

PRODUCT MONOGRAPH

Pr **SEASONALE**[®]

levonorgestrel and ethinyl estradiol tablets, USP

0.15 mg and 0.03 mg

Oral Contraceptive

Teva Women's Health, Inc.
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Pr **SEASONALE®**

(levonorgestrel and ethinyl estradiol, USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non Medicinal Ingredients
Oral	Tablet 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol	Anhydrous lactose <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

Seasonale® (levonorgestrel and ethinyl estradiol, USP) tablets are indicated for:

- The prevention of pregnancy.

CONTRAINDICATIONS

Oral contraceptives should not be used in women who have the following conditions:

- Patients who are hypersensitive 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.
- 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 symptoms
 - severe hypertension (persistent values of $\geq 160/100$ mm 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 neurological symptoms.

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 diseases including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

Use of Seasonale™ 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 hormonal exposure per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic diseases, studies to date with Seasonale™ 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.

Seasonale™ Oral Contraceptive

Seasonale™ is a 91-day cyclic dosing regimen (84 days with active oral tablets of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol, followed by 7 days with placebo tablets). 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. 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.

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

Some studies suggest that oral contraceptive use has been associated with an increase in risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which the findings may be due to differences in sexual behaviours and other factors.

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.

Also see **Product Monograph Part II, Toxicology**.

Cardiovascular

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

Use of Seasonale™ 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 hormonal exposure per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic diseases, studies to date with Seasonale™ have not suggested, nor can exclude, this additional risk. Two subjects had pulmonary embolism and one subject had myocardial infarction while on Seasonale™ in clinical studies. Coagulation profile has not been studied with Seasonale™.

In the post-market period, there have been cases of myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism reported with the use of Seasonale™.

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 Seasonale™.

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 oral 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.

Genitourinary**Vaginal Bleeding and Bleeding Irregularities**

In the pivotal, controlled clinical study 7.7% of subjects on Seasonale™ discontinued medication prematurely due to unacceptable bleeding vs. 1.8% of subjects on the 28-day cycle regimen.

The following table shows the percentage of subjects with inter-menstrual bleeding and /or spotting.

Table 1. Percentage of Subjects with Inter-menstrual Bleeding and/or Spotting

Days of inter-menstrual bleeding and/or spotting	Percentage of Subjects*	
	Seasonale™	28-day regimen
	Cycle 1 (N=385)	Cycle 4 (N=261)
≥ 7 days	65%	42%
≥ 20 days	35%	15%
	Cycles 1-4 (N=194)	Cycles 10-13 (N=158)
≥ 7 days	38%	39%
≥ 20 days	6%	4%

* Based on spotting and/or bleeding on days 1-84 of a 91-day cycle in the Seasonale™ subjects and days 1-21 of a 28-day cycle over 4 cycles in the 28-day dosing regimen.

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 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 carries an increased risk of venous thromboembolism (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. (See Reference section, item no. 10)

Other risk factors for venous thromboembolism

Other generalized risk factors for venous thromboembolism include, but are not limited to, a personal history, obesity, 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 >30 kg/m²) 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.

Neurologic

Migraine and headache

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

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, a trial of an alternate method of contraception should be made, which may help to 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

Seasonale™ is a 91-day cyclic dosing regimen (84 days with active oral tablets of 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol, followed by 7 days with placebo tablets). 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.

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. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk.

A few adverse effects on the child have been reported, including jaundice and breast enlargement. 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.

Pediatrics

The safety and efficacy of Seasonale™ has not been established in women under the age of 18 years.

Use of this product before menarche is not indicated.

Geriatrics

Seasonale™ is not indicated for use in post-menopausal women.

Monitoring and Laboratory Tests

Physical Examination and Follow-up

Before hormonal contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined. A Papanicolaou 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:

- thrombophlebitis
- pulmonary embolism
- mesenteric thrombosis
- neuro-ocular lesions (e.g., retinal thrombosis)
- myocardial infarction
- cerebral thrombosis
- cerebral hemorrhage
- hypertension
- benign hepatic tumours
- gallbladder disease
- congenital anomalies

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:

- gastrointestinal symptoms (such as abdominal cramps and bloating)
- breakthrough bleeding
- spotting
- change in menstrual flow
- dysmenorrhea
- amenorrhea during and after treatment
- temporary infertility after discontinuation of treatment
- edema
- chloasma or melasma which may persist
- breast changes (tenderness, enlargement, secretion)
- change in weight (increase or decrease)
- endocervical hyperplasia
- possible diminution in lactation when given immediately postpartum
- cholestatic jaundice
- migraine
- increase in size of uterine leiomyomata
- rash (allergic)
- mental depression
- reduced tolerance to carbohydrates
- vaginal candidiasis
- premenstrual like syndrome
- intolerance to contact lenses
- change in corneal curvature (steepening)
- cataracts
- optic neuritis
- retinal thrombosis
- changes in libido
- chorea
- changes in appetite
- cystitis-like syndrome
- rhinitis
- headache
- nervousness
- dizziness
- hirsutism
- loss of scalp hair
- erythema multiforme
- erythema nodosum
- hemorrhagic eruption
- vaginitis
- porphyria
- impaired renal function
- Raynaud's phenomenon

- auditory disturbances
- hemolytic uremic syndrome
- pancreatitis

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.

Seasonale™ included 15,027 28-day equivalent cycles for the safety ITT data. Across studies SEA-301, SEA-301A and SEA 303, 609 subjects completed 1 year treatment, 123 subjects completed 18 months treatment and 108 subjects completed 2 years treatment.

Two subjects had pulmonary embolism and one subject had myocardial infarction while on Seasonale™ in clinical studies.

The comparative safety data with a conventional monthly oral contraceptive containing similar strength synthetic estrogens and progestins on lipids profile, liver functions and endometrial biopsies (50 subjects only) is available for one year only.

Study SEA-301 (A Phase III, Parallel, Randomized, Multicenter, Open-Label Clinical Study to Evaluate the Efficacy and Safety of Seasonale™ Extended Oral Contraceptive Therapy - 84-Day Active Cycle)

Table 2 shows the incidence rates for the most frequently reported adverse events for all treated patients. The table displays results where the 5% or greater criterion was observed within any treatment group.

Table 2: Study SEA 301: Incidence of Most Frequently Reported Adverse Events Occurring in 5% or More Patients - All Treated Patients (ITT)

MedDRA System Organ Class	Seasonale (N=456)		Control (N=226)	
	N	%	N	%
INFECTIONS AND INFESTATIONS				
NASOPHARYNGITIS	100	21.93	67	29.65
SINUSITIS NOS	45	9.87	25	11.06
INFLUENZA	32	7.02	15	6.64
FUNGAL INFECTION NOS	27	5.92	11	4.87
UPPER RESPIRATORY TRACT INFECTION NOS	25	5.48	22	9.73
URINARY TRACT INFECTION NOS	20	4.39	14	6.19
NERVOUS SYSTEM DISORDERS				
HEADACHE NOS	94	20.61	64	28.32
REPRODUCTIVE SYSTEM AND BREAST DISORDERS				
MENORRHAGIA	53	11.62	6	2.65
DYSMENORRHOEA	26	5.70	9	3.98
GASTROINTESTINAL DISORDERS				
PHARYNGOLARYNGEAL PAIN	37	8.11	12	5.31
NAUSEA	34	7.46	20	8.85
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
BACK PAIN	29	6.36	19	8.41
PSYCHIATRIC DISORDERS				
DEPRESSION NOS	10	2.19	13	5.75

Study SEA-301A (A Phase IIIb, Parallel, Multicenter, Open-Label Clinical Study To Evaluate The Safety Of Seasonale™ Extended Oral Contraceptive Therapy – 84-Day Active Cycle)

Table 3 shows the incidence rates for the most frequently reported adverse events for all treated patients. The table displays results where the 5% or greater criterion was observed within any treatment group.

