PRODUCT MONOGRAPH

PrQUATERNA™

levonorgestrel and ethinyl estradiol tablets, Mfr. Std.
0.15 mg and 0.03 mg
and
ethinyl estradiol tablets, Mfr. Std.
0.01 mg

Oral Contraceptive

Manufactured by:
Famy Care Limited.
Ahmedabad – 382 213, Gujarat, India.

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Oral	Tablets 0.15 mg Levonorgestrel / 0.03 mg Ethinyl Estradiol and 0.01 mg Ethinyl Estradiol	Levonorgestrel 0.15 mg / Ethinyl Estradiol 0.03 tablet: lactose monohydrate, polacrilin potassium, D&C Yellow No. 10, FD&C Blue No. 1 aluminum lake, FD&C Yellow No. 6, magnesium stearate. Ethinyl Estradiol 0.01 mg tablet: anhydrous and monohydrate lactose, microcrystalline cellulose, polacrilin potassium, D&C Yellow No. 10 aluminum, FD&C Yellow No. 6/Sunset yellow FCF aluminum lake, povidone, dl-α-tocopherol, magnesium stearate and isopropyl alcohol (in traces).

INDICATIONS AND CLINICAL USE

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

- The prevention of pregnancy.

CONTRAINDICATIONS

QUATERNA™ should not be used in women who have the following conditions:

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **Dosage Forms, Composition and Packaging** section of the product monograph.
- History of or actual thrombophlebitis or thromboembolic disorders.
- History of or actual cerebrovascular disorders.
- History of or actual myocardial infarction or coronary artery disease.
- Valvular heart disease with complications.
- History of/or actual prodromi of a thrombosis (e.g. transient ischemic attack, angina pectoris)
- Active liver disease or history of or actual benign or malignant liver tumours.
- Steroid-dependent jaundice, cholestatic jaundice, history of jaundice in pregnancy
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal vaginal bleeding.
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
- Known or suspected pregnancy.
- Presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
  -diabetes mellitus with vascular involvement
  -severe hypertension (persistent values of ≥160/100mm Hg)
  -severe dyslipoproteinemia
  -hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia (e.g. due to MTHFR C677 T, A1298 mutations), prothrombin mutation G20210A and antiphospholipid-antibodies (Anti-cardiolipin antibodies, lupus anticoagulant).
  -major surgery associated with an increased risk of post-operative thromboembolism
  -prolonged immobilization
  -heavy smoking (>15 cigarettes per day) and over age 35
- Current or history of migraine with focal aura.
- History of/or actual pancreatitis if associated with severe hypertriglyceridemia
- Use of Hepatitis C drug combinations containing, glecaprevir/pibrentasvir and sofosbuvir / velpatasvir / voxilaprevir due to the potential for ALT elevations.

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. For this reason, Combination Oral Contraceptives, including QUATERNA™ are contraindicated in women over 35 years of age and who smoke (see Contraindications and **Cardiovascular** sections).

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

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

General

Discontinue Medication at the Earliest Manifestation of:

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

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

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

D. **Papilledema or ophthalmic vascular lesions**

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

F. **Increase in epileptic seizures**

QUATERNA™ Oral Contraceptive

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

The following information is provided from studies of combination oral contraceptives (COCs).

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

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

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

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

Carcinogenesis and Mutagenesis

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

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

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

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

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

Cardiovascular

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

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

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

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 QUATERNA.

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

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

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

Thromboembolism
See **Haematologic** section.

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

Endocrine and Metabolism

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

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

Gastrointestinal

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

Genitourinary

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

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

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

Hematologic
Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in users of oral contraceptives with low estrogen content (<50 mcg ethinyl estradiol) ranges from about 20 to

40 cases per 100,000 women-years, but this risk estimate varies according to the progestogen. This compares with 5 to 10 cases per 100,000 women-years for non-users.

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

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

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

Hepatic/Biliary/Pancreatic

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

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

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

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

Risk of ALT Elevations with Concomitant Hepatitis C Treatment

Discontinue QUATERNA prior to starting therapy with the hepatitis C combination drug regimen glecaprevir / pibrentasvir and sofosbuvir / velpatasvir / voxilaprevir due to the potential for ALT elevations (see CONTRAINDICATIONS).

QUATERNA can be restarted approximately 2 weeks following completion of treatment with the Hepatitis C combination drug regimen.

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

Immune

Angioedema
Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary and acquired angioedema

Chloasma
Chloasma may occur with combination oral contraceptives use including QUATERNA, especially in women with a history of chloasma gravidarum. Women who tend to develop chloasma should avoid exposure to the sun or ultraviolet radiation while taking QUATERNA.

Neurologic

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

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

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

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

Psychiatric

Emotional Disorders/Depression
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, QUATERNA should be discontinued and an alternate method of contraception should be used temporarily in order to help clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

Renal

Fluid retention
Hormonal contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

Sexual Function/Reproduction

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

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

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

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

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

Special Populations

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

Nursing Women
In breast-feeding women, the use of hormonal contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. Published studies have

indicated that during lactation, 0.1% of the daily maternal dose of levonorgestrel (27) and 0.02% of the daily maternal dose of ethinyl estradiol (28) could be transferred to the newborn via milk. Adverse effects on the child have been reported, including jaundice and breast enlargement (29). The nursing mother should be advised not to use combination oral contraceptives, but to use other forms of contraception until she has completely weaned her child. There have been no formal studies of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets in nursing women.

Pediatrics
The safety and efficacy of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets has not been established in women under the age of 18 years.

Use of this product before menarche is not indicated.

Geriatrics
QUATERNA is not indicated for use in post-menopausal women.

Monitoring and Laboratory Tests

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

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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

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

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

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

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

Clinical Trial Adverse Drug Reactions

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

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

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

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

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

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

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

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

MedDRA System Organ Class and Preferred Term	Pivotal Study PSE-301		Supportive Study PSE-302			
	Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=1006)		Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=95)		21/7 Regimen[a] (N=93)	
	N	%	N	%	N	%
Blood and Lymphatic System Disorders						
Anemia NOS	1	0.10	1	1.05	0	0.00
Ear and Labyrinth Disorders						
Vertigo	2	0.20	1	1.05	0	0.00
Ear pain	1	0.10	2	2.11	0	0.00
Labyrinthitis NOS	0	0.00	1	1.05	0	0.00
Eye Disorders						
Conjunctivitis	5	0.50	1	1.05	0	0.00
Gastrointestinal Disorders						
Nausea	45	4.47	3	3.16	7	7.53
Abdominal distension	25	2.49	2	2.11	2	2.15
Diarrhoea NOS	19	1.89	1	1.05	0	0.00
Vomiting NOS	18	1.79	1	1.05	3	3.23
Abdominal pain NOS	17	1.69	4	4.21	1	1.08
Dental discomfort	12	1.19	1	1.05	2	2.15
Dyspepsia	12	1.19	1	1.05	1	1.08
Abdominal pain upper	9	0.89	1	1.05	0	0.00
Abdominal pain lower	5	0.50	1	1.05	0	0.00
Food poisoning	1	0.10	1	1.05	0	0.00
Aphthous stomatitis	0	0.00	1	1.05	0	0.00
General Disorders and Administration Site Conditions						
Fatigue	29	2.88	0	0.00	1	1.08
Influenza like illness	5	0.50	2	2.11	4	4.30
Pyrexia	4	0.40	1	1.05	1	1.08

MedDRA System Organ Class and Preferred Term	Pivotal Study PSE-301		Supportive Study PSE-302			
	Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=1006)		Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=95)		21/7 Regimen[a] (N=93)	
	N	%	N	%	N	%
Immune System Disorders						
Hypersensitivity NOS	10	0.99	1	1.05	1	1.08
Seasonal allergy	8	0.80	2	2.11	0	0.00
Infections And Infestations						
Nasopharyngitis	72	7.16	8	8.42	12	12.90
Sinusitis NOS	65	6.46	7	7.37	3	3.23
Upper respiratory tract infection NOS	49	4.87	4	4.21	1	1.08
Urinary tract infection NOS	45	4.47	4	4.21	7	7.53
Pharyngitis streptococcal	31	3.08	5	5.26	2	2.15
Fungal infection NOS	26	2.58	1	1.05	4	4.30
Bronchitis NOS	25	2.49	3	3.16	1	1.08
Vaginosis fungal NOS	20	1.99	0	0.00	0	0.00
Influenza	18	1.79	3	3.16	3	3.23
Vaginitis bacterial NOS	13	1.29	3	3.16	3	3.23
Gastroenteritis viral NOS	12	1.19	0	0.00	0	0.00
Ear infection NOS	10	0.99	2	2.11	1	1.08
Herpes simplex	9	0.89	2	2.11	0	0.00
Vaginal candidiasis	6	0.60	2	2.11	2	2.15
Gastroenteritis NOS	5	0.50	2	2.11	4	4.30
Pneumonia NOS	3	0.30	1	1.05	1	1.08
Vaginitis	2	0.20	2	2.11	0	0.00
Cystitis NOS	1	0.10	1	1.05	0	0.00
Infected insect bite	1	0.10	1	1.05	1	1.08
Respiratory tract infection NOS	1	0.10	1	1.05	0	0.00
Body tinea	0	0.00	1	1.05	0	0.00
Breast infection NOS	0	0.00	1	1.05	0	0.00
Endometritis NOS	0	0.00	1	1.05	0	0.00
Injury, Poisoning and procedural complications						
Post procedural pain	6	0.60	2	2.11	1	1.08
Foot fracture	2	0.20	1	1.05	0	0.00
Limb injury NOS	2	0.20	1	1.05	0	0.00
Muscle strain	2	0.20	1	1.05	0	0.00
Rib fracture	0	0.00	1	1.05	0	0.00
Investigations						
Weight increased	53	5.27	0	0.00	1	1.08
Blood pressure increased	4	0.40	2	2.11	0	0.00

MedDRA System Organ Class and Preferred Term	Pivotal Study PSE-301		Supportive Study PSE-302			
	Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=1006)		Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=95)		21/7 Regimen[a] (N=93)	
	N	%	N	%	N	%
Blood triglycerides increased	1	0.10	1	1.05	0	0.00
Blood glucose increased	0	0.00	1	1.05	0	0.00
Metabolism and Nutrition Disorders						
Appetite increased NOS	6	0.60	1	1.05	0	0.00
Fluid retention	1	0.10	1	1.05	0	0.00
Musculoskeletal and Connective Tissue Disorders						
Back pain	21	2.09	1	1.05	2	2.15
Arthralgia	17	1.69	0	0.00	0	0.00
Peripheral swelling	11	1.09	1	1.05	1	1.08
Muscle cramp	5	0.50	1	1.05	0	0.00
Myalgia	5	0.50	1	1.05	0	0.00
Neck pain	4	0.40	1	1.05	1	1.08
Tendonitis	3	0.30	1	1.05	0	0.00
Osteoarthritis NOS	0	0.00	1	1.05	0	0.00
Pain in limb	0	0.00	2	2.11	0	0.00
Nervous System Disorders						
Headache NOS	39	3.88	3	3.16	3	3.23
Migraine NOS	18	1.79	1	1.05	1	1.08
Headache NOS aggravated	11	1.09	1	1.05	0	0.00
Dizziness	8	0.80	2	2.11	0	0.00
Syncope	3	0.30	1	1.05	1	1.08
Pregnancy, Puerperium and Perinatal Conditions						
Pregnancy NOS	3	0.3	1	1.05	2	2.15
Psychiatric Disorders						
Mood swings	35	3.48	2	2.11	2	2.15
Depression	30	2.98	4	4.21	1	1.08
Libido decreased	14	1.39	2	2.11	1	1.08
Anxiety	11	1.09	0	0.00	0	0.00
Irritability	10	0.99	1	1.05	0	0.00
Major depressive disorder	1	0.10	1	1.05	0	0.00
NOS						
Anxiety aggravated	1	0.10	1	1.05	1	1.08
Mood alteration NOS	0	0.00	1	1.05	0	0.00
Renal and Urinary Disorders						

MedDRA System Organ Class and Preferred Term	Pivotal Study PSE-301		Supportive Study PSE-302			
	Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=1006)		Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=95)		21/7 Regimen[a] (N=93)	
	N	%	N	%	N	%
Calculus renal NOS	2	0.20	1	1.05	0	0.00
Reproductive system and Breast Disorders						
Intermenstrual bleeding	116	11.53	10	10.53	2	2.15
Menorrhagia	58	5.77	4	4.21	2	2.15
Dysmenorrhoea	36	3.58	2	2.11	4	4.30
Breast tenderness	29	2.88	1	1.05	1	1.08
Cervical dysplasia	6	0.60	3	3.16	1	1.08
Dyspareunia NOS	3	0.30	1	1.05	0	0.00
Vaginal discharge	3	0.30	1	1.05	1	1.08
Genital pruritus female	2	0.20	1	1.05	0	0.00
Pelvic pain NOS	2	0.20	1	1.05	2	2.15
Post coital bleeding	2	0.20	1	1.05	1	1.08
Mastitis	0	0.00	1	1.05	0	0.00
Nipple pain	0	0.00	1	1.05	0	0.00
Ovarian cyst ruptured	0	0.00	1	1.05	0	0.00
Respiratory, Thoracic and Mediastinal Disorders						
Pharyngitis	20	1.99	1	1.05	3	3.23
Sinus congestion	18	1.79	1	1.05	1	1.08
Cough	9	0.89	2	2.11	0	0.00
Rhinitis allergic NOS	4	0.40	1	1.05	1	1.08
Skin And Subcutaneous Tissue Disorders						
Acne NOS	52	5.17	8	8.42	1	1.08
Acne aggravated	4	0.40	1	1.05	1	1.08
Dermatitis exfoliative NOS	0	0.00	1	1.05	0	0.00
Epidermal cyst	0	0.00	1	1.05	0	0.00
Seborrhoea	0	0.00	1	1.05	0	0.00
Skin lesion NOS	0	0.00	1	1.05	0	0.00

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

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

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

MedDRA System Organ Class and Preferred Term	Study PSE-304 Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=173)	
	N	%
Blood and Lymphatic System Disorders		
Lymphadenopathy	2	1.16
Ear and Labyrinth Disorders		
Motion sickness	3	1.73
Eye Disorders		
Conjunctivitis	2	1.16
Gastrointestinal Disorders		
Abdominal pain upper	7	4.05
Diarrhoea	7	4.05
Dyspepsia	6	3.47
Nausea	5	2.89
Constipation	4	2.31
Stomach discomfort	4	2.31
Abdominal distension	3	1.73
Toothache	3	1.73
Vomiting	3	1.73
Abdominal pain lower	2	1.16
Flatulence	2	1.16
Food poisoning	2	1.16
Gastrooesophageal reflux disease	2	1.16
Irritable bowel syndrome	2	1.16
General Disorders and Administration Site Conditions		
Fatigue	4	2.31
Chest discomfort	3	1.73
Pyrexia	3	1.73
Immune System Disorders		
Hypersensitivity	3	1.73
Seasonal allergy	3	1.73
Infections and Infestations		
Upper respiratory tract infection	34	19.65
Nasopharyngitis	26	15.03
Vaginitis bacterial	19	10.98

MedDRA System Organ Class and Preferred Term	Study PSE-304 Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=173)	
	N	%
Influenza	18	10.40
Sinusitis	18	10.40
Urinary tract infection	16	9.25
Bronchitis	13	7.51
Vulvovaginal mycotic infection	13	7.51
Fungal infection	7	4.05
Gastroenteritis	7	4.05
Pharyngitis streptococcal	6	3.47
Gastroenteritis viral	5	2.89
Herpex simplex	5	2.89
Ear infection	3	1.73
Pneumonia	3	1.73
Tooth abscess	3	1.73
Vaginal candidiasis	3	1.73
Candidiasis	2	1.16
Condyloma acuminatum	2	1.16
Cystitis	2	1.16
Pharyngitis	2	1.16
Tonsillitis	2	1.16
Tooth infection	2	1.16
Viral infection	2	1.16
Injury, Poisoning and Procedural Complications		
Procedural pain	5	2.89
Arthropod sting	3	1.73
Contusion	3	1.73
Road traffic accident	3	1.73
Joint sprain	2	1.16
Muscle strain	2	1.16
Tendon injury	2	1.16
Investigations		
Weight Increased	16	9.25
Blood pressure increased	8	4.62
Smear cervix abnormal	2	1.16
Musculoskeletal and Connective Tissue Disorders		
Back pain	21	12.14
Arthralgia	7	4.05
Myalgia	6	3.47

MedDRA System Organ Class and Preferred Term	Study PSE-304 Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=173)	
	N	%
Muscle spasms	5	2.89
Intervertebral disc protrusion	3	1.73
Shoulder pain	3	1.73
Musculoskeletal pain	2	1.16
Nervous System Disorders		
Headache	38	21.97
Migraine	8	4.62
Sinus headache	6	3.47
Dizziness	3	1.73
Psychiatric Disorders		
Insomnia	13	7.51
Anxiety	10	5.78
Depression	10	5.78
Libido decreased	3	1.73
Bipolar disorder	2	1.16
Reproductive system and Breast Disorders		
Metrorrhagia	16	9.25
Dysmenorrhoea	15	8.67
Cervical dysplasia	11	6.36
Breast mass	4	2.31
Cervix erythema	3	1.73
Vaginal haemorrhage	3	1.73
Breast tenderness	2	1.16
Cervical cyst	2	1.16
Menorrhagia	2	1.16
Vaginal discharge	2	1.16
Respiratory, Thoracic and Mediastinal disorders		
Pharyngolaryngeal pain	8	4.62
Sinus congestion	7	4.05
Cough	5	2.89
Nasal congestion	5	2.89
Respiratory tract congestion	2	1.16
Skin and Subcutaneous Tissue Disorders		
Rash	5	2.89
Dermatitis contact	4	2.31
Acne	3	1.73

MedDRA System Organ Class and Preferred Term	Study PSE-304 Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=173)	
	N	%
Surgical and Medicinal Procedures		
Tooth extraction	3	1.73
Wisdom teeth removal	2	1.16
Vascular Disorders		
Hot flush	3	1.73
Hypertension	2	1.16

Note: all subjects in the higher dose 91-day treatment group were eventually switched over to levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets but were analyzed separately. Adverse events observed in subjects originally assigned to the higher dose group were generally similar to those observed with levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets.

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

The following adverse events were reported in the levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets treatment arm at a frequency <1% in studies PSE-301, PSE-302 and PSE-304:

Cardiac disorders: mitral valve prolapse, palpitations, tachycardia

Ear and labyrinth disorders: ear congestion.

Endocrine disorders: acquired hypothyroidism, goitre, thyroid nodule.

Eye disorders: dry eye, optic neuritis.

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

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

Hepatobiliary disorders: cholelithiasis, cholecystitis.

Immune systems disorders: drug hypersensitivity.

Infections and infestations: abscess, bacterial infection, bladder infection, breast cellulitis, candidial infection, cervicitis, dermatophytosis, dry socket, eye infection, gastroenteritis salmonella, gastroenteritis shigella, genitourinary chlamydia infection, gingivitis infection, helicobacter infection, herpes zoster, hordeolum, infectious mononucleosis, kidney infection, laryngitis chronic, localised infection, otitis media, pelvic inflammatory disease, periodontitis, post procedural site

wound infection, sialoadenitis, skin and subcutaneous tissue abscess, skin infection, tooth caries, vaginal infection, vulvovaginitis trichomonal.

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

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

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

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

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

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

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

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

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

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

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

Social circumstances: exposure to communicable disease.

Vascular disorders: hypertension aggravated, orthostatic hypotension.

Vaginal bleeding

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

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

Unscheduled bleeding and/or spotting per 28-day patient-month
In pivotal study PSE-301, the median number of days of unscheduled bleeding and/or spotting decreased from 2.8 days per patient-month in the first 91-day cycle to 1.0 day per patient-month in the 4th 91-day cycle.

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

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

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

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

In supportive study PSE-302, the median number of total bleeding and/or spotting days in the levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets treatment arm decreased from 4.3 days per patient-month in the first 91-day cycle to 3.1 days per patient-month in the 4th 91-day

cycle. The median number of total bleeding and/or spotting days in the subjects treated with LNG 0.150mg/EE 0.03mg for 21 days followed by 7 days placebo ranged from 3-5 days per month over the course of the 13 28-day cycles.

Endometrial biopsies

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

Thromboembolic events

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

Weight

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

Abnormal Haematologic and Clinical Chemistry Findings

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

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

In study PSE-302, 6.3% of subjects in the levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets treatment arm versus 4.8% of subjects in the LNG 0.15 mg/EE 0.03 mg (21/7

regimen) treatment arm with normal serum glucose at baseline had values at end of treatment that exceeded the upper limit of normal. In PSE-301 2.1% of subjects on levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets with normal serum glucose levels at baseline had values at end of treatment that exceeded the upper limit of normal.

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

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

Post-Market Adverse Drug Reactions

The following other serious and unexpected adverse events have been reported in users of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets 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 levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets has been established.

Gastrointestinal Disorders: rectal spasm.

Infections and Infestations: Appendicitis.

Investigations: Blood lactate dehydrogenase increased.

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

Neoplasm: Uterine leiomyoma.

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary embolism.

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

Vascular Disorders: Deep vein thrombosis, thrombosis.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

Table 3: Drugs Which May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifabutin Rifampin (30)	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	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.	
Anticonvulsants (31-33)	Carbamazepine Ethosuximide Felbamate Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone Topiramate	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose oral contraceptives (50 mcg ethinyl estradiol), another drug or another method.

Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy.	Use another method.

Table 3: Drugs Which May Decrease the Efficacy of Oral Contraceptives			
Class of Compound	**Drug**	**Proposed Mechanism**	**Suggested Management**
HIV protease inhibitors (34)	Ritonavir	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Non-nucleoside reverse transcriptase inhibitors (29, 35)	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Sedatives and Hypnotics	Barbiturates Benzodiazepines 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.
Other Drugs	Analgesics Antihistamines Antimigraine preparations Phenylbutazone Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	

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

Table 4: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Modification of Drug Action**	**Suggested Management**
Alcohol		Possible increased levels of ethanol or acetaldehyde	Use with caution.

Alpha-II adrenoreceptor agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients.	Use another method.

Table 4: Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another method.
	Lamotrigine (36-40)	Combination oral contraceptives have been shown to significantly decrease plasma concentrations of lamotrigine likely due to induction of lamotrigine glucoronidation. Decreased lamotrigine levels may lead to breakthrough seizures.	Use another method.
Antidiabetic drugs	Oral hypoglycaemics and insulin	Oral contraceptives may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin oral contraceptive or another method. Monitor blood glucose.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen oral contraceptive or use another method.
	Beta blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.

	ASA	Effects of ASA may be decreased by the short-term use of oral contraceptives.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic acid		Theoretically, a hypercoagulable state may occur because oral contraceptives augment clotting factors.	Avoid concomitant use.

Table 4: Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
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.
Hepatis C drug combinations	glecaprevir/ pibrentasvir and sofosbuvir/ velpatasvir/ voxilaprevir	Potential ALT elevations	Avoid concomitant use.
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.
Vitamin B_{12}		Oral contraceptives have been reported to reduce serum levels of Vitamin B_{12}	May need to increase dietary intake, or supplement.

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

No formal drug-drug interaction studies have been conducted with levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

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

Drug-Laboratory Test Interactions

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

The following laboratory tests are modified:

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

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

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

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

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

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

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

Drug-Lifestyle Interactions

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

No studies on the effects of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets on the ability to drive or use machines have been performed.

Non-contraceptive Benefits of Oral Contraceptives

Several have been reported.

1. Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

Correct use of contraceptives can result in lower failure rates. If withdrawal bleeding does not occur while taking yellow (ethinyl estradiol) tablets, the possibility of pregnancy must be considered. Appropriate diagnostic measures to rule out pregnancy should be taken at the time of any missed menstrual period. QUATERNA 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 blister card should be kept in the foil pouch until dispensed to the patient.

Recommended Dose and Dosage Adjustment

The dosage of QUATERNA
consists of the daily administration of one bluish-green (levonorgestrel/ethinyl estradiol) tablet taken for 84 consecutive days followed by 7 days of yellow (ethinyl estradiol) tablets; therefore patients should expect to have 4 menstrual periods per year. To achieve maximum contraceptive effectiveness QUATERNA 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 QUATERNA on the first Sunday after the onset of menstruation. If menstruation begins on a Sunday, the first bluish-green (levonorgestrel/ethinyl estradiol) tablet is taken that day. One bluish-green (levonorgestrel/ethinyl estradiol) tablet should be taken daily for 84 consecutive days, followed by a 7- day period during which a yellow (ethinyl estradiol) tablet is taken daily. Withdrawal bleeding should occur during the 7-day period following discontinuation of bluish-green active tablets.

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

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

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

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her healthcare provider.

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

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

This product (like all oral contraceptives) is intended to prevent pregnancy. Oral contraceptives do not protect against transmission of HIV (AIDS) and other sexually transmitted diseases such as chlamydia, genital herpes, genital warts, gonorrhea, hepatitis B and syphilis.

Administration

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

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

Switching from a progestogen-only method (mini-pill, injection): The patient may switch from the mini-pill to QUATERNA on any day of her cycle. Patients using a progestogen injection should start QUATERNA on the day the next injection is due. In all cases, the patient should be advised to use an additional (barrier) method for the first 7 days of QUATERNA use.

Following first trimester abortion: The patient may start using QUATERNA immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second trimester abortion: Patients should be advised to start QUATERNA on day 21 to 28 after delivery or second trimester abortion, after consulting with their physician. When starting later, the patient should be advised to use an additional (barrier) method for the first seven days of QUATERNA use. However, if intercourse has already occurred, pregnancy should be

excluded before the actual start of use, or the woman should be advised to wait for her next menstrual period prior to starting QUATERNA. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered.

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

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

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

Missed Dose

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

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

OVERDOSAGE

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

Serious ill effects have not been reported following accidental ingestion of large doses of oral contraceptives by young children. Symptoms of combined oral contraceptive (COC) overdosage in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms. Liver function tests should be conducted, particularly transaminase levels, 2 to 3 weeks after consumption.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Combination oral contraceptives act by suppression of gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and changes in the endometrium (which reduce the likelihood of implantation).

Pharmacodynamics

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

Pharmacokinetics

Absorption: Ethinyl estradiol and levonorgestrel are rapidly absorbed with maximum plasma concentrations occurring within 2 hours after levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets administration. No specific investigation of the absolute bioavailability of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets in humans has been conducted. However, published literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism (41-46). Ethinyl estradiol is rapidly and almost completely absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, the bioavailability of ethinyl estradiol is approximately 55% (46).

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

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

Table 5: Mean Pharmacokinetic Parameters for Levonorgestrel / Ethinyl Estradiol Tablets and Ethinyl Estradiol Tablets During Daily One Tablet Dosing for 84 Days

	AUC_{0-24} (mean ± SD)	C_{max} (mean ± SD)	T_{max} (mean ± SD)	$T_{1/2\ el}$ (h)
	Levonorgestrel (N= 28-30)			

Day 1	18.2 ± 6.1 ng•hr/mL	3.0 ± 1.0 ng/mL	1.3 ± 0.4 hours	
Day 21	64.4 ± 25.1 ng•hr/mL	6.2 ± 1.6 ng/mL	1.3 ± 0.4 hours	
Day 84	60.2 ± 24.6 ng•hr/mL	5.5 ± 1.6 ng/mL	1.3 ± 0.3 hours	39 ± 12 hours
	Ethinyl Estradiol (N= 28-30)			
Day 1	509.3 ± 172.0 pg•hr/mL	69.8 ± 25.9 pg/mL	1.5 ± 0.3 hours	
Day 21	837.1 ± 271.2 pg•hr/mL	99.6 ± 31.3 pg/mL	1.5 ± 0.3 hours	
Day 84	791.5 ± 215.0 pg•hr/mL	91.3 ± 32.5 pg/mL	1.6 ± 0.3 hours	
Day 91	867.5 ± 277.6 pg•hr/mL	102.3 ± 50.4 pg/mL	1.4 ± 0.4 hours	18 ± 4 hours

Distribution: The apparent volume of distribution of each levonorgestrel and ethinyl estradiol are reported to be approximately 1.8 L/kg and 4.3 L/kg, respectively (41, 47). Levonorgestrel is about 97.5-99% protein-bound, principally to the sex hormone binding globulin (SHBG) and, to a lesser extent, serum albumin (41). Ethinyl estradiol is about 95-97% bound to serum albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis, which leads to decreased levonorgestrel clearance (48). Following repeated daily dosing of combination levonorgestrel and ethinyl estradiol oral contraceptives, levonorgestrel plasma concentrations accumulate more than predicted based on single-dose kinetics, due in part, to increased SHBG levels that are induced by ethinyl estradiol and a possible reduction in hepatic metabolic capacity.

Metabolism: Following absorption, levonorgestrel is conjugated at the 17β-OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma (49). Significant amounts of conjugated and unconjugated 3α,5β-tetrahydrolevonorgestrel are also present in plasma, along with much smaller amounts of 3α,5α-tetrahydrolevonorgestrel and 16β-hydroxylevonorgestrel (50). Levonorgestrel and its Phase I metabolites are excreted primarily as glucuronide conjugates. Metabolic clearance rates may differ among individuals by several-fold, and this may account in part for the wide variation observed in levonorgestrel concentrations among users (50).

First-pass metabolism of ethinyl estradiol involves formation of ethinyl estradiol-3-sulfate in the gut wall followed by 2-hydroxylation of a portion of the remaining untransformed ethinyl estradiol by hepatic CYP3A4 (42, 51). Levels of CYP3A4 vary widely among individuals and can explain the variation in rates of ethinyl estradiol hydroxylation. Hydroxylation at the 4-, 6- and 16- positions may also occur, although to a much lesser extent than 2-hydroxylation (51). The various hydroxylated metabolites are subject to further methylation and/or conjugation.

Excretion: About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in feces, mostly as glucuronide conjugates (48). The terminal elimination half life for levonorgestrel after a single dose of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets was found to be about 39 hours. Ethinyl estradiol is excreted in the urine and feces as glucuronide and sulfate conjugates and it undergoes enterohepatic recirculation (52, 53). The terminal elimination half-life of ethinyl estradiol after a single dose of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets was found to be about 18 hours.

Special Populations and Conditions

Pediatrics: The safety and efficacy of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets has not been established in women under the age of 18 years.

Use of this product before menarche is not indicated.

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

Race: No formal studies on the effect of race on the pharmacokinetics of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets have been conducted.

Hepatic Insufficiency: No formal studies have been conducted to evaluate the effect of hepatic disease on the pharmacokinetics of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets. 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 levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets.

Genetic Polymorphism: No data are available.

STORAGE AND STABILITY

Store between 15°C to 30°C. Keep out of the reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

QUATERNA™ (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg combination and ethinyl estradiol 0.01 mg) tablets are available in Extended-Cycle Tablet Blister Card. Altogether, the Tablet Blister Card holds 91 tablets consisting of 84 bluish-green tablets (each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol) and 7 yellow tablets (each containing 0.01 mg ethinyl estradiol). The bluish-green tablets are round, uncoated, biconvex, unscored tablets with a debossed **417** on one side and blank on the other side. The yellow tablets are round, biconvex, unscored with a debossed with **419** on one side and blank on the other side.

The Tablet Blister Card consists of three blisters. Each of these blisters 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 bluish-green tablets and the third blister card contains 28 active bluish-green tablets and 7 active yellow tablets for a total of 35 tablets. The Blister Card is then packaged in a foil pouch.

Levonorgestrel 0.15 mg / Ethinyl Estradiol 0.03 mg is a bluish-green tablet containing the following inactive ingredients: lactose monohydrate, polacrilin potassium, D&C Yellow No. 10, FD&C Blue No. 1 aluminum lake, FD&C Yellow No. 6, magnesium stearate.

Ethinyl Estradiol 0.01 mg is a yellow tablet containing the following inactive ingredients: anhydrous and monohydrate lactose, microcrystalline cellulose, polacrilin potassium, D&C Yellow No. 10 aluminum, FD&C Yellow No. 6/Sunset yellow FCF aluminum lake, povidone, dl-α-tocopherol, magnesium stearate and isopropyl alcohol (in traces).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Levonorgestrel

Ethinyl Estradiol

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

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

Molecular formula: Levonorgestrel: $C_{21}H_{28}O_2$

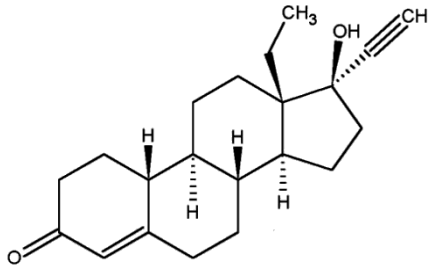
Ethinyl Estradiol: $C_{20}H_{24}O_2$

molecular mass: Levonorgestrel: 312.45 g/mol

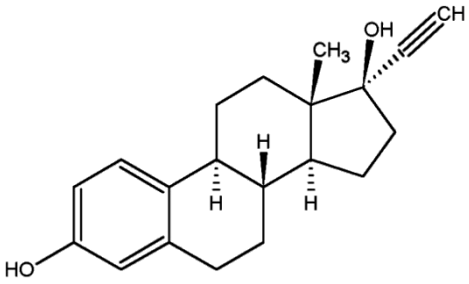
Ethinyl Estradiol: 296.40 g/mol

Structural formula:

Levonorgestrel:



Ethinyl Estradiol:



Solubility: Levonorgestrel: Practically insoluble in water and n-hexane, slightly soluble in acetone and ethanol, sparingly soluble in dichloromethane and soluble in chloroform

Ethinyl Estradiol: Freely soluble in ether, ethanol, acetone, dioxane, soluble in alkali hydroxide solutions, sparingly soluble in chloroform and practically insoluble in water.

Melting points:

Levonorgestrel: 232-239°C
Ethinyl Estradiol: 180-186 °C

Biological properties:

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

Ethinyl Estradiol: This is a synthetic estrogen.

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY STUDIES

A randomized, single dose (2 x levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg), crossover comparative bioavