesics<br>Antihistamines<br>Antimigraine preparations<br>Phenylbutazone<br>Vitamin E | Reduced oral contraceptive efficacy has been reported. Remains to be confirmed. | |

Oral contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (eg, cyclosporine) or decrease (eg, lamotrigine).

| Table 4: Modification of Other Drug Action by Oral Contraceptives | | | |
|---|---|---|---|
| **Class of Compound** | **Drug** | **Modification of Drug Action** | **Suggested Management** |
| Alcohol | | Possible increased levels of ethanol or acetaldehyde | Use with caution. |
| Alpha-II adrenoreceptor agents | Clonidine | Sedation effect increased. | Use with caution. |
| Anticoagulants | All | Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients. | Use another method. |
| Anticonvulsants | All | Estrogens may increase risk of seizures. | Use another method. |
| | Lamotrigine (36-40) | Combination oral contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine likely due to induction of lamotrigine glucoronidation.<br><br>Decreased lamotrigine levels may lead to breakthrough seizures. | Use another method. |

| **Table 4: Modification of Other Drug Action by Oral Contraceptives** | | | |
|---|---|---|---|
| **Class of Compound** | **Drug** | **Modification of Drug Action** | **Suggested Management** |
| Antidiabetic drugs | Oral hypoglycaemics and insulin | Oral contraceptives may impair glucose tolerance and increase blood glucose. | Use low-dose estrogen and progestin oral contraceptive or another method. Monitor blood glucose. |
| Antihypertensive agents | Guanethidine and methyldopa | Estrogen component causes sodium retention, progestin has no effect. | Use low-dose estrogen oral contraceptive or use another method. |
| | Beta blockers | Increased drug effect (decreased metabolism). | Adjust dose of drug if necessary. Monitor cardiovascular status. |
| Antipyretics | Acetaminophen | Increased metabolism and renal clearance. | Dose of drug may have to be increased. |
| | Antipyrine | Impaired metabolism. | Decrease dose of drug. |
| | ASA | Effects of ASA may be decreased by the short-term use of oral contraceptives. | Patients on chronic ASA therapy may require an increase in ASA dosage. |
| Aminocaproic acid | | Theoretically, a hypercoagulable state may occur because oral contraceptives augment clotting factors. | Avoid concomitant use. |
| Betamimetic agents | Isoproterenol | Estrogen causes decreased response to these drugs. | Adjust dose of drug as necessary. Discontinuing oral contraceptives can result in excessive drug activity. |
| Caffeine | | The actions of caffeine may be enhanced as oral contraceptives may impair the hepatic metabolism of caffeine. | Use with caution. |
| Cholesterol lowering agents | Clofibrate | Their action may be antagonized by oral contraceptives. Oral contraceptives may also increase metabolism of clofibrate. | May need to increase dose of clofibrate. |
| Corticosteroids | Prednisone | Markedly increased serum levels. | Possible need for decrease in dose. |
| Cyclosporine | | May lead to an increase in cyclosporine levels and hepatotoxicity. | Monitor hepatic function. The cyclosporine dose may have to be decreased. |
| Folic acid | | Oral contraceptives have been reported to impair folate metabolism. | May need to increase dietary intake, or supplement. |

| Table 4: Modification of Other Drug Action by Oral Contraceptives | | | |
|---|---|---|---|
| **Class of Compound** | **Drug** | **Modification of Drug Action** | **Suggested Management** |
| Meperidine | | Possible increased analgesia and CNS depression due to decreased metabolism of meperidine. | Use combination with caution. |
| Phenothiazine tranquilizers | All phenothiazines, reserpine and similar drugs | Estrogen potentiates the hyperprolactinemia effect of these drugs. | Use other drugs or lower dose oral contraceptives. If galactorrhea or hyperprolactinemia occurs, use other method. |
| Sedatives and hypnotics | Chlordiazepoxide<br>Lorazepam<br>Oxazepam<br>Diazepam | Increased effect (increased metabolism). | Use with caution. |
| Theophylline | All | Decreased oxidation, leading to possible toxicity. | Use with caution. Monitor theophylline levels. |
| Tricyclic antidepressants | Clomipramine (possibly others) | Increased side effects: i.e., depression | Use with caution. |
| Vitamin $B_{12}$ | | Oral contraceptives have been reported to reduce serum levels of Vitamin $B_{12}$ | May need to increase dietary intake, or supplement. |

Several of the anti-HIV protease inhibitors (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine) have been studied with co-administration of combination oral contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestogen and the potential to affect hepatic metabolism have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected. Healthcare providers should refer to the label of the individual anti-HIV protease inhibitor for further drug-drug interaction information.

No formal drug-drug interaction studies have been conducted with Seasonique.

## Drug-Food Interactions

Interactions with food have not been established.

## Drug-Herb Interactions

Herbal products containing St. John's Wort (hypericum perforatum) may induce hepatic enzymes (cytochrome P450) and p-glycoprotein transporter and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding.

## Drug-Laboratory Test Interactions

Results of laboratory tests should be interpreted with the knowledge that the patient is taking an oral contraceptive.

The following laboratory tests are modified:

**Liver Function Tests**
Aspartate serum transaminase (AST) - variously reported elevations
Alkaline phosphatase and gamma-glutamyl transferase (GGT) - slightly elevated.

**Coagulation Tests**
Minimal elevation of test values reported for such parameters as prothrombin and Factors VII, VIII, IX and X.

**Thyroid Function Tests**
Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T3 resin uptake.

**Lipoproteins**
Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.

**Gonadotropins**
LH and FSH levels are suppressed by the use of oral contraceptives. Wait two weeks after discontinuing the use of oral contraceptives before measurements are made.

**Glucose tolerance**
Oral glucose tolerance remained unchanged or was slightly decreased.

**Tissue Specimens**
Pathologists should be advised of hormonal contraceptive use when specimens from surgical procedures and/or Pap smears are submitted for examination.

## Drug-Lifestyle Interactions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in oral contraceptive users older than 35 years of age. Women should be counselled not to smoke.

No studies on the effects of Seasonique® on the ability to drive or use machines have been performed.

**Non-contraceptive Benefits of Oral Contraceptives**

Several have been reported.

1. Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.
2. Oral contraceptives reduce the likelihood of developing benign breast disease and, as a result, decrease the incidence of breast biopsies.
3. Oral contraceptives reduce the likelihood of development of functional ovarian cysts.
4. Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
5. The use of oral contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome, and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders.
6. Oral contraceptives decrease the incidence of acute pelvic inflammatory disease and, thereby, reduce as well the incidence of ectopic pregnancy.
7. Oral contraceptives have potential beneficial effects on endometriosis.

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**

Correct use of contraceptives can result in lower failure rates. If withdrawal bleeding does not occur while taking yellow (ethinyl estradiol) tablets, the possibility of pregnancy must be considered. Appropriate diagnostic measures to rule out pregnancy should be taken at the time of any missed menstrual period. Seasonique® should be discontinued if pregnancy is confirmed.

The tablets should not be removed from the protective blister packaging to avoid damage to the product. The plastic dispenser should be kept in the foil pouch until dispensed to the patient.

**Recommended Dose and Dosage Adjustment**

The dosage of Seasonique® consists of the daily administration of one light blue-green (levonorgestrel/ethinyl estradiol) tablet taken for 84 consecutive days followed by 7 days of yellow (ethinyl estradiol) tablets; therefore patients should expect to have 4 menstrual periods per year. To achieve maximum contraceptive effectiveness, Seasonique® must be taken exactly as directed and at intervals not exceeding 24 hours. Ideally, the tablets should be taken at the same time of the day on each day of active treatment.

During the first cycle of medication, the patient is instructed to begin taking Seasonique® on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first light blue-green (levonorgestrel/ethinyl estradiol) tablet is taken that day. One light blue-green (levonorgestrel/ethinyl estradiol) tablet should be taken daily for 84 consecutive days, followed

by a 7- day period during which a yellow (ethinyl estradiol) tablet is taken daily. Withdrawal bleeding should occur during the 7-day period following discontinuation of light blue-green active tablets.

During the first cycle, contraceptive reliance should not be placed on Seasonique® until light blue-green tablets have been taken daily for 7 consecutive days and a non-hormonal back-up method of birth control (such as condoms or spermicide) should be used during those 7 days. The possibility of ovulation and conception prior to initiation of medication should be considered.

The patient begins all subsequent 91-day courses of tablets without interruption and on the same day of the week on which she began her first course, i.e. Sunday. The same administration schedule is followed: daily administration of one light blue-green (levonorgestrel/ethinyl estradiol) tablet taken for 84 consecutive days followed by 7 days of yellow (ethinyl estradiol) tablets.

If in any cycle the patient starts the tablets later than the proper day, she should protect herself against pregnancy by using a non-hormonal back-up method of birth control until she has taken light blue-green tablets daily for 7 consecutive days.

If spotting or breakthrough 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 healthcare provider.

In the non-lactating mother, Seasonique® may be initiated no earlier than Day 28 of postpartum for contraception due to the increased risk of thromboembolism. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (see also **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).

The patient should be advised to use a non-hormonal back-up method for the first 7 days of tablet-taking. However, if intercourse has already occurred, the possibility of ovulation and conception prior to initiation of medication should be considered. Seasonique® may be initiated immediately after a first-trimester abortion; if the patient starts Seasonique® immediately, additional contraceptive measures are not needed.

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 such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B and syphilis.

**Administration**

**No hormonal contraceptive use in the preceding cycle:** Tablet taking should start on the first Sunday after the onset of menstruation. See above.

**Switching from another combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch):** The patient should start Seasonique® on the day she would normally start her next pack of combined oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using Seasonique® preferably on the day of removal, but at the latest when the next application would have been due.

**Switching from a progestogen-only method (mini-pill, injection):** The patient may switch from the mini-pill to Seasonique® on any day of her cycle. Patients using a progestogen injection should start Seasonique® on the day the next injection is due. In all cases, the patient should be advised to use an additional (barrier) method for the first 7 days of Seasonique® use.
**Following first trimester abortion:** The patient may start using Seasonique® immediately. When doing so, she need not take additional contraceptive measures.

**Following delivery or second trimester abortion:** Patients should be advised to start Seasonique® on day 21 to 28 after delivery or second trimester abortion, after consulting with their physician. When starting later, the patient should be advised to use an additional (barrier) method for the first seven days of Seasonique® use. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of use, or the woman should be advised to wait for her next menstrual period prior to starting Seasonique®. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered.

**Withdrawal / Breakthrough bleeding:** If spotting or breakthrough bleeding occurs while taking Seasonique®, the patient should be instructed to continue taking Seasonique® as instructed and by the regimen described above. She should be instructed that this type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient should be advised to consult her physician.

Although the occurrence of pregnancy is unlikely if Seasonique® is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed dosing schedule, the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed.

**Advice in case of vomiting:** If vomiting occurs within 3 to 4 hours after a tablet is taken, absorption may not be complete. In such an event, the advice concerning management of missed pills is applicable.

**Missed Dose**

Detailed patient instructions regarding missed pills are presented in Part III of the product monograph, in the subsection entitled “WHAT TO DO IF YOU MISS PILLS”.

If a patient misses one light blue-green tablet, she should take it as soon as possible, meaning she can take two tablets in one day. If a patient misses two light blue-green tablets, she should take 2

tablets on the day she remembers and 2 tablets on the following day. Should three or more tablets be missed, the regular dosing schedule should be resumed, that is one light blue-green tablet per day. Any time the patient misses two or more light blue-green tablets, she should also use another method of non-hormonal back-up contraception until she has taken light blue-green tablets daily for seven consecutive days. If the patient misses one or more yellow (ethinyl estradiol) tablets, she is still protected against pregnancy provided she begins taking light blue-green tablets again on the appropriate day. The possibility of ovulation increases with each successive day that scheduled light blue-green tablets are missed. The risk of pregnancy increases with each light blue-green tablet missed.

## OVERDOSAGE

| For management of suspected drug overdose, contact your regional Poison Control Centre. |
|---|

Serious ill effects have not been reported following accidental ingestion of large doses of oral contraceptives by young children. Symptoms of combined oral contraceptive (COC) 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. Liver function tests should be conducted, particularly transaminase levels, 2 to 3 weeks after consumption.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism 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 changes in the endometrium (which reduce the likelihood of implantation).

### Pharmacodynamics

Norgestrel is a racemate containing equal parts of D- and L- enantiomers. The L-enantiomer has been tested in a broad range of biological assays and its inactivity has been confirmed. The D-enantiomer (named levonorgestrel) accounts for all the biological activity found in norgestrel, as levonorgestrel was twice as potent as the racemate in experiments in which norgestrel was effective.

### Pharmacokinetics

**Absorption:** Ethinyl estradiol and levonorgestrel are rapidly absorbed with maximum plasma concentrations occurring within 2 hours after Seasonique® administration. No specific

investigation of the absolute bioavailability of Seasonique® in humans has been conducted. However, published literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism (41-46). 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 approximately 55% (46).

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

The single-dose and steady state pharmacokinetics of Seasonique™ after daily dosing over the entire 91-day extended cycle was evaluated. The daily exposure to levonorgestrel and ethinyl estradiol on Day 21, corresponding to the end of a typical 3-week contraceptive regimen, and on Day 84, at the end of an extended cycle regimen, were similar. The mean plasma pharmacokinetic parameters of Seasonique® following a single daily dose of one levonorgestrel/ethinyl estradiol combination tablet, for 84 days, in normal healthy women are reported in Table 5.

**Table 5: Mean Pharmacokinetic Parameters for Seasonique® During Daily One Tablet Dosing for 84 Days**

| | **$AUC_{0-24}$ (mean ± SD)** | **$C_{max}$ (mean ± SD)** | **$T_{max}$ (mean ± SD)** | **$T_{1/2\ el}$ (h)** |
|---|---|---|---|---|
| | **Levonorgestrel (N= 28-30)** | | | |
| Day 1 | 18.2 ± 6.1 ng•hr/mL | 3.0 ± 1.0 ng/mL | 1.3 ± 0.4 hours | |
| Day 21 | 64.4 ± 25.1 ng•hr/mL | 6.2 ± 1.6 ng/mL | 1.3 ± 0.4 hours | |
| Day 84 | 60.2 ± 24.6 ng•hr/mL | 5.5 ± 1.6 ng/mL | 1.3 ± 0.3 hours | 39 ± 12 hours |
| | **Ethinyl Estradiol (N= 28-30)** | | | |
| Day 1 | 509.3 ± 172.0 pg•hr/mL | 69.8 ± 25.9 pg/mL | 1.5 ± 0.3 hours | |
| Day 21 | 837.1 ± 271.2 pg•hr/mL | 99.6 ± 31.3 pg/mL | 1.5 ± 0.3 hours | |
| Day 84 | 791.5 ± 215.0 pg•hr/mL | 91.3 ± 32.5 pg/mL | 1.6 ± 0.3 hours | |
| Day 91 | 867.5 ± 277.6 pg•hr/mL | 102.3 ± 50.4 pg/mL | 1.4 ± 0.4 hours | 18 ± 4 hours |

**Distribution:** The apparent volume of distribution of each levonorgestrel and ethinyl estradiol are reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively (41, 47). Levonorgestrel is about 97.5-99% protein-bound, principally to the sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin (41). Ethinyl estradiol is about 95-97% bound to serum albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis, which leads to decreased levonorgestrel clearance (48). Following repeated daily dosing of combination levonorgestrel and ethinyl estradiol oral contraceptives, levonorgestrel plasma concentrations accumulate more than predicted based on single-dose kinetics, 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 17β-OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma (49). Significant amounts of conjugated and unconjugated 3α,5β-tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3α,5α-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel (50). 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 (50).

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 CYP3A4 (42, 51). 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 (51). 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 (48). The terminal elimination half-life for levonorgestrel after a single dose of Seasonique® was found to be about 39 hours. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates and it undergoes enterohepatic recirculation (52, 53). The terminal elimination half-life of ethinyl estradiol after a single dose of Seasonique® was found to be about 18 hours.

**Special Populations and Conditions**

**Pediatrics:** The safety and efficacy of Seasonique® has not been established in women under the age of 18 years.

Use of this product before menarche is not indicated.

**Geriatrics:** Seasonique® is not indicated for use in post-menopausal women.

**Race:** No formal studies on the effect of race on the pharmacokinetics of Seasonique® have been conducted.

**Hepatic Insufficiency:** No formal studies have been conducted to evaluate the effect of hepatic disease on the pharmacokinetics of Seasonique®. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

**Renal Insufficiency:** No formal studies have been conducted to evaluate the effect of renal disease on the pharmacokinetics of Seasonique®.

**Genetic Polymorphism:** No data are available.

## STORAGE AND STABILITY

Store at room temperature (15 to 30°C). Keep out of the reach of children and pets.

## SPECIAL HANDLING INSTRUCTIONS

Not applicable.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

Seasonique® (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg combination and ethinyl estradiol 0.01 mg) tablets are available in Extended-Cycle Tablet Dispensers. Altogether, the Tablet Dispenser holds 91 tablets consisting of 84 light blue-green tablets (each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol) and 7 yellow tablets (each containing 0.01 mg ethinyl estradiol). The light blue-green tablets are round, film-coated, biconvex, unscored tablets with a debossed **b** on one side and **555** on the other side. The yellow tablets are round, biconvex, unscored with a debossed with **b** on one side and **556** on the other side.

The Tablet Dispenser consists of three plastic leaves in a booklet configuration where individual blister cards are inserted and held in place. Each of these leaves contains either 28 or 35 holes for tablets to be pushed out of the blister cards through the aluminum foil. The first two blister cards contain 28 active light blue-green tablets and the third blister card contains 28 active light blue-green tablets and 7 active yellow tablets for a total of 35 tablets. The compact is then packaged in a foil pouch with a desiccant. Three foil pouches are packaged in each carton.

Each light blue-green tablet contains the following inactive ingredients: anhydrous lactose, FD&C Blue No. 1 aluminum lake, FD&C Yellow No. 10 aluminum lake, FD&C Yellow No. 6 aluminum lake, glycerol triacetate (triacetin), hypromellose (hydroxypropyl methylcellulose), lactose monohydrate, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

Each yellow tablet contains the following inactive ingredients: anhydrous lactose, FD&C Yellow No. 10 aluminum lake, FD&C Yellow No. 6 aluminum lake, hypromellose (hydroxypropyl methylcellulose), magnesium stearate, microcrystalline cellulose, polacrilin potassium, polyethylene glycol, polysorbate 80 and titanium dioxide.

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

**Drug Substance**

Proper name: Levonorgestrel
Ethinyl Estradiol

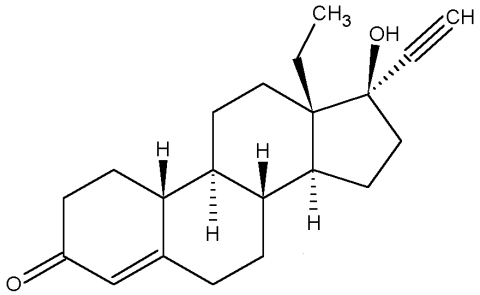
Chemical name: Levonorgestrel: 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one

Ethinyl Estradiol: 17α-Ethynyl-1,3,5(10)-estratriene-3,17-β-diol

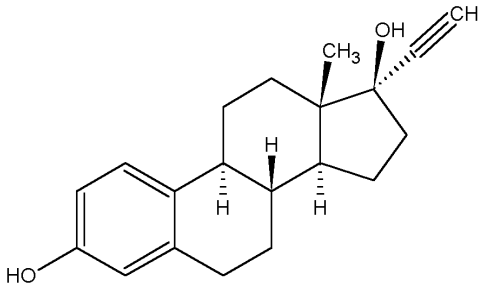
Molecular formula: Levonorgestrel: $C_{21}H_{28}O_2$
Ethinyl Estradiol: $C_{20}H_{24}O_2$

molecular mass: Levonorgestrel: 312.45
Ethinyl Estradiol: 296.40

Structural formula:
Levonorgestrel:




Ethinyl Estradiol:



Physicochemical properties:

| | | |
|---|---|---|
| Solubility: | Levonorgestrel: | Slightly soluble in alcohol, insoluble in water |
| | Ethinyl Estradiol: | Insoluble in water, soluble in alcohol, chloroform, ether, vegetable oil and in alkaline solutions |
| Melting points: | Levonorgestrel: | 232-239°C |
| | Ethinyl Estradiol: | 180-186 °C |

Biological properties:

| | |
|---|---|
| Levonorgestrel: | This is a synthetic progestogen in the (-)-isomer of norgestrel. It is the biologically active form of the racemic norgestrel. |
| Ethinyl Estradiol: | This is a synthetic estrogen. |

## CLINICAL TRIALS

### Study demographics and trial design

Pivotal study PSE-301 was a Phase III, randomized, multicenter clinical trial conducted to evaluate the efficacy and safety of Seasonique® and another 91-day oral contraceptive regimen for one year (four 91-day cycles). The second 91-day regimen is identical to Seasonique®, except that a higher dose of ethinyl estradiol-alone is administered during the last 7 days of each 91-day cycle. This second higher-dose regimen is investigational and is not approved for use in Canada.

A total of 1006 subjects were treated with at least one dose of Seasonique®. Of these, 799 subjects completed at least one 91-day complete cycle on treatment (ITT cohort). The PITT cohort was the primary cohort used for the efficacy analyses, and was comprised of patients 18-35 years of age with at least one complete cycle on treatment. See the Table below for a summary of patient cohorts analyzed in PSE-301.

**Patient Cohorts Analyzed in study PSE-301**

| | Seasonique® (N=1024) | |
|---|---|---|
| | **N** | **%** |
| Randomized | 1024 | 100.0 |
| Treated Patients (Safety) | 1006 | 98.2 |
| Treated at Least 1 Complete Cycle (ITT) | 799 | 78.0 |
| ITT, 18-35 Years of Age (PITT) | 708 | 69.1 |

The discontinuation rate was 50.3% in the Seasonique® arm (506/1006 patients discontinued the study early). Among all treated patients, the most common reasons for discontinuation were adverse events (16.3% in the Seasonique arm). The most commonly reported adverse events (AEs) leading to study discontinuation were intermenstrual bleeding and menorrhagia. In the Seasonique arm, 62 of 164 (37.8%) AEs that lead to study discontinuation were related to bleeding and/or spotting.

In all cohorts (safety, ITT and PITT), over 95% of the patients took their daily pill over 80% of the time.

See the Table below for a summary of demographics of the PITT cohort. Results were generally similar for the ITT cohort.

**Demographic Information at Screening: Patients 18-35 Years of Age with at Least One Complete Cycle on Treatment (PITT) in study PSE-301**

| | Seasonique® (N=708) |
|---|---|
| ***Race*** | |
| African-American | 80 (11.3%) |
| Asian | 16 (2.3%) |
| Caucasian | 562 (79.4%) |
| Hispanic | 34 (4.8%) |
| Other | 16 (2.3%) |
| ***Smoking Status*** | |
| Non-Smoker | 570 (80.5%) |
| Smoker | 138 (19.5%) |

**Demographic Information at Screening: Patients 18-35 Years of Age with at Least One Complete Cycle on Treatment (PITT) in study PSE-301**

| | **Seasonique® (N=708)** |
|---|---|
| ***OC Use History*** | |
| Continuous User[1] | 484 (68.4%) |
| Prior User[2] | 152 (21.5%) |
| Fresh-Start[3] | 72 (10.2%) |
| ***Age at Screening*** **(yrs)** | |
| N | 708 |
| Mean (Std) | 26.2 (4.64) |
| Median | 25.9 |
| (Min, Max) | (18.0, 35.0) |
| ***Weight*** **(lbs)** | |
| N | 708 |
| Mean (Std) | 154.9 (38.62) |
| Median | 146.0 |
| (Min, Max) | (94.0, 360.0) |
| ***Body Mass Index*** **(kg/m$^2$)** | |
| N | 707 |
| Mean (Std) | 25.9 (6.19) |
| Median | 24.3 |
| (Min, Max) | (17.1, 56.5) |

[1]Had history of oral contraceptive (OC) use prior to enrollment
[2]Had a history of OC use, but not within the six months prior to enrollment
[3]Had no prior history of OC use

## Study results

As noted above, the PITT cohort was the primary cohort used for the efficacy analyses, and was comprised of patients 18-35 years of age with at least one complete cycle on treatment. Cycles in which another form of birth control was used (including condoms) were excluded from the assessment of the Pearl Index. The Pearl Index for Seasonique® for the PITT cohort, excluding cycles in which another birth control method was used was 1.77 (95% CI 0.71-3.65), based on 7 pregnancies that occurred on-treatment over 5125.25 28-day equivalent patient months (1577 91-day cycles). The Pearl Index for Seasonique® for the subset of the PITT cohort with compliant use, excluding cycles in which another birth control method was used 0.78 (95% CI 0.16-2.28),

based on 3 pregnancies that occurred on-treatment over 4982.25 28-day equivalent patient-months (1533 91-day cycles). In the compliant-use subset analysis, patient cycles that were deemed non-compliant (where non-compliance is defined as all cycles in which a patient skipped two or more consecutive pills or had a pattern of substantial non-compliance with study medication or used a prohibited concomitant medication that may interact with oral contraceptive therapy) were not used. Substantial non-compliance was defined as an overall pill compliance of less than 80%.

The cumulative failure rate for Seasonique® at the end of one year of treatment, estimated by the life table method, was 0.89% (95% CI 0.37%, 2.18%).

See summary table of Pearl Indices and Life Table Analyses for Seasonique, below.

**Pearl Index Calculation of Treatment Failure Rates: Patients 18-35 Years of Age With at Least One Complete Cycle of Treatment (PITT) - Excluding Cycles in Which Another Birth Control Method was Used**

| Treatment Group | Number of Cycles | Number of 28-Day Patient Months | Number of On-Drug Pregnancies | Pearl Index (95% CI) |
|---|---|---|---|---|
| Seasonique® | 1577 | 5125.25 | 7 | 1.77 (0.71,3.65) |

**Life Table Estimates of Treatment Failure Rates - Patients 18-35 Years of Age With at Least One Complete Cycle of Treatment (PITT)**

| Seasonique® | | | |
|---|---|---|---|
| Cycle | N | Pregnancy Rate | 95% C.I. |
| 1 | 709 | 0.0029 | 0.0007-0.0115 |
| 2 | 667 | 0.0045 | 0.0015-0.0140 |
| 3 | 530 | 0.0065 | 0.0024-0.0174 |
| 4 | 464 | 0.0089 | 0.0037-0.0218 |

See also **Clinical trial adverse drug reactions** section for discussion of safety results from PSE-301.

General Information

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

**Reported Pregnancies per 100 Women per Year:**

| | |
|---|---|
| Combination pill | less than 1 to 2 |
| Intrauterine device (IUD) | less than 1 to 6 |
| Condom with spermicidal foam or gel | 1 to 6 |
| Mini-pill | 3 to 6 |
| Condom | 2 to 12 |
| Diaphragm with spermicidal foam or gel | 3 to 18 |
| Spermicide | 3 to 21 |
| Sponge with spermicide | 3 to 28 |
| Cervical cap with spermicide | 5 to 18 |
| Periodic abstinence (rhythm), all types | 2 to 20 |
| No birth control | 60 to 85 |

## DETAILED PHARMACOLOGY

Intensive biological investigations have been carried out with norgestrel alone and in combinations with ethinyl estradiol in rats, mice, rabbits, dogs and monkeys.

In tests for progestational alteration of the endometrium of rabbits, norgestrel by the subcutaneous route proved to be about nine times more active than progesterone and about one hundred times more active than norethisterone by oral and subcutaneous routes. In contrast to norethisterone, which is inactive, norgestrel will maintain pregnancy in spayed laboratory rats and produce endometrial gland development in rabbits when administered directly into the uterine lumen. In a broad series of biological tests, its activities are similar to those of progesterone. Although certain androgenic effects typical of many relatives of 19-nortestosterone are evident at high doses, norgestrel is devoid of such effects at usual clinical doses, and the separation of progestational from androgenic effects for norgestrel is greater than for related compounds. Norgestrel is not estrogenic, nor is it apparently converted *in vivo* to estrogen; it is an exceedingly potent antagonist. When combined with ethinyl estradiol, norgestrel tends to ameliorate the effects of the estrogen, while the estrogen will modify the effects of the progestogen. In rats, suppression of fertility with norgestrel/ethinyl estradiol combinations is followed by recovery of normal fertility and fecundity.

Additional experiments in laboratory animals were directed toward evaluating the endocrine effects and safety of the norgestrel and ethinyl estradiol formulation at dose levels approximating those employed clinically (on a milligram per kilogram basis). Metrotropic effect (uterine glandular development and growth) was most clearly demonstrated. Blockade of pituitary gonadotrophins can be produced by the estrogenic component alone at the clinical dose range;

this pituitary effect does not appear to be modified by addition of the progestogen.

The following properties, observed with high doses of norgestrel or norgestrel/ethinyl estradiol combinations, were absent at doses, approximating the clinical range: pregnancy maintenance in spayed female rats; parturition delay in pregnant rats; estrogenic changes in mouse vaginal cytology; anti-estrogenic effect in mouse uterine growth or vaginal smear tests; androgenic, myotrophic or fetal masculinizing effects in rats; claudogenic (antinidatory) effects in rats; thymolymphatic involution in mice, mineralocorticoid effects in rats and dogs and antimineralocorticoid effects in rats. No glucocorticoid (rat liver glycogen) or anti-inflammatory (Selye pouch, TBR-arthritis or granuloma pellet tests) effects have been seen at any dose.

Progestogens can have, in addition to progestational activity, estrogenic, anti-estrogenic and androgenic activity. When combined with estrogen, the progestogen will markedly affect the overall biological activity by producing a synergistic, summative or diminutional effect on activity. Comparisons of progestogen potency are not considered scientifically valid because the effects of one progestogen cannot be directly compared with those of another.

A study of serum luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone and 17β-estradiol in patients taking 150 µg *d*-norgestrel (as the *dl*-racemate) plus 30 µg ethinyl estradiol indicated reduction or abolition of the mid-cycle ovulatory peak and post-ovulatory levels commonly associated with these hormones and gonadotrophins, respectively.

Endometrial biopsies taken during the course of therapy with 250 µg *d*-norgestrel (as the *d1*-racemate) plus 50µg ethinyl estradiol revealed a histological sequence in the menstrual cycle of early glandular epithelial stimulation followed by later inhibition after the first half of the menstrual cycle.

Cervical mucus studies with 250 µg *d*-norgestrel (as the *dl*-racemate) plus 50 µg ethinyl estradiol, and 37.5 µg *d*-norgestrel (as the *dl*-racemate) revealed absence of ferning and decreased spinnbarkeit, indicative of poor conditions for sperm penetration and migration.

The results of assays for prolactin in a group of 11 normally ovulating women given 150 µg d-norgestrel (as the dl-racemate) plus 30 µg ethinyl estradiol over a continuous period of three months indicated no clinically or statistically significant elevation or depression of hormone levels during the course of active drug ingestion, nor in the post-treatment cycle.

A human study of the metabolism of $^{14}$C-labelled norgestrel, revealed that most of the urinary excretion of norgestrel occurred on the first day. There was no difference in the rate of excretion of norgestrel whether administered orally or intravenously. The amount of radioactivity in plasma fell rapidly within the first few hours and at the end of two days only small amounts were present. The foregoing and other studies with $^{14}$C-labelled and unlabelled norgestrel have shown that saturation of the 4,5-double bond with and without concomitant reduction of the 3-carbonyl to a 3-hydroxyl group are important reactions during metabolism.

## MICROBIOLOGY

Not applicable.

## TOXICOLOGY

Levonorgestrel and ethinyl estradiol have been extensively studied and are well-characterized pharmaceuticals. These approved pharmaceuticals in combination are both safe and effective when indicated for the prevention of pregnancy.

The association of mammary tumours in beagle dogs and steroid contraceptive use has been extensively reported in the published literature. Much of the published literature looked at the suitability of the beagle dog as a test model to assess the tumourigenic potential of certain progestogens in inducing mammary tumours and comparing it to the human model. Early toxicology studies in beagle dogs showed the overall incidence of mammary tumours were more common and frequent by a factor of three to four than in women. However, the beagle dog differs significantly from other animal species and humans mainly due to its differences in reproductive physiology and endocrinology. The beagle dog species is more susceptible to show mammary tumours as it has a fairly high natural incidence of mammary cancer. Some of the published literature has reported that many of the more potent progestogens have been shown to induce mammary tumours compared to the less potent progestational compounds. Evidence has shown that long-term administration of norgestrel has less progestational activity and incidence of mammary tumours over more potent progestogens.

Steroid-related canine mammary tumours were unlikely to be indicative of a potential hazard to women.

## REFERENCES


1. Asherson RA, Cervera R, Font J. Multiorgan thrombotic disorders in systemic lupus erythematosus: a common link? Lupus 1992;1:199-203.
2. Kwaan HC, Ganguly P. Introduction: thrombotic thrombocytopenic purpura and the hemolytic uremic syndrome. Semin Hematol 1997;34(2):81-9.
3. Sibai BM, Kustermann L, Velasco J. Current understanding of severe preeclampsia, pregnancy-associated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, hemolysis, elevated liver enzymes, and low platelet syndrome, and post partum acute renal failure: different clinical syndromes or just different names? Curr Opin Nephrol Hypertension 1994;3:436-45.
4. Stewart CL, Tina LU. Hemolytic uremic syndrome. Pediatr Rev 1993;14(6):218-24.
5. Koenigs KP, McPhedran P, Spiro HM. Thrombosis in inflammatory bowel disease. J Clin Gastroenterol 1987;9(6):627-31.
6. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Sickle cell disease. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 243-6.
7. Adams HP, Biller J. Ischemic cerebrovascular disease. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, editors. Neurology in clinical practice. Boston: Butterworth-Heinemann; 1996. p. 1014-9.
8. Carlone JP, Keen PD. Oral contraceptive use in women with chronic medical conditions. Nurse Pract 1989;14(9):9-10, 12-13, 16.
9. Gross U, Honcamp M, Daume E, Frank M, Dusterberg B, Doss MO. Hormonal oral contraceptives, urinary porphyrin excretion and porphyrias. Horm Metab Res 1995;27(8):379-83.
10. Petri M, Robinson C. Oral contraceptives and systemic lupus erythematosus. Arthritis Rheum 1997;40(5):797-803.
11. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Hemolytic uremic syndrome. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 211-8.
12. Galimberti D. Chorea induced by the use of oral contraceptives. Report of a case and review of the literature. Ital J Neurol Sci 1987;8(4):383-6.
13. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Sydenham's chorea. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 415-9.
14. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Herpes gestationis. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 367-70.

15. Morgan JK. Herpes gestationis influenced by an oral contraceptive. Br J Dermatol 1968;80(7):456-8.

16. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Otosclerosis. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 387-91.

17. Boyko EJ, Theis MK, Vaughan TL, Nicol-Blades B. Increased risk of inflammatory bowel disease associated with oral contraceptive use. Am J Epidemiol 1994;140(3):268-78.

18. Godet PG, May GR, Sutherland LR. Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. Gut 1995;37(5):668-73.

19. Logan RF, Kay CR. Oral contraception, smoking and inflammatory bowel disease--findings in the Royal College of General Practitioners Oral Contraception Study. Int J Epidemiol 1989;18(1):105-7.

20. Ramcharan S, Pellegrin FA, Ray R, Hsu J-P, Vessey MP. General summary of findings; general conclusions; implications. In: The Walnut Creek Contraceptive Drug Study: a prospective study of the side effects of oral contraceptives. Volume III: An interim report: a comparison of disease occurrence leading to hospitalization or death in users and nonusers of oral contraceptives. NIH Publication No. 81-564. Bethesda (MD): US Department of Health, Education, and Welfare, Center for Population Research; 1981. p. 211-38.

21. Sutherland LR, Ramcharan S, Bryant H, Fick G. Effect of oral contraceptive use on reoperation following surgery for Crohn's disease. Dig Dis Sci 1992;37(9):1377-82.

22. Vessey M, Jewell D, Smith A, Yeates D, McPherson K. Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives: findings in a large cohort study of women of childbearing age. Br Med J (Clin Res Ed) 1986;292(6528):1101-3.

23. EMEA. CPMP Public assessment report: combined oral contraceptives and venous thromboembolism. London: EMEA Committee for Proprietary Medicinal Products (CPMP); 2001 Sep 28. Report No.: EMEA/CPMP/2201/01/en Final.

24. Binkley KE, Davis A, 3rd. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. J Allergy Clin Immunol 2000;106(3):546-50.

25. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. Am J Med 2003;114(4):294-8.

26. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med 2001;161(20):2417-29.

27. Heikkila M, Haukkamaa M, Luukkainen T. Levonorgestrel in milk and plasma of breast-feeding women with a levonorgestrel-releasing IUD. Contraception 1982;25(1):41-9.

28. Nilsson S, Nygren KG, Johansson ED. Ethinyl estradiol in human milk and plasma after oral administration. Contraception 1978;17(2):131-9.

29. WHO. Medical eligibility criteria for contraceptive use. Geneva: World Health Organization, Reproductive Health and Research; 2004: 1-176.

30. Barditch-Crovo P, Trapnell CB, Ette E, Zacur HA, Coresh J, Rocco LE, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. Clin Pharmacol Ther 1999;65(4):428-38.

31. Krauss GL, Brandt J, Campbell M, Plate C, Summerfield M. Antiepileptic medication and oral contraceptive interactions: a national survey of neurologists and obstetricians. Neurology 1996;46:1534-39.

32. Riva R, Albani F, Contin M, Baruzzi A. Pharmacokinetic interactions between antiepileptic drugs: clinical considerations. Clin Pharmacokinet 1996;31(6):470-93.

33. Saano V, Glue P, Banfield CR, Reidenberg P, Colucci RD, Meehan JW, et al. Effects of felbamate on the pharmacokinetics of a low-dose combination oral contraceptive. Clin Pharmacol Ther 1995;58(5):523-31.

34. Ouellet D, Hsu A, Qian J, Locke CS, Eason CJ, Cavanaugh JH, et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. Br J Clin Pharmacol 1998;46(2):111-6.

35. Mildvan D, Yarrish R, Marshak A, Hutman HW, McDonough M, Lamson M, et al. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. J Acquir Immune Defic Syndr 2002; 29(5):471-7.

36. Christensen J, Petrenaite V, Atterman J, Sidenius P, Ohman I, Tomson T, Sabers A. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. *Epilepsia* 2007 48(3)484-489.

37. Contin M, Albani F, Ambrosetti G, Avoni P, Bisulli F, Riva R, Tinuper P, Baruzzi A. Variation in Lamotrigine Plasma Concentrations with Hormonal Contraceptive Monthly Cycle in Patients with Epilepsy. Epilepsia 2006 47(9) 1573-1575.

38. Sabers A, Buchholt J, Uldall P, Hansen E. Lamotrigine plasma levels reduced by oral contraceptives. Epilepsy Research. 2001; 47:151-154.

39. Sabers A, Ohman I, Christensen J, Tomson T. Oral contraceptices reduce lamotrigine plasma levels. Neurology 2008 61; 570-571.

40. Sidhu J, Job S, Singh S, Philipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. British Journal of Clinical Pharmacology 2005; 61(2): 191-199.

41. Fotherby, K. Levonorgestrel. Clinical pharmacokinetics. Clin Pharmacokinet 1995;28(3): 203-15.

42. Fotherby, K. Pharmacokinetics of ethynyloestradiol in humans. Methods Find Exp Clin Pharmacol 1982;4(2): 133-41.

43. Back, D. J., Grimmer, S.F.M., Rogers, C., Stevenson, P.J., Orme, M.L'E. Comparative pharmacokinetics of levonorgestrel and ethinyloestradiol following intravenous, oral and vaginal administration. Contraception 1987 Oct;36(4): 471-9.

44. Humpel, M., Wendt, H., Pommerenke, G., Weiβ, Speck, U. Investigations of pharmacokinetics of levonorgestrel to specific consideration of a possible first-pass effect in women. Contraception 1978 March;17(3): 207-20.

45. Back, D. J., Bates, M., Breckenridge, A.M., Hall, J.M., MacIver, M., Orme, M.L'E., Park, B.K. Rowe, P.H. The pharmacokinetics of levonorgestrel and ethynyl estradiol in women - studies with Ovran and Ovranette. Contraception 1981 March;23(3): 229-39.

46. Fotherby, K. Bioavailability of orally administered sex steroids used in oral contraception and hormone replacement therapy. Contraception 1996;54(2): 59-69.

47. Stanczyk, F. Z., Lobo, R.A., Chiang, S.T. Woutersz, T.B. Pharmacokinetic comparison of two triphasic oral contraceptive formulations containing levonorgestrel and ethinylestradiol. Contraception 1990a Jan;41(1): 39-53.

48. Sisenwine, S. F., Kimmel, H.B., Liu, A.L., Ruelius, H.W. Excretion and stereoselective biotransformations of dl-, d- and l-norgestrel in women. Drug Metab Dispos 1975b May-Jun;3(3): 180-8.

49. Sisenwine, S. F., Kimmel, H.B., Liu, A.L., Ruelius, H.W. The presence of dl-, d- and l-norgestrel and their metabolites in the plasma of women. Contraception 1975a Sep;12(3): 339-53.

50. Stanczyk, F. Z., Roy, S. Metabolism of levonorgestrel, norethindrone, and structurally related contraceptive steroids. Contraception 1990b Jul;42(1): 67-96.

51. Guengerich, F. P. (1990). Metabolism of 17 alpha-ethynyl estradiol in humans. Life Sci 1990;47(22):1981-8.

52. Williams, M. C., Helton, E.D., Goldzieher, J.W. The urinary metabolites of 17alpha-ethynylestradiol-9alpha,11xi-3H in women. Chromatographic profiling and indentification of ethynyl and non-ethynyl compounds. Steroids 1975 Feb;25(2):229-46.

53. Maggs, J. L., Park, B.K. A comparative study of biliary and urinary 2-hydroxylated metabolites of (6,7-3H)17 alpha-ethynyl estradiol in women. Contraception 1985 Aug;32(2):173-82.

## PART III: CONSUMER INFORMATION

**Seasonique™**

(levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg tablets, USP and ethinyl estradiol 0.01 mg tablets, USP)

**This leaflet is Part III of a three-part "Product Monograph" published when Seasonique® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Seasonique®. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
Seasonique™ is indicated for the prevention of pregnancy.

**What it does:**
Seasonique® is a birth control pill (oral contraceptive) that contains two female sex hormones (levonorgestrel and ethinyl estradiol). It has been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills, except in smokers older than age 35.
Birth control pills work in two ways:

1. They inhibit the monthly release of an egg by the ovaries.

2. They change the mucus produced by the cervix. This slows the movement of the sperm through the mucus and through the uterus (womb).

**What You Should Know About Your Menstrual Cycle When Taking Seasonique®**

When you take Seasonique®, which has a 91 day treatment cycle, you should expect to have 4 menstrual periods per year (bleeding between days 85 to 91 when you take the 7 yellow pills). However, you should initially expect to have more bleeding or spotting between your menstrual periods than if you were taking an oral contraceptive with a 28-day treatment. This bleeding or spotting tends to decrease during later cycles. Do not stop Seasonique® because of the bleeding. If the spotting continues for more than a few days or if the bleeding is heavy, call your healthcare professional.

**Effectiveness of Birth Control Pills**

Combination birth control pills are more than 99 percent effective in preventing pregnancy when:
• the pill is **TAKEN AS DIRECTED**, and
• the amount of estrogen is 20 micrograms or more.

A 99 percent effectiveness rate means that if 100 women used birth control pills for one year, one woman in the group would get pregnant.

The chance of becoming pregnant increases with incorrect use.

**Other Ways to Prevent Pregnancy**

Other methods of birth control are available to you. They are usually less effective than birth control pills. When used properly, however, other methods of birth control are effective enough for many women.

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year:

| | |
|---|---|
| Combination pill | less than 1 to 2 |
| Intrauterine device (IUD) | less than 1 to 6 |
| Condom with spermicidal foam or gel | 1 to 6 |
| Mini-pill | 3 to 6 |
| Condom | 2 to 12 |
| Diaphragm with spermicidal foam or gel | 3 to 18 |
| Spermicide | 3 to 21 |
| Sponge with spermicide | 3 to 28 |
| Cervical cap with spermicide | 5 to 18 |
| Periodic abstinence (rhythm), all types | 2 to 20 |
| No birth control | 60 to 85 |

Pregnancy rates vary widely because people differ in how carefully and regularly they use each method. (This does not apply to IUDs since they are implanted in the uterus). Regular users may achieve pregnancy rates in the lower ranges. Others may expect pregnancy rates more in the middle ranges.

The effective use of birth control methods other than birth control pills and IUDs requires more effort than taking a single pill every day. It is an effort that many couples undertake successfully.

**When it should not be used:**
The birth control pill is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a risk to you. The use of the birth control pill should always be supervised by your doctor.

**You should not use Seasonique®** if you have or have had any of the following conditions:

- blood clots in the legs, lungs, eyes, or elsewhere, or thrombophlebitis (inflammation of the veins)

- stroke, heart attack, or coronary artery disease (e.g. angina pectoris), or a condition that may be a first sign of a stroke (such as a transient ischemic attack or small reversible stroke)
- disease of the heart valves with complications
- severe high blood pressure
- diabetes with complications
- known abnormalities of the blood clotting system that increases your risk for developing blood clots
- very high blood cholesterol or triglyceride levels
- heavy smoking (>15 cigarettes per day) and over age 35
- migraine headache
- you are scheduled for major surgery
- prolonged bed rest
- jaundice (yellowing of the eyes or skin), liver disease or liver tumour
- known or suspected cancer of the breast or uterus (womb) or other estrogen-dependent cancer
- unusual vaginal bleeding without a known reason
- loss of vision due to blood vessel disease of the eye
- you are pregnant or suspect you may be pregnant
- pancreatitis (inflammation of the pancreas) associated with high levels of fatty substances in your blood
- allergy (hypersensitivity) to ethinyl estradiol, levonorgestrel or to any of the other ingredients in Seasonique® (see **What the medicinal ingredients are** and **What the non medicinal ingredients are**)

**What the medicinal ingredients are:**

The light blue-green tablet contains levonorgestrel and ethinyl estradiol, and the yellow tablet contains ethinyl estradiol.

**What the non medicinal ingredients are:**

Each light blue-green tablet contains the following non medicinal ingredients: anhydrous lactose, FD&C Blue No. 1 aluminum lake, FD&C yellow No. 10 aluminum lake, FD&C yellow No. 6 aluminum lake, glycerol triacetate (triacetin), hypromellose (hydroxypropyl methylcellulose), lactose monohydrate, magnesium stearate, microcrystalline cellulose, and titanium dioxide.

Each yellow tablet contains the following non medicinal ingredients: anhydrous lactose, FD&C yellow No. 10 aluminum lake, FD&C yellow No. 6 aluminum lake, hypromellose (hydroxypropyl methylcellulose), magnesium stearate, microcrystalline cellulose, polacrilin potassium, polyethylene glycol, polysorbate 80 and titanium dioxide.

**What dosage forms it comes in:**

Seasonique® (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg combination and ethinyl estradiol 0.01 mg) tablets are available in Extended-Cycle Tablet Dispensers. Altogether, the Tablet Dispenser holds 91 tablets consisting of 84 light blue-green tablets (each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol) and 7 yellow tablets (each containing 0.01 mg ethinyl estradiol).

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

**Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in hormonal contraceptive users older than 35 years of age. Women should not smoke.**

**Birth control pills DO NOT PROTECT against Sexually Transmitted Infections (STIs), including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms IN COMBINATION WITH birth control pills.**

**Use of Seasonique® provides women with more hormonal exposure on a yearly basis than conventional monthly oral contraceptives containing similar strength synthetic estrogens and progestins (9 additional weeks of combined estrogen/progestin and 4 additional weeks of estrogen-alone per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic diseases (blood clots), studies to date with Seasonique® have not suggested, nor can exclude, this additional risk.**

**Seasonique® Oral Contraceptive**

Seasonique® is a 91-day cyclic dosing regimen (84 days with oral light blue-green tablets of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol, followed by 7 days with 0.01 mg ethinyl estradiol yellow tablets). Pregnancy should be ruled out in cases of unanticipated bleeding/spotting, missed withdrawal bleeding/amenorrhea (missed period) or signs and symptoms of pregnancy.

**BEFORE you use Seasonique® talk to your doctor or pharmacist if you:**

- smoke
- have a history of breast disease (e.g. breast lumps) or a family history of breast cancer
- have high blood pressure
- have high cholesterol

- have diabetes
- have heart or kidney disease
- have a history of seizures/epilepsy
- have a history of depression
- have a history of liver disease or jaundice
- wear contact lenses
- have uterine fibroids (benign tumours of the uterus)
- may be pregnant or are breast feeding
- have systemic lupus erythematosus
- have inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- have hemolytic uremic syndrome
- have sickle cell disease
- have any problems with the valves in your heart and/or have an irregular heart rhythm
- have been told that you have a condition called hereditary angioedema or if you have had episodes of swelling in body parts such as hands, feet, face, or airway passages

You should also inform your doctor about a family history of blood clots, heart attacks, or strokes.

If you see a different doctor, inform him or her that you are using Seasonique®.

Tell your doctor if you are scheduled for any laboratory tests since certain blood tests may be affected by hormonal contraceptives.

Also tell your doctor if you are scheduled for **MAJOR** surgery. You should consult your doctor about stopping the use of Seasonique® four weeks before surgery and not using Seasonique® for a time period after surgery or during bed rest.

Seasonique® should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year. Use Seasonique® only on the advice of your doctor and carefully follow all directions given to you. You must use the birth control pill exactly as prescribed. Otherwise, you may become pregnant.

If you and your doctor decide that, for you, the benefits of Seasonique® outweigh the risks, you should be aware of the following:

**THE RISKS OF USING SEASONIQUE®**

**1. Circulatory disorders (including blood clot in legs, lungs, heart, eyes or brain)**

Blood clots are the most common serious side effects of birth control pills. The risk of developing blood clots is especially high during the first year a woman ever uses a hormonal contraceptive. Clots can occur in many parts of the body.
Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:

- sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung.
- pain and/or swelling in the calf. These symptoms could indicate a possible blood clot in the leg.
- crushing chest pain or heaviness. These symptoms could indicate a possible heart attack.
- sudden severe or worsening headache or vomiting, dizziness or fainting, disturbances of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke.
- sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.

Any of these conditions can cause death or disability. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impaired vision or in a blood vessel leading to an arm or leg, resulting in damage to or loss of a limb.

Women who use hormonal contraceptives have a higher incidence of blood clots. The risk of clotting seems to increase with higher estrogen doses. It is important, therefore, to use as low a dosage of estrogen as possible.

**2. Breast cancer**
The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include obesity, never having children, and having your first full-term pregnancy at a late age.

Some women who use hormonal contraceptives may be at increased risk of developing breast cancer before menopause, which occurs around age 50. These women may be long-term users of birth control pills (more than eight years) or women who start using birth control pills at an early age. In a few women, the use of birth control pills may accelerate the growth of an existing, but undiagnosed, breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to birth control pills seem to be small,

however. A yearly breast examination by a health care professional is recommended for all women.
**ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.**

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

**4. Liver tumours**
The short and long-term use of birth control pills have also been linked with the growth of liver tumours. Such tumours are **extremely** rare.
Contact your doctor immediately if you experience severe pain or a lump in the abdomen.

**5. Gallbladder disease**
Users of birth control pills have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

**6. Use in pregnancy**
Birth control pills should not be taken by pregnant women. There is no evidence, however, that the birth control pill can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

**7. Use after pregnancy, miscarriage or an abortion**
Your doctor will advise you of the appropriate time to start the use of Seasonique® after childbirth, miscarriage, or therapeutic abortion.

**8. Pregnancy after stopping Seasonique®**
You will have a menstrual period when you stop using Seasonique®.You should delay pregnancy until another menstrual period occurs within four to six weeks. In this way, the pregnancy can be more accurately dated. Contact your doctor for recommendations on alternate methods of contraception during this time.

**9. Use while breast feeding**
If you are breast-feeding, consult your doctor before starting the birth control pill. The hormones in birth control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. Adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. You should use another method of contraception and only consider starting the birth control pill once you have weaned your child completely.

## INTERACTIONS WITH THIS MEDICATION

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Please inform your doctor or pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription. Also tell any other doctor or dentist who prescribes another drug (or the dispensing pharmacist) that you use Seasonique®. They can tell you if you need to use an additional method of contraception and if so, for how long.

**Drugs that may interact with Seasonique® include:**

- drugs used for the treatment of epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, lamotrigine, oxcarbazepine, topiramate, felbamate),
- drug used for the treatment of tuberculosis (e.g. rifampin, rifabutin)
- drugs used for the treatment of HIV infection (e.g. ritonavir, nevirapine)
- antibiotics (e.g. penicillins, tetracyclines) for infectious diseases; you may be at higher risk of a specific type of liver dysfunction if you take troleandomycin and oral contraceptives at the same time.
- Cyclosporine
- antifungals (griseofulvin)
- the herbal remedy St. John's Wort (primarily used for the treatment of depressive moods)
- cholesterol-lowering drugs (e.g. clofibrate)
- antihypertensive drugs (for high blood pressure)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (e.g. benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- pain medication (meperidine)
- antidepressants (e.g. clomipramine)
- some nutritional supplements (e.g. Vit. B12, folic acid)
- antacids (use 2 hours before or after taking Seasonique®

The pill may also interfere with the working of other drugs.

*This is not a complete list of possible drug interactions with Seasonique®. Talk to your doctor for more information about drug interactions.*

## PROPER USE OF THIS MEDICATION

1. BE SURE TO READ THESE DIRECTIONS:
   - Before you start taking your pills.
   - Anytime you are not sure what to do.

2. THE RIGHT WAY TO TAKE SEASONIQUE® IS TO TAKE ONE PILL EVERY DAY AT THE SAME TIME.
   If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

3. MANY WOMEN MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST FEW WEEKS OF TAKING PILLS.
   If you feel sick to your stomach, do not stop taking the pill. The problem will usually go away. If it doesn't go away, check with your healthcare professional.

4. MANY WOMEN HAVE IRREGULAR SPOTTING OR LIGHT BLEEDING DURING THE FIRST FEW MONTHS OF TAKING SEASONIQUE®. **Do not stop taking your pills even if you are having irregular bleeding.** If the bleeding lasts for more than a few days, talk to your healthcare professional.

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 HAVE VOMITING OR DIARRHEA, or IF YOU TAKE SOME MEDICINES, including some antibiotics and the herbal supplement St. John's Wort, Seasonique® may not work as well. Use a back-up method (such as condoms or spermicides) until you check with your healthcare professional.

7. IF YOU HAVE TROUBLE REMEMBERING TO TAKE SEASONIQUE®, talk to your healthcare provider 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 healthcare professional.

### BEFORE YOU START TAKING SEASONIQUE®

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.

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 light blue-green pills (active pills with two hormones) and 7 yellow pills (pills with one hormone). Trays 1 and 2 each contain 28 light blue-green pills (4 rows of 7 pills). Tray 3 contains 35 pills consisting of 28 light blue-green pills (4 rows of 7 pills) and 7 yellow pills (1 row of 7 pills).

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).

2. 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 SEASONIQUE®

1. Take the first light blue-green pill on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the first light blue-green pill that same day.

2. *Use another method of birth control (such as condom or spermicide)* as a back-up method if you have sex anytime from the Sunday you start your first light blue-green pill until the next Sunday (first 7 days).

### HOW TO TAKE SEASONIQUE®

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 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 light blue-green pill from a new Extended-Cycle Tablet Dispenser **the very next day** regardless of when your period started. This should be on a Sunday.

3. **If you miss your period when you are taking the yellow pills, call your healthcare provider because you may be pregnant.**

**Usual dose:**
One light blue-green tablet should be taken daily for 84 consecutive days, followed by 7 days of yellow tablets.

**Overdose:**
Symptoms of overdose may include nausea, vomiting or vaginal bleeding. Available information from cases of accidental ingestion of oral contraceptives by children indicates no serious effects.

| |
|---|
| In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. |

**Missed Dose:**

If you **MISS one** light blue-green pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you 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 two** light blue-green 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 restart your pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up on the 7 days after you restart your pills.

If you **MISS 3 OR MORE** light blue-green pills in a row:
1. Do not remove the missed pills from the pack as they will not be taken. Keep taking 1 pill every day as indicated on the pack until you have completed all of the pills in the pack. For example: if you resume taking the pill on Thursday, take the pill under "Thursday" and do not take the previous 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 you restart 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 miss your period when you are taking the yellow pills, call your healthcare professional 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 can consult your healthcare professional.

**IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW, TALK TO YOUR DOCTOR OR CLINIC** about ways to make pill-taking easier or about using another method of birth control.

**Non-contraceptive Benefits of Birth Control Pills**
Several health advantages have been linked to the use of birth control pills:
- Combination estrogen and progestin birth control pills reduce the incidence of cancer of the uterus and ovaries.
- Birth control pills reduce the likelihood of developing benign (non-cancerous) breast disease and ovarian cysts.
- Users of birth control pills lose less menstrual blood and have more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and in premenstrual syndrome (PMS).
- Acne, excessive hair growth and male-hormone-related disorders also may be improved.
- Ectopic (tubal) pregnancy may occur less frequently.
- Acute pelvic inflammatory disease may occur less frequently.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects have been observed in studies of women taking Seasonique:

Common: nausea, vomiting, diarrhea, flatulence, constipation, abdominal pain, bleeding or spotting between menstrual periods, painful menstrual periods, heavy menstrual bleeding, high blood pressure, migraine, mood swings, anxiety, weight gain, increased appetite, breast tenderness, fluid retention, hot flushes, headache, depression, dizziness, vertigo, insomnia, decreased libido, flu-like symptoms, cough, back and pelvic pain, fatigue, muscle cramps, toothache, acne, rash, urinary tract infections or inflammation , vaginal irritation and infections, upper respiratory tract infections (colds, bronchitis, runny or stuffy nose, sore throat, etc) and allergic reactions. Some of these side effects, especially nausea and vomiting may subside within the first 3 months of use.

Uncommon: darkening of the skin, heart palpitations, skin irritation, dry eye, thirst, weakness, decreased appetite, swelling or stiffness of joints, nail disorders, night sweats.

In the post-market period, there have been cases of stroke, deep vein thrombosis and pulmonary embolism (blood clots in the brain, arms or legs and lungs) reported with the use of Seasonique®.

If you experience new onset of high blood pressure or worsening of high blood pressure, contact your doctor or pharmacist.

The following additional symptoms have been reported in women taking hormonal contraceptives in general:

- amenorrhea (lack of a period or breakthrough bleeding)
- fever
- difficulty wearing contact lenses
- severe headaches

Many women have spotting or light bleeding or may feel sick to their stomach during the first three months on the pill. If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic. See also the **ABOUT THIS MEDICATION, What you should know about your menstrual cycle when taking Seasonique®** section of this leaflet."

## SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / possible side effect | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| **Common** | Persistent sad mood | | | ✓ |
| **Uncommon** | Abdominal pain, nausea or vomiting or lump in the abdomen | | ✓ | |
| | Breast lump | | ✓ | |
| | Crushing chest pain or heaviness | | | ✓ |
| | Pain or swelling in the leg | | | ✓ |
| | Sharp pain in the chest, coughing blood, or sudden shortness of breath | | | ✓ |
| | Sudden partial or complete loss of vision or double vision | | | ✓ |
| | Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm or leg | | | ✓ |
| | Unexpected vaginal bleeding | | ✓ | |
| | Unusual swelling of the extremities | | ✓ | |
| | Yellowing of the skin or eyes (jaundice) | | | ✓ |

***This is not a complete list of side effects. For any unexpected effects while taking Seasonique®, contact your doctor or pharmacist.***

## HOW TO STORE IT

Store at room temperature (15°C to 30°C).

Keep out of reach of children and pets.

Medicines should not be disposed of *via* wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**REPORTING SUSPECTED SIDE EFFECTS**

**To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance.**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to : Canada Vigilance Program**
    **Health Canada**
    **Postal Locator 0701D**
    **Ottawa, ON K1A 0K9**

**Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***Note: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.paladinlabs.com or by contacting the distributor, Paladin Labs Inc. at:

1-866-940-3687

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