Table 3: Study SEA-301A: Incidence of Treatment - Emergent Adverse Events Occurring in 5% or More of All Treated Patients

MedDRA System Organ Class and Preferred Term	Seasonale (N=189)	
	N	%
INFECTIONS AND INFESTATIONS		
SINUSITIS NOS	36	19.05
NASOPHARYNGITIS	31	16.40

MedDRA System Organ Class and Preferred Term	Seasonale (N=189)	
	N	%
UPPER RESPIRATORY TRACT INFECTION NOS	31	16.40
URINARY TRACT INFECTION NOS	19	10.05
VAGINOSIS FUNGAL NOS	12	6.35
NERVOUS SYSTEM DISORDERS		
HEADACHE NOS	32	16.93
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
DYSMENORRHOEA	18	9.52
MENORRHAGIA*	15	7.94
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
INFLUENZA LIKE ILLNESS	17	8.99
INVESTIGATIONS		
SMEAR CERVIX ABNORMAL	17	8.99
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
BACK PAIN	15	7.94
GASTROINTESTINAL DISORDERS		
NAUSEA	12	6.35
PHARYNGOLARYNGEAL PAIN	11	5.82
ABDOMINAL PAIN NOS	10	5.29
IMMUNE SYSTEM DISORDERS		
SEASONAL ALLERGY	10	5.29

* Due to coding differences between studies SEA-301 and SEA-301A, “intermenstrual bleeding” should be combined with “menorrhagia” in study SEA-301A for comparison with “menorrhagia” in study SEA-301

Study SEA-303 (A Phase IIIb, Multicenter, Double-Blind Clinical Study to Evaluate the Safety and Tolerability of Seasonale™ Ultra-Lo Following a Run-In of Seasonale™ Extended Regimen Oral Contraceptive Therapy)

Tables 4 and 5 show the incidence rates for the most frequently reported adverse events for all treated patients. The table displays results where the 5% or greater criterion was observed within any treatment group.

Table 4: Study SEA-303: Incidence of Treatment Emergent Adverse Events During the 6-Month Run-In Period Occurring in 5% or More of Treated Patients

MedDRA System Organ Class and Preferred Term	All Patients** (N=1070)	
	N	%
NERVOUS SYSTEM DISORDERS		
HEADACHE NOS	248	23.18
INFECTIONS AND INFESTATIONS		
NASOPHARYNGITIS	98	9.16
UPPER RESPIRATORY TRACT INFECTION NOS	70	6.54
SINUSITIS NOS	61	5.70
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
DYSMENORRHOEA	75	7.01
INTERMENSTRUAL BLEEDING	89	8.32
MENORRHAGIA*	43	4.02
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
BACK PAIN	81	7.57
GASTROINTESTINAL DISORDERS		
NAUSEA	91	8.50
INVESTIGATIONS		
WEIGHT INCREASED	57	5.33

* Menorrhagia is listed even though the incidence is < 5% for all treatment groups for completeness when looking at bleeding and/or spotting related AEs

** All patients (N=1070) entered a 6-month Seasonale Run-in period. Characteristics of those discontinuing during the run-in period can be found in the SEA-303 study report. Those completing the run-in period were randomized 1:2 to Seasonale (N=229) or Seasonale Lo (N=465).

Table 5: Study SEA-303: Incidence of Treatment-Emergent Adverse Events During the 9-Month Randomized Double-Blind Period Occurring in 5% or More of All Treated Patients

MedDRA System Organ Class and Preferred Term	Seasonale Randomized (N=229)	
	N	%
NERVOUS SYSTEM DISORDERS		
HEADACHE NOS	58	25.33
INFECTIONS AND INFESTATIONS		
NASOPHARYNGITIS	30	13.10
UPPER RESPIRATORY TRACT INFECTION NOS	22	9.61
SINUSITIS NOS	27	11.79
URINARY TRACT INFECTION NOS	13	5.68
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
INTERMENSTRUAL BLEEDING	8	3.49
DYSMENORRHOEA	15	6.55
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
BACK PAIN	22	9.61

* Menorrhagia is listed even though the incidence is <5% for all treatment groups for completeness when looking at bleeding and/or spotting related AEs

Less Common Clinical Trial Adverse Drug Reactions (≥1% to <5%)

Study SEA-301

Infections and Infestations: Urinary Tract Infection, Bronchitis, Pharyngitis Streptococcal, Ear Infection, Vaginitis Bacterial, Vaginosis Fungal, Bladder Infection, Pharyngitis, Vaginal Candidiasis

Gastrointestinal Disorders: Abdominal Pain Upper, Vomiting, Dyspepsia, Toothache, Abdominal Pain, Diarrhoea, Abdominal Distension, Constipation

Nervous System: Migraine, Dizziness (Excl. Vertigo), Sinus Headache

Musculoskeletal and Connective Tissue Disorders: Muscle Cramps, Arthralgia, Pain In Limb, Myalgia, Neck Pain, Muscle Spasms, Tendonitis

Reproductive System and Breast Disorders: Breast Tenderness

Skin and Subcutaneous Tissue Disorders: Acne, Acne Aggravated, Rash

General Disorders and Administration Site Conditions: Influenza Like Illness, Fatigue, Pain, Pyrexia, Chest Pain

Respiratory, Thoracic and Mediastinal Disorder: Sinus Congestion, Cough, Nasal Congestion, Asthma

Psychiatric Disorders: Depression, Insomnia, Mood Swings, Libido Decreased

Injury, Poisoning and Procedural Complications: Muscle Strain, Post Procedural Pain, Accident, Road Traffic Accident

Investigations: Weight Increased

Immune System Disorders: Hypersensitivity, Seasonal Allergy

Ear and Labyrinth Disorders: Ear Pain

Study SEA-301A

Infections and Infestations: Bronchitis, Candidal Infection, Cervicitis, Ear Infection, Folliculitis, Fungal Infection, Gastroenteritis Viral, Gingivitis Infection, Herpes Simplex Infection, Influenza, Laryngitis, Nail Infection, Otitis Media, Papilloma Viral Infection, Pharyngitis Streptococcal, Pneumonia, Post-Operative Wound Infection, Tooth Caries, Tooth Infection, Vaginitis Bacterial

Gastrointestinal Disorders: Abdominal Pain Upper, Constipation, Diarrhoea, Dyspepsia, Food Poisoning, Gastro-Oesophageal Reflux Disease, Toothache, Vomiting

Nervous System Disorders: Dizziness (Excl Vertigo), Hypoaesthesia, Migraine, Sinus Headache, Vasovagal Attack

Reproductive System and Breast Disorders: Breast Cyst, Breast Tenderness, Intermenstrual Bleeding, Premenstrual Syndrome, Vaginal Discharge

Musculoskeletal and Connective Tissue Disorders: Arthralgia, Joint Swelling, Muscle Spasms, Myalgia, Neck Pain, Pain In Limb

Investigations: Alanine Aminotransferase Increased, Blood Pressure Increased, Liver Function Tests Abnormal, Weight Increased

General Disorders and Administration Site Conditions: Chest Tightness, Fall, Fatigue, Pain, Pyrexia

Skin and Subcutaneous Tissue Disorders: Acne, Contusion, Dermatitis Atopic, Erythema, Rash, Urticaria

Injury, Poisoning and Procedural Complications: Arthropod Bite, Post Procedural Pain, Road Traffic Accident, Animal Bite, Muscle Strain, Burns, Laceration, Sunburn

Psychiatric Disorders: Anxiety, Depression, Insomnia, Libido Decreased, Stress Symptoms

Respiratory, Thoracic and Mediastinal Disorders: Cough, Nasal Congestion, Sinus Congestion

Immune Systems Disorders: Allergy Aggravated, Hypersensitivity

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Breast Lump, Uterine Fibroids

Vascular Disorders: Hypertension

Cardiac Disorders: Arrhythmia

Ear and Labyrinth Disorders: Vertigo

Renal and Urinary Disorders: Calculus Renal

Hepatobiliary Disorders: Cholelithiasis

Eye Disorders: Dry Eye

Study SEA-303

Incidence of Treatment-Emergent Adverse Events During 6-Month Seasonale™ Run-In - All Treated Patients (Safety)

Infections and Infestations: Bronchitis, Ear Infection, Fungal Infection, Influenza, Pharyngitis Streptococcal, Urinary Tract Infection, Vaginitis Bacterial, Vaginosis Fungal

Nervous System Disorders: Dizziness (Excl. Vertigo), Headache Aggravated, Migraine, Sinus Headache

Gastrointestinal Disorders: Abdominal Distension, Abdominal Pain, Diarrhoea, Dyspepsia, Pharyngolaryngeal Pain, Toothache, Vomiting

Musculoskeletal and Connective Tissue Disorders: Arthralgia, Muscle Cramps, Myalgia, Neck Pain, Pain In Limb

Reproductive System and Breast Disorders: Breast Tenderness, Menorrhagia

General Disorders and Administration Site Conditions: Fatigue, Pain, Pyrexia

Skin and Subcutaneous Tissue Disorders: Acne, Rash

Psychiatric Disorders: Anxiety, Depression, Insomnia, Irritability, Mood Swings

Injury, Poisoning and Procedural Complications: Muscle Strain, Post Procedural Pain

Respiratory, Thoracic and Mediastinal Disorders: Cough, Nasal Congestion, Sinus Congestion

Ear and Labyrinth Disorders: Ear Pain

Study SEA-303

Incidence of Treatment-Emergent Adverse Events During 9-Month Double Blind Period - All Treated Patients (Safety)

Infections and Infestations: Bladder Infection, Bronchitis, Ear Infection, Fungal Infection, Gastroenteritis Viral, Influenza, Pharyngitis, Pharyngitis Streptococcal, Vaginitis Bacterial, Vaginitis Fungal

Nervous System Disorders: Dizziness (Excl. Vertigo), Headache Aggravated, Migraine, Sinus Headache,

Musculoskeletal and Connective Tissue Disorders: Arthralgia, Muscle Cramps, Myalgia, Neck Pain, Pain In Limb,

Reproductive System and Breast Disorders: Intermenstrual Bleeding, Menorrhagia

Gastrointestinal Disorders: Abdominal Distension, Abdominal Pain, Abdominal Pain Upper, Constipation, Diarrhoea, Dyspepsia, Nausea, Pharyngolaryngeal Pain, Toothache, Vomiting

Respiratory, Thoracic and Mediastinal Disorders: Cough, Nasal Congestion, Sinus Congestion, Sinus Pain

Psychiatric Disorders: Anxiety, Depression, Insomnia, Mood Swings, Stress Symptoms

Injury, Poisoning and Procedural Complications: Back Injury, Concussion, Joint Sprain, Muscle Strain, Post Procedural Pain

General Disorders and Administration Site Conditions: Chest Pain, Influenza Like Illness, Pain, Pyrexia

Skin and Subcutaneous Tissue Disorders: Acne

Immune System Disorders: Hypersensitivity

Investigations: Weight Increased

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

Study SEA-301

Infections and Infestations: Tonsillitis, Tooth Abscess, Cervicitis, Gastroenteritis Viral, Cystitis, Gastroenteritis, Herpes Simplex, Herpes Viral Infection, Herpes Zoster, Lice Infestation, Lower Respiratory Tract Infection, Meningitis Viral, Pneumonia, Staphylococcal Infection, Tooth Infection, Upper Respiratory Tract Infection Viral, Bacterial Infection, Eye Infection, Furuncle (Excl Genital), Genital Warts, Gingival Abscess, Kidney Infection, Laryngitis, Localised Infection, Lyme Disease, Malaria, Nail Fungal Infection, Oral Candidiasis, Otitis Media, Pertussis, Respiratory Tract Infection, Sinusitis Acute, Skin Bacterial Infection, Stye, Upper Respiratory Tract Infection, Vaginal Infection, Vaginitis, Viral Infection, Vulvitis, Wound Infection

Gastrointestinal Disorders: Flatulence, Gastro-Oesophageal Reflux Disease, Abdominal Pain Lower, Gastric Ulcer, Tooth Disorder, Abdominal Discomfort, Colitis, Colon Spastic, Constipation Aggravated, Dry Mouth, Gastrointestinal Upset, Hemorrhoidal Bleeding, Hiatus Hernia, Inguinal Hernia, Irritable Bowel Syndrome, Oral Pain, Rectal Haemorrhage, Salivary Gland Calculus

Nervous System: Tension Headaches, Hypoaesthesia, Headache Aggravated, Migraine Aggravated, Cluster Headaches, Disturbance In Attention, Facial Palsy, Paraesthesia, Sciatica, Syncope, Vasovagal Attack

Musculoskeletal and Connective Tissue Disorders: Bursitis, Joint Swelling, Arthritis, Bone Disorder, Plantar Fasciitis, Bone Spur, Intervertebral Disc Herniation, Musculoskeletal Chest Pain, Neck Stiffness, Rotator Cuff Syndrome, Swelling, Temporomandibular Joint Disorder

Reproductive System and Breast Disorders: Breast Enlargement, Dyspareunia, Premenstrual Syndrome, Oligomenorrhoea, Pelvic Pain, Uterine Cervix Ulcer, Vaginal Discharge, Vulvovaginal Dryness, Breast Discharge, Breast Fibrosis, Cervical Cyst, Genital Rash, Ovarian Cyst, Ovarian Pain, Post-Coital Bleeding, Uterine Cervical Disorder, Uterine Cyst , Vaginal Irritation, Vaginal Odour, Vulval Disorder

Skin and Subcutaneous Tissue Disorders: Genital Pruritus Female, Night Sweats, Pruritus, Contusion, Dermatitis Atopic, Skin Cysts, Urticaria, Alopecia, Dermatitis Contact, Eczema, Erythema, Onychoclasia, Rash Papular, Skin Disorder, Skin Lesion, Skin Ulcer, Solar Urticaria, Sweating Increased

General Disorders and Administration Site Conditions: Facial Pain, Analgesic Effect, Fatigue Aggravated, Feeling Hot, Groin Pain, Injection Site Pain, Limb Discomfort, Oedema Lower Limb, Thirst

Respiratory, Thoracic and Mediastinal Disorder: Rhinitis, Upper Respiratory Tract Congestion, Asthma Aggravated, Nasal Sinus Drainage, Pulmonary Congestion, Rhinitis Allergic, Sinus Pain, Chest Wall Pain, Dyspnoea, Postnasal Drip, Rhinitis Atrophic, Rhinitis Seasonal, Sinus Disorder

Psychiatric Disorders: Anxiety, Irritability, Mood Alteration, Attention Deficit/Hyperactivity Disorder, Bipolar I Disorder, Emotional Disturbance, Loss Of Libido, Nervousness, Obsessive-Compulsive Disorder, Panic Attack, Sleep Disorder, Stammering

Injury, Poisoning and Procedural Complications: Arthropod Bite, Joint Sprain, Back Injury, Limb Injury, Animal Bite, Bite, Burns, Burns Second Degree, Caustic Injury, Concussion, Ear Canal Abrasion, Facial Bones Fracture, Foot Fracture, Gun Shot Wound, Hand Fracture, Laceration, Ligament Injury, Ligament Sprain, Nerve Injury, Post-Traumatic Wound, Infection, Sunburn, Whiplash Injury

Investigations: Smear Cervix Abnormal, Weight Decreased, Blood Cholesterol Increased, Blood Pressure Increased, Blood Urine Present, Colonoscopy, Heart Rate Increased, Helicobacter Pylori, Antibody Positive, Lipids Increased, Liver Function Tests Abnormal, White Blood Cell Count Increase

Immune System Disorders: Allergy Aggravated, Drug Hypersensitivity, Allergy to Insect Sting, Food Allergy

Ear and Labyrinth Disorders: Motion Sickness, Ear Congestion, Eustachian Tube Disorder, Labyrinthitis, Sensation of Block in Ear, Vertigo

Surgical and Medical Procedures: Tooth Extraction, Eye Operation, Breast Operation, Cervical Cautery, Cholecystectomy, Dental Operation, Knee Operation, Ligament Repair

Blood and Lymphatic System Disorders: ABO Haemolytic Disease of Newborn, Anaemia, Lymphadenopathy, Iron Deficiency Anaemia, Mononucleosis Syndrome

Vascular Disorders: Carotid Artery Occlusion, Hot Flushes, Hypertension

Eye Disorders: Conjunctivitis, Vision Blurred, Conjunctival Hyperaemia, Corneal Ulcer, Eye Irritation, Lacrimal Disorder, Pterygium, Retinal Detachment

Metabolism and Nutrition Disorders: Appetite Increased, Fluid Retention, Hunger

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Breast Lump, Basal Cell Carcinoma, Fibrocystic Breast Disease

Renal and Urinary Disorders: Loin Pain, Urinary Frequency, Urine Odour Foul

Cardiac Disorders: Palpitations, Palpitations Aggravated

Endocrine Disorders: Goitre

Hepatobiliary Disorders: Cholecystitis

Study SEA-301A

Infections and Infestations: Bacterial Infection, Bladder Infection, Carbuncle (Excl Genital), Dry Socket, Eye Infection, Folliculitis, Gingivitis Infection, Kidney Infection, Oral Infection, Pelvic Inflammatory Disease, Pharyngitis, Pyelonephritis, Respiratory Tract Infection, Stye, Tooth Abscess, Viral Infection, Vulvitis

Gastrointestinal Disorders: Abdominal Distension, Abdominal Pain Lower, Crohn's Disease, Gastrointestinal Upset, Gingivitis, Irritable Bowel Syndrome, Oral Pain, Tooth Impacted

Nervous System Disorders: Carpal Tunnel Syndrome, Headache Aggravated, Hypertonia, Migraine Aggravated, Sciatica, Sleep Apnoea Syndrome, Tension Headaches

Reproductive System and Breast Disorders: Amenorrhoea, Breast Pain, Cervical Dysplasia, Cervical Friability, Cervical Polyp, Ovarian Cyst, Vaginal Cyst, Vaginal Pain, Vulvovaginal Discomfort

Musculoskeletal and Connective Tissue Disorders: Back Disorder, Back Pain Aggravated, Fibromyalgia, Foot Deformity, Muscle Cramps, Myositis, Neck Stiffness, Tendonitis

Investigations: Arthroscopy, Aspartate Aminotransferase Increased, Cardiac Murmur, Urine Analysis Abnormal, White Blood Cell Count Increased

General Disorders and Administration Site Conditions: Axillary Pain, Chest Pain, Injection Site Pain, Oedema, Rigors

Skin and Subcutaneous Tissue Disorders: Acne Aggravated, Alopecia, Dermatitis Contact, Dermatitis, Erythema Nodosum, Genital Pruritus Female, Milia, Pruritus, Psoriasis, Rash Generalised, Rash Papular, Sebaceous Cyst, Skin Discolouration, Skin Lesion, Sweating Increased

Injury, Poisoning and Procedural Complications: Accident, Arthropod Sting, Heat Stroke, Joint Dislocation, Joint Sprain, Limb Injury, Muscle Injury, Neck Injury, Tendon Injury

Psychiatric Disorders: Anxiety Aggravated, Depression Aggravated, Emotional Disturbance, Insomnia Exacerbated, Mood Swings, Panic Attack

Respiratory, Thoracic and Mediastinal Disorders: Asthma Aggravated, Asthma, Dyspnoea, Epistaxis, Nasal Sinus Drainage, Postnasal Drip, Upper Respiratory Tract Congestion

Immune Systems Disorders: Drug Hypersensitivity, Food Allergy

Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps): Benign Breast Neoplasm, Benign Neoplasm, Breast Mass, Cyst, Hepatic Neoplasm, Vulval Cancer

Vascular Disorders: Hot Flashes

Cardiac Disorders: Palpitations

Ear and Labyrinth Disorders: Ear Pain, Motion Sickness, Tinnitus

Renal and Urinary Disorders: Haematuria, Polyuria, Urinary Frequency

Surgical and Medical Procedures: Carpal Tunnel Decompression, Ear Operation, Lump Excision, Oral Surgery, Scar Excision, Wisdom Teeth Removal

Hepatobiliary Disorders: Cholecystitis

Blood and Lymphatic System Disorders: Anaemia, Mononucleosis Syndrome

Congenital, Familial and Genetic Disorders: Dentofacial Anomaly

Endocrine Disorders: Hypothyroidism

Metabolism and Nutrition Disorders: Appetite Increased

Study SEA-303

Incidence of Treatment-Emergent Adverse Events During 6-Month Seasonale™ Run-In - All Treated Patients (Safety)

Infections and Infestations: Bacterial Infection, Bartholin's Abscess, Bladder Infection, Bronchitis Acute, Candidal Infection, Cellulitis, Chlamydial Infection, Cystitis, Endometritis, Eye Infection, Furuncle (Excl Genital), Gastroenteritis, Gastroenteritis Bacterial, Gastroenteritis Viral, Gingivitis Infection, Herpes Simplex, Herpes Zoster, Infection, Kidney Infection, Meningitis Viral, Nail Fungal Infection, Otitis Externa, Otitis Media, Papilloma Viral Infection, Pharyngitis, Pleurisy Viral, Pneumonia, Rash Pustular, Respiratory Tract Infection, Skin Infection, Stye, Tonsillitis, Tooth Abscess, Tooth Caries, Tooth Infection, Upper Respiratory Tract Infection, Upper Respiratory Tract Infection Viral, Vaginal Candidiasis, Vaginitis, Viral Infection

Nervous System Disorders: Amnesia, Carpal Tunnel Syndrome, Head Discomfort, Hypertonia, Hypoaesthesia, Migraine Aggravated, Multiple Sclerosis, Nerve Compression, Somnolence, Syncope, Tension Headaches

Gastrointestinal Disorders: Abdominal Discomfort, Abdominal Pain Lower, Abdominal Pain

Upper, Constipation, Flatulence, Food Poisoning, Gastric Ulcer, Gastric Ulcer Helicobacter, Gastritis, Gastro-Oesophageal Reflux Disease, Gingival Oedema, Gingival Recession, Haemorrhoids, Irritable Bowel Syndrome Aggravated, Lip Disorder, Mouth Ulceration, Oral Pain, Stomach Discomfort, Throat Irritation

Musculoskeletal and Connective Tissue Disorders: Arthritis, Back Pain Aggravated, Bunion, Bursitis, Costochondritis, Jaw Disorder, Muscle Atrophy, Muscle Spasms, Muscle Stiffness, Muscle Tightness, Myalgia Aggravated, Neck Stiffness, Nodule On Extremity, Pain In Jaw, Peripheral Swelling, Plantar Fasciitis, Swelling, Temporomandibular Joint Disorder, Tendonitis Exacerbated

Reproductive System and Breast Disorders: Amenorrhoea, Breast Discharge, Breast Enlargement, Breast Oedema, Breast Pain, Cervical Dysplasia, Dyspareunia, Hypomenorrhoea, Pelvic Pain, Premenstrual Syndrome, Post-Coital Bleeding, Uterine Haemorrhage, Vaginal Discharge, Vaginal Irritation, Vulvovaginal Disorder, Vulvovaginal Discomfort, Vulvovaginal Dryness

General Disorders and Administration Site Conditions: Axillary Pain, Chest Pain, Chest Pressure Sensation, Chest Tightness, Fall, Fatigue Aggravated, Inflammation, Influenza Like Illness, Injection Site Pain, Injection Site Reaction, Mucous Membrane Disorder, Oedema Lower Limb, Oedema, Oedema Peripheral, Pain Exacerbated, Ulcer

Skin and Subcutaneous Tissue Disorders: Acne Aggravated, Alopecia, Contusion, Dermatitis Contact, Dermatitis, Dry Skin, Eczema, Erythema Nodosum, Genital Pruritus Female, Ingrown Hair, Ingrowing Nail, Night Sweats, Photosensitivity Allergic Reaction, Pigmentation Disorder, Pruritus, Pruritus Breast, Psoriasis, Rash Erythematous, Rosacea, Seborrhoea, Skin Irritation, Skin Lesion, Sweat Gland Disorder, Urticaria

Psychiatric Disorders: Alcoholic Hangover, Anxiety Disorder, Bipolar Disorder, Depression Aggravated, Emotional Disturbance, Libido Decreased, Libido Increased, Mood Alteration, Panic Attack, Sleep Disorder, Stress Symptoms

Injury, Poisoning and Procedural Complications: Abrasion, Animal Bite, Ankle Fracture, Arthropod Bite, Arthropod Sting, Back Injury, Bite, Foot Fracture, Headache Postoperative, Heat Stroke, Injury, Joint Sprain, Laceration, Ligament Injury, Limb Injury, Mouth Injury, Muscle Injury, Nausea Postoperative, Neck Injury, Postoperative Wound Complication, Post Vaccination Syndrome, Road Traffic Accident, Sunburn, Tooth Injury

Respiratory, Thoracic and Mediastinal Disorders: Asthma Exercise Induced, Asthma, Dyspnoea, Epistaxis, Laryngeal Oedema, Lung Disorder, Nasal Polyps, Respiratory Disorder, Rhinitis Allergic, Rhinorrhoea, Sinus Pain

Investigations: Antinuclear Antibody, Blood Cholesterol Increased, Blood in Stool, Blood Pressure Increased, Blood Triglycerides Increased, Heart Rate Increased, Liver Function Tests Abnormal, Smear Cervix Abnormal, Weight Increased

Ear and Labyrinth Disorders: Motion Sickness

Surgical and Medical Procedures: Breast Cosmetic Surgery, Dental Operation, Endodontic Procedure, Hernia Repair, Oral Surgery, Septoplasty, Tooth Extraction, Tooth Repair

Immune System Disorders: Allergy Aggravated, Drug Hypersensitivity, Hypersensitivity, Seasonal Allergy

Renal and Urinary Disorders: Bladder Discomfort, Bladder Irritability, Bladder Pain, Dysuria, Haematuria, Urinary Frequency, Urine Odour Foul

Vascular Disorders: Hot Flashes, Hypertension, Pulmonary Embolism, Varicose Veins

Eye Disorders: Conjunctivitis, Conjunctivitis Hyperaemia, Dry Eye, Eye Disorder, Eye Irritation, Eye Swelling, Vision Blurred

Metabolism and Nutrition Disorders: Appetite Increased, Dehydration, Hunger, Hyponatraemia Ketoacidosis

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Cervical Carcinoma Stage III, Cyst, Fibromatosis, Papilloma, Uterine Fibroids

Blood and Lymphatic System Disorders: Lymphadenopathy, Mononucleosis Syndrome

Cardiac Disorders: Angina Pectoris, Palpitations, Tachycardia

Endocrine Disorders: Hyperthyroidism Aggravated, Thyroiditis

Hepatobiliary Disorders: Fatty Liver Alcoholic

Pregnancy, Puerperium and Perinatal Conditions: Ectopic Pregnancy

Study SEA-303

Incidence of Treatment-Emergent Adverse Events During 9-Month Double Blind Period - All Treated Patients (Safety)

Infections and Infestations: Cellulitis, Eye Infection, Gastroenteritis Salmonella, Herpes Simplex, Oral Candidiasis, Pharyngitis Viral, Pneumonia, Pyelonephritis, Respiratory Tract Infection, Skin Infection, Tonsillitis, Trichomoniasis

Nervous System Disorders: Carpal Tunnel Syndrome, Hypoaesthesia, Multiple Sclerosis Aggravated, Nerve Compression, Tension Headaches

Musculoskeletal and Connective Tissue Disorders: Intervertebral Disc Herniation, Muscle Spasms, Neck Stiffness, Pain In Jaw, Peripheral Swelling, Shoulder Blade Pain, Tendonitis

Reproductive System and Breast Disorders: Breast Discharge, Breast Pain, Breast Tenderness, Endometrial Atrophy, Endometriosis, Hypomenorrhoea, Ovarian Pain, Pelvic Pain, Premenstrual Syndrome, Vaginal Irritation

Gastrointestinal Disorders: Food Poisoning, Gastric Ulcer, Gastritis, Gastro-Oesophageal Reflux Disease, Irritable Bowel Syndrome, Rectal Haemorrhage

Respiratory, Thoracic and Mediastinal Disorders: Asthma Aggravated, Asthma, Pulmonary Congestion, Rhinitis Allergic, Rhinorrhoea, Sinus Disorder

Psychiatric Disorders: Alcoholic Hangover, Anxiety Aggravated, Confusion, Depression Aggravated, Irritability, Libido Decreased, Mood Alteration, Panic Disorder

Injury, Poisoning and Procedural Complications: Animal Bite, Arthropod Bite, Arthropod Sting, Corneal Abrasion, Foot Fracture, Laceration, Limb Injury, Nausea Postoperative, Road Traffic Accident, Sunburn

General Disorders and Administration Site Conditions: Chest Tightness, Fatigue, Fatigue Aggravated, Inflammation Localised

Skin and Subcutaneous Tissue Disorders: Acne Aggravated, Contusion, Dermatitis, Eczema, Hair Growth Abnormal, Pruritus, Rash, Urticaria

Immune System Disorders: Allergy Aggravated, Drug Hypersensitivity, Seasonal Allergy

Investigations: Blood Cholesterol Increased, Skin Test Positive, Smear Cervix Abnormal, X-Ray Chest Abnormal

Ear and Labyrinth Disorders: Ear Disorder, Ear Pain

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Cyst, Fibrocystic Breast Disease, Skin Papilloma

Surgical and Medical Procedures: Breast Cosmetic Surgery, Eye Operation, Meniscectomy (Knee), Rotator Cuff Repair, Tooth Extraction, Wisdom Teeth Removal

Metabolism and Nutrition Disorders: Dehydration, Diabetes Mellitus, Fluid Retention, Hypercholesterolaemia

Vascular Disorders: Hot Flushes

Blood and Lymphatic System Disorders: Anaemia, Lymphadenopathy, Mononucleosis Syndrome

Renal and Urinary Disorders: Bladder Pain, Calculus Renal, Cystitis Interstitial

Cardiac Disorders: Palpitations

Hepatobiliary Disorders: Cholecystitis

Abnormal Haematologic and Clinical Chemistry Findings

In study SEA-301 (1-year trial), for triglycerides, the percentage of patients on Seasonale™ going from normal to high was 6.2% compared to that of 1.9% for patients on control (median increase of 136 (43.6%) for Seasonale™ patients compared to 206 (63.1%) for control patients). For LDL, 17.9% of patients on Seasonale™ shifted from normal to high values, compared to that of 14.6% for patients on control (median increase in LDL of 40 (27.2%) for Seasonale™ patients compared to an increase of 37 (22.8%) for control patients). The percentage of Seasonale™ patients who went from normal to high for total cholesterol was 22.1% compared to that of 23.4% for patients on control (median increase of 37 (17.2%) for Seasonale™ patients compared to 29 (13.3%) for control patients).

In study SEA-301A (2-year extension trial of SEA-301 with no control), 5 subjects had increase in cholesterol/LDL or triglycerides above the normal ranges among 173 tested Seasonale® subjects. Seven subjects had increase in liver enzymes above the normal range excluding the subject with large common bile duct stone.

The coagulation profile was not studied with this Seasonale™ regimen.

Post-Market Adverse Drug Reactions

The following other serious and unexpected adverse events have been reported in users of Seasonale™ 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 Seasonale™ has been established.

Blood and Lymphatic System Disorders: Anaemia

Cardiac Disorders: Cardiac Arrest, Supraventricular Tachycardia

Congenital, Familial and Genetic Disorders: Arnold-Chiari Malformation, Bicuspid Aortic Valve, Brain Malformation, Patent Ductus Arteriosus, Spina Bifida, Talipes

Endocrine Disorders: Hyperprolactinaemia

Gastrointestinal Disorders: Colitis Ischemic

Musculoskeletal and Connective Tissue Disorders: Acquired Macrocephaly, Muscle Mass

Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps): Renal Neoplasm

Nervous System Disorders: Brain Damage, Convulsion, Epilepsy, Hydrocephalus, Hypotonia

Pregnancy, Puerperium and Perinatal Conditions: Abortion Spontaneous, Intra-Uterine Death

Psychiatric Disorders: Suicidal Ideation

Renal and Urinary Disorders: Neurogenic Bladder

Reproductive System and Breast Disorders: Cervical Polyp, Dysfunctional Uterine Bleeding, Pelvic Pain, Vaginal Haemorrhage

Skin and Subcutaneous Tissue Disorders: Acute Febrile Neutrophilic Dermatitis, Leukocytoclastic Vasculitis, Skin Lesion

In the post-market period, there have been cases of myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism reported with the use of Seasonale™.

DRUG INTERACTIONS

Overview

The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent (see Tables 6 and 7). 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

Refer to *Oral Contraceptives 1994* (Chapter 8), Health Canada, for possible drug interactions with hormonal contraceptives.

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	Carbamazepine Ethosuximide Phenobarbital Phenytoin Primidone Lamotrigine	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.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifampin	Increased metabolism of progestin. Suspected acceleration of estrogen metabolism.	Use another method.

Table 6: Drugs Which May Decrease the Efficacy of Oral Contraceptives			
Class of Compound	Drug	Proposed Mechanism	Suggested Management
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides 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.	
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.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral hydrate Glutethimide 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.
Antacids		Decreased intestinal absorption of progestin	Dose two hours apart.
Other Drugs	Phenylbutazone Antihistamines Analgesics Antimigraine preparations Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	

Table 7: 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.

Table 7: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	Drug	Modification of Drug Action	Suggested Management
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	Combination oral contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine likely due to induction of lamotrigine glucuronidation. Decreased lamotrigine levels may lead to breakthrough seizures.	Use another method.
Antidiabetic drugs	Oral hypoglycaemic 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.

Table 7: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	Drug	Modification of Drug Action	Suggested Management
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.
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 Lorazepam Oxazepam 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.

Table 7: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	Drug	Modification of Drug Action	Suggested Management
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 have been studied with co-administration of combination oral contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestogen 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.

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

Laboratory Tests

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

The following laboratory tests are modified:

A. Liver Function Tests

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

B. Coagulation Tests

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

C. Thyroid Function Tests

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

D. Lipoproteins

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

E. 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.

F. 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 cardiovascular side effects from oral contraceptive use. This risk increases with age and heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

Several health advantages other than contraception 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 white (inactive) 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. Seasonale™ 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 Seasonale™ is one pink (active) tablet taken daily for 84 consecutive days followed by 7 days of white (inert) tablets. To achieve maximum contraceptive effectiveness,

Seasonale™ 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 Seasonale™ on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first tablet (pink) is taken that day. One pink tablet should be taken daily for 84 consecutive days, followed by 7 days on which a white (inert) tablet is taken. Withdrawal bleeding should occur during the 7 days following discontinuation of pink active tablets. During the first cycle, contraceptive reliance should not be placed on Seasonale™ until a pink (active) tablet has 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 her next and all subsequent 91-day course of tablets without interruption on the same day of the week (Sunday) on which she began her first course, following the same schedule: 84 days on which pink tablets are taken followed by 7 days on which white tablets are taken. 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 a pink tablet 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, Seasonale™ may be initiated no earlier than Day 28 of postpartum for contraception due to the increased risk for 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. Seasonale™ may be initiated immediately after a first-trimester abortion; if the patient starts Seasonale™ 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.

Missed Dose

Detailed patient instructions regarding missed pills are presented in the “HOW TO TAKE SEASONALE™”, Missed Dose section of Part III in the product monograph. If a patient misses one pink tablet, she should take it as soon as possible, meaning she can take two tablets in one

day. If a patient misses two pink 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 pink tablet per day. Any time the patient misses two or more pink tablets, she should also use another method of non-hormonal back-up contraception until she has taken a pink tablet daily for seven consecutive days. If the patient misses one or more white tablets, she is still protected against pregnancy provided she begins taking pink tablets again on the appropriate day. The possibility of ovulation increases with each successive day that scheduled pink tablets are missed. The risk of pregnancy increases with each active (pink) tablet missed.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, and withdrawal bleeding may occur in females. There is no antidote and further treatment should be symptomatic.

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: No specific investigation of the absolute bioavailability of Seasonale™ 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. 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 43%.

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

The mean plasma pharmacokinetic parameters of Seasonale™ following a single dose of two tablets in normal healthy women under fasting conditions are reported in Table 8.

Table 8: Summary of Mean ± SD Pharmacokinetic Parameters Following a Single Dose Administration of Seasonale™ in Healthy Female Subjects Under Fasting Conditions

Analyte	C _{max} (mean ± SD)	t _½ (mean ± SD)	AUC ₀₋₄ (mean ± SD)	T _{max}
Levonorgestrel	5.6 ± 1.5 ng/mL	29.8 ± 8.3 hours	60.8 ± 25.6 ng*hr/mL	1.4 ± 0.3 hrs
Ethinyl Estradiol	145 ± 45 pg/mL	15.4 ± 3.2 hours	1307 ± 361 pg*hr/mL	1.6 ± 0.5 hrs

Distribution: The apparent volume of distribution of levonorgestrel and ethinyl estradiol are reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively. Levonorgestrel is about 97.5-99% protein-bound, principally to the sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin. 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. Following repeated daily dosing of combination levonorgestrel and ethinyl estradiol oral contraceptives, levonorgestrel plasma concentrations accumulate more than when 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. 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. Levonorgestrel and its Phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users.

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

Excretion: About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates. The terminal elimination half-life for levonorgestrel after a single dose of Seasonale™ was found to be about 30 hours.

Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates and it undergoes enterohepatic recirculation. The terminal elimination half-life of ethinyl estradiol

after a single dose of Seasonale™ was found to be about 15 hours.

Special Populations and Conditions

Pediatrics: The safety and efficacy of Seasonale™ has not been established in women under the age of 18 years.

Use of this product before menarche is not indicated.

Geriatrics: Seasonale™ is not indicated for use in post-menopausal women.

Race: No formal studies on the effect of race on the pharmacokinetics of Seasonale™ have been conducted.

Hepatic Insufficiency: No formal studies have been conducted to evaluate the effect of hepatic disease on the pharmacokinetics of Seasonale™. 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 Seasonale™.

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

Seasonale™ (levonorgestrel and ethinyl estradiol, USP) tablets are available in Extended-Cycle Tablet Dispensers. 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 pink tablets and the third blister card contains 28 active pink tablets and 7 inert white tablets for a total of 35 tablets. Altogether, the 3 blister cards hold 91 tablets consisting of 84 active pink tablets (each containing 0.15 mg of

levonorgestrel and 0.03 mg ethinyl estradiol) and 7 inert white tablets. The compact is then packaged in a foil pouch with a desiccant. Three foil pouches are packaged in each carton. The active pink tablets are round, film-coated, biconvex, unscored tablets with a debossed **S** on one side and **62** on the other side. The inert tablets are white, round, biconvex, unscored tablets debossed with **S** on one side and **197** on the other side.

Each pink active tablet contains the following inactive ingredients: anhydrous lactose, FD&C Blue No. 1, FD&C Red No. 40, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide. Each white inert tablet contains the following inactive ingredients: anhydrous lactose, hydroxypropyl methylcellulose, magnesium stearate and microcrystalline cellulose.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

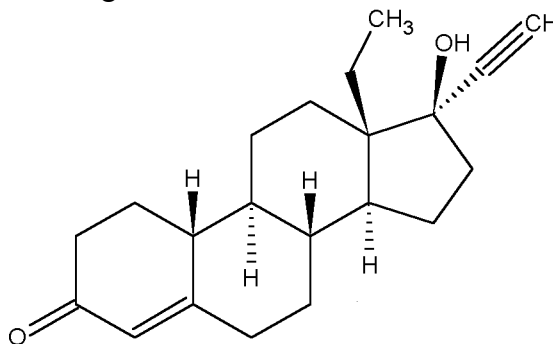
Proper name: Levonorgestrel
Ethinyl Estradiol

Chemical name: Levonorgestrel: 13 β -ethyl-17 β -hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one
Ethinyl Estradiol: 17 α -Ethinyl-1,3,5(10)-estratriene-3,17- β -diol

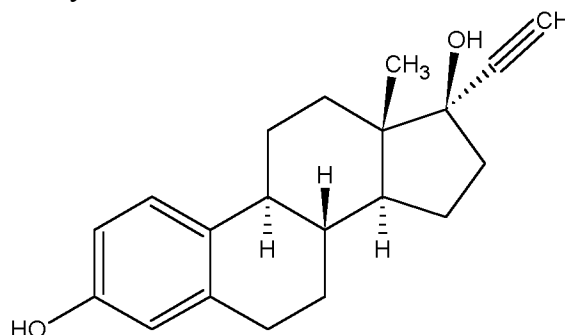
Molecular formula and molecular mass: Levonorgestrel: C₂₁H₂₈O₂, 312.45
Ethinyl Estradiol: C₂₀H₂₄O₂, 296.40

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:	234-240 °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

Study results

In a 1-year controlled clinical trial, 4 pregnancies occurred in women 18-35 years of age during 809 completed 91-day cycles of Seasonale™ during which no backup contraception was utilized. This represents an overall use-efficacy Pregnancy rate of 1.98 per 100 women-years of use.

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

Table 9 presents summary statistics for vital signs at baseline for studies SEA-301, SEA-301A and SEA-303. The treatment groups were well balanced both within and across studies with respect to systolic and diastolic blood pressure, heart rate and temperature.

	SEA-301				SEA-301A*		SEA-303		
	Seasonale (N=456)	Nordette (N=226)	Seasonale Lo (N=463)	Levlite (N=231)	Seasonale (N=189)	Seasonale Lo (N=161)	All Patients** (N=1070)	Seasonale Randomized (N=229)	Seasonale Lo Randomized (N=465)
Age (yrs)									
N	456	226	463	231	189	161	1070	229	465
Mean (SD)	27.8 (5.89)	27.83 (5.93)	27.75 (5.89)	27.36 (5.31)	30.5 (6.09)	30.18 (5.88)	29.1 (7.06)	30.2 (7.16)	29.4 (7.18)
Median	27.5	27.5	27	26	30.38	29.69	28.0	29.0	28.2
(Min, Max)	(18,40)	(19, 40)	(18, 40)	(18, 39)	(20.07, 42.08)	(19.58, 42.27)	(18.1, 45.7)	(18.1, 45.7)	(18.2, 45.6)

Table 9: Demographic Information of All Treated Patients in Studies SEA-301, SEA-301A and SEA-303

Weight (lbs)									
N	452	226	461	231	189	161	1069	229	465
Mean (SD)	156.39 (38.04)	156.58 (38.65)	156.32 (39.94)	153.97 (40.25)	159.39 (38.25)	156.06 (40.20)	153.6 (37.17)	153.9 (36.02)	153.6 (37.81)
Median	148	146.15	146.5	145	150	150	146.0	146.0	146.0
(Min, Max)	(84, 304)	(87, 296)	(92, 335)	(96, 350)	(105, 286)	(86, 357)	(92.0, 363.0)	(101.0, 363.0)	(92.0, 332.0)
BMI (kg/m²)									
N	452	226	461	231	189	161	1068	229	464
Mean (SD)	26.16 (5.90)	26.31 (6.25)	26.08 (6.25)	25.95 (6.41)	26.76 (6.39)	26.20 (6.56)	25.9 (6.12)	26.1 (6.21)	25.9 (6.15)
Median	24.55	24.32	24.74	24.43	24.68	25.23	24.5	24.6	24.6
(Min, Max)	(14.47, 45.29)	(15.95, 47.53)	(15.82, 61.40)	(16.23, 58.36)	(18.75, 49.19)	(14.79, 62.32)	(15.7, 62.4)	(17.0, 62.4)	(15.7, 51.3)
Race									
Afr American	50 (10.96%)	29 (12.83%)	53 (11.45%)	32 (13.85%)	19 (10.05%)	24 (14.91%)	89 (8.3%)	15 (6.6%)	38 (8.2%)
Asian	10 (2.19%)	2 (0.88%)	5 (1.08%)	6 (2.60%)	1 (0.53%)	3 (1.86%)	17 (1.5%)	5 (2.2%)	7 (1.5%)
Caucasian	351 (76.97%)	169 (74.78%)	361 (77.97%)	171 (74.03%)	152 (80.42%)	125 (77.64%)	877 (82.0%)	200 (87.3%)	388 (83.4%)
Hispanic	32 (7.02%)	18 (7.96%)	36 (7.78%)	17 (7.36%)	15 (7.94%)	7 (4.35%)	70 (6.5%)	6 (2.6%)	27 (5.8%)
Other / Unknown	13 (2.85%)	8 (3.54%)	8 (1.73%)	5 (2.16%)	2 (1.06%)	2 (1.24%)	17 (1.6%)	3 (1.3%)	5 (1.1%)
Smoking Status									
Unknown	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.43%)	N/A	N/A	N/A	N/A	N/A
No (Non-Smoker)	373 (81.80%)	191 (84.51%)	366 (79.05%)	188 (81.39%)	170 (89.95%)	145 (90.06%)	699 (65.3%)	153 (66.8%)	323 (69.5%)
Yes (Current Smoker)	83 (18.20%)	35 (15.49%)	97 (20.95%)	42 (18.18%)	19 (10.05%)	16 (9.94%)	205 (19.2%)	38 (16.6%)	75 (16.1%)
Oral Contraceptive Use History									
Unknown	1 (0.22%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0	0	17 (1.6%)	3 (1.3%)	5 (1.1%)
Continuous	288 (63.16%)	142 (62.83%)	277 (59.83%)	139 (60.17%)	189 (100.0%)	161 (100.0%)	629 (58.8%)	151 (65.9%)	310 (66.7%)
Fresh Start	35 (7.68%)	14 (6.19%)	36 (7.78%)	21 (9.09%)	0	0	138 (12.9%)	20 (8.7%)	46 (9.9%)
Prior User	132 (28.95%)	70 (30.97%)	150 (32.40%)	7 (3.074%)	0	0	286 (26.7%)	55 (24.0%)	104 (22.4%)
<p>* Of the 161 patients receiving Seasonale Lo in SEA-301A, 96 previously received 1 year of Seasonale Lo in SEA-301 while 48 received Levlite, 9 received Seasonale and 8 received Nordette. Of the 189 patients receiving Seasonale in SEA-301A, 103 previously received 1 year of Seasonale in SEA-301 while 58 received Nordette, 16 received Levlite and 12 received Seasonale Lo.</p> <p>** All patients (N=1070) entered a 6-month Seasonale run-in period. Characteristics of those discontinuing during the run-in period can be found in the SEA-303 study report. Those completing the run-in period were randomized 1:2 to Seasonale (N=229) or Seasonale Lo (N=465).</p>									

Comparative Bioavailability Studies

Bioequivalence Study A, was a randomized, single-dose, crossover study in normal healthy women under fasting conditions, which compared Seasonale™ (0.15 mg levonorgestrel/0.03 mg

ethinyl estradiol) film-coated immediate-release tablet formulation to the 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol film-coated immediate-release tablets.

Thirty healthy (medical history, ECG, physical exam and laboratory tests), non-pregnant, Caucasian female subjects, 18-35 years of age (mean age 27 years old) participated.

Study A demonstrated that Seasonale™ (0.15 mg levonorgestrel/0.03 mg ethinyl estradiol film-coated) immediate-release tablet formulation was bioequivalent to the 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol film coated immediate-release tablet formulation.

<p>Levonorgestrel (2 X 0.15 mg) From measured data Geometric Mean Arithmetic Mean (CV %)</p>

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _{0-72h} (pg·h/mL)	69714.04 (54.26)	65301.71 (49.21)	106.04	99.72-115.28
AUC _I (units)	86366.33 (68.38)	81965.86 (58.98)	103.11	96.58-110.08
C _{MAX} (pg/mL)	6347.68 (35.77)	5255.60 (34.98)	121.00	113.48-129.03
T _{MAX} (h)	1.32 (1.80)	2.14 (0.79)		
T _½ (h)	28.62 (37.06)	30.53 (11.82)		

* Seasonale™

† 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol film coated immediate-release tablet

<p>Ethinyl Estradiol (2 X 0.03 mg) From measured data Geometric Mean Arithmetic Mean (CV %)</p>
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Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC _T (pg·h/mL)	1434.64 (34.31)	1434.30 (30.70)	98.96	94.49-103.65
AUC _I (units)	1650.33 (36.30)	1643.44 (31.53)	95.24	95.24-103.71
C _{MAX} (pg/mL)	147.13 (34.37)	140.59 (26.40)	97.05	97.05-107.88

Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
T _{MAX} (h)	1.74 (24.11)	1.53 (0.36)		
T _½ (h)	17.22 (48.41)	17.12 (5.86)		

* Seasonale™

† 0.15 mg levonorgestrel/0.03 mg ethinyl estradiol film coated immediate-release tablet

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 gonadotropins 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 rate; 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 17 β -estradiol in patients taking 150 μ g *d*-norgestrel (as the *dl*-racemate) plus 30 μ g ethinyl estradiol indicated reduction or abolition of the mid-cycle ovulatory peak and post-ovulatory levels commonly associated with these hormones and gonadotropins respectively.

Endometrial biopsies taken during the course of therapy with 250 μ g *d*-norgestrel (as the *dl*-racemate) plus 50 μ g 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 μ g *d*-norgestrel (as the *dl*-racemate) plus 50 μ g ethinyl estradiol, and 37.5 μ g *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 μ g *d*-norgestrel (as the *dl*-racemate) plus 30 μ g 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 ¹⁴C-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 ¹⁴C-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 are more susceptible to show mammary tumours as they have 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.

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PART III: CONSUMER INFORMATION

**Seasonale®
(levonorgestrel and ethinyl estradiol USP)**

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

ABOUT THIS MEDICATION

What the medication is used for:

Seasonale® is indicated for the prevention of pregnancy.

Seasonale™ 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 Seasonale™

When you take Seasonale™, which has a 91-day treatment cycle, you should expect to have 4 menstrual periods per year (bleeding when you are taking the 7 white pills). However, you should expect to have more bleeding or spotting between your menstrual periods than if you were taking an oral contraceptive with a 28-day treatment cycle. During the first Seasonale™ treatment cycle, about 1 in 3 women may have 20 or more days of unplanned bleeding or spotting (bleeding when you are taking pink pills). This bleeding or spotting tends to decrease during later cycles. Do not stop Seasonale™ because of the bleeding. If the spotting continues for more than 7 consecutive 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 Seasonale™ 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 Seasonale™ (see **What the medicinal ingredients are** and **What the non medicinal ingredients are**)

What the medicinal ingredients are:

Levonorgestrel and ethinyl estradiol

What the important non medicinal ingredients are:

Each active pink tablet contains the following non medicinal ingredients: anhydrous lactose, FD&C Blue No. 1, FD&C Red No. 40, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80 and titanium dioxide.

Each inert white tablet contains the following non medicinal ingredients: anhydrous lactose, hydroxypropyl methylcellulose, magnesium stearate and microcrystalline cellulose.

What dosage forms it comes in:

Tablets. Seasonale™ is used with a 91-day schedule (84

days of pink tablets followed by 7 days of white tablets).

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 diseases (STDs), including HIV/AIDS.

For protection against STDs, it is advisable to use latex condoms IN COMBINATION WITH birth control pills.

Use of Seasonale™ 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 hormonal exposure per year). While this added exposure may pose an additional risk of thrombotic and thromboembolic diseases, studies to date with Seasonale™ have not suggested, nor can exclude, this additional risk.

Seasonale™ Oral Contraceptive

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

BEFORE you use Seasonale™ 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

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 Seasonale™.

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 Seasonale™ four weeks before surgery and not using Seasonale™ for a time period after surgery or during bed

Seasonale™ 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 Seasonale™ 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 Seasonale™ outweigh the risks, you should be aware of the following:

THE RISKS OF USING SEASONALE™

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 uses of birth control pills have also been linked with the growth of liver tumors. Such tumors 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 Seasonale™ after childbirth, miscarriage, or therapeutic abortion.

8. Pregnancy after stopping Seasonale™

You will have a menstrual period when you stop using Seasonale™. 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 Seasonale™. 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 Seasonale™ include:

- drugs used for the treatment of epilepsy (e.g. primidone, phenytoin, barbiturates, carbamazepine, lamotrigine, oxcarbazepine, topiramate, felbamate); tuberculosis (e.g. rifampin, rifabutin) and HIV infections (e.g. ritonavir)
- 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 Seasonale™.)

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

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

PROPER USE OF THIS MEDICATION

- BE SURE TO READ THESE DIRECTIONS:
 - Before you start taking your pills.
 - Anytime you are not sure what to do.
- THE RIGHT WAY TO TAKE SEASONALE™ 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.
- 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.
- MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING DURING THE FIRST FEW MONTHS OF TAKING SEASONALE™. **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.
- 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.
- IF YOU HAVE VOMITING OR DIARRHEA, or IF YOU TAKE SOME MEDICINES, including some antibiotics and the herbal supplement St. John's Wort, Seasonale™ may not work as well. Use a back-up method (such as condoms or spermicide) until you check with your healthcare professional.
- IF YOU HAVE TROUBLE REMEMBERING TO TAKE SEASONALE™, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.
- IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET, call your healthcare professional.

BEFORE YOU START TAKING SEASONALE™

- 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 pink pills (active pills with hormones) and 7 white pills (inactive pills without hormone). Trays 1 and 2 each contain 28 pink pills (4 rows of 7 pills). Tray 3 contains 35 pills consisting of 28 pink pills (4 rows of 7 pills) and 7 white 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).
- BE SURE YOU HAVE READY AT ALL TIMES ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicide), to use as a back-up in case you miss pills.

WHEN TO START SEASONALE™

- Take the first "active" pink pill on the *Sunday after your period starts*, even if you are still bleeding. If your period begins on Sunday, start the first pink pill that same day.
- 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 pink pill until the next Sunday (first 7 days).*

HOW TO TAKE SEASONALE™

- 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 white pill, start taking the first pink pill from a new Extended-Cycle Tablet Dispenser **the very next day** regardless of when your period started. This should be on a Sunday.

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

Usual dose:

One pink tablet should be taken daily for 84 consecutive days, followed by 7 days of white 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 an overdose, contact your healthcare professional or pharmacist.

Missed Dose:

If you **MISS one** pink “active” 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** pink “active” 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** pink “active” 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 white pills, call your healthcare professional because you may be pregnant.**

If you **MISS ANY** of the 7 white inactive 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 Seasonale™.

Most side effects when using the birth control pill are not serious. The most common side effects are nausea, vomiting, bleeding or spotting between menstrual periods, weight gain, breast tenderness and difficulty wearing contact lens. Some of these side effects, especially nausea and vomiting may subside within the first 3 months of use.

Other side effects can occur such as fluid retention, darkening of the skin (particularly on the face), headache, nervousness, depression, dizziness, loss of scalp hair, vaginal infections and allergic reactions. If any of these side effects occur, consult your healthcare professional.

Two subjects had pulmonary embolism and one subject had myocardial infarction while on Seasonale™ in clinical studies.

You will have more bleeding or spotting between your menstrual periods than if you were taking an oral contraceptive with a 28-day treatment cycle. During the first Seasonale™ treatment cycle, about 1 in 3 women may have 20 or more days of unplanned bleeding or spotting (bleeding when you are taking pink pills)

Irregular bleeding may vary from slight staining between menstrual periods to breakthrough bleeding which is a flow much like a regular period. Irregular bleeding occurs most often during the first few 91-day cycles of Seasonale™ use, tends to decrease during later cycles, but may also occur after you have been taking Seasonale™ for some time. Such bleeding usually does not indicate any serious problems. **It is important to continue taking your pills on schedule even if you are having irregular bleeding.** If the bleeding lasts for more than 7 consecutive days, talk to your healthcare professional.

Unscheduled bleeding and/or spotting as a reason for discontinuation for women using Seasonale™ was reported more often during the first seven months of treatment as opposed to the last five months of treatment. The pattern of unscheduled bleeding and/or spotting continued to decrease as women continued treatment.

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

- difficulty wearing contact lenses
- vaginal irritation or infections
- urinary tract infections or inflammation
- upper respiratory tract infections (colds, bronchitis, runny or stuffy nose, sore throat, etc.)
- severe headaches
- insomnia
- amenorrhea (lack of a period or breakthrough bleeding)
- flu-like symptoms
- allergy, fatigue, fever
- diarrhea, flatulence

In the post-market period, there have been cases of myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism reported with the use of Seasonale™. These adverse events have been reported and their relationship to Seasonale™ drug usage is not known.

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon			
Sharp chest pain, coughing of blood, sudden shortness of breath			X
Pain in the calf			X
Crushing chest pain or heaviness in the chest			X
Sudden, severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness or numbness in an arm or leg			X
Sudden partial or complete loss of vision			X
Breast lumps		X	
Severe pain or tenderness in the stomach area		X	
Difficulty sleeping, weakness, lack of energy, fatigue or change in mood			X
Jaundice or yellowing of the skin or eyeballs accompanied frequently by fever, fatigue, loss of appetite, dark-coloured urine, or light-coloured bowel movements			X
High blood pressure			X
Unusual swelling of extremities		X	

This is not a complete list of side effects. For any unexpected effects while taking Seasonale™ contact your doctor or pharmacist.

HOW TO STORE IT

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

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>), the manufacturer's website (<http://www.tevacanadainnovation.ca>), or by calling 1-855-223-6838.

This leaflet was prepared by Teva Canada Innovation.

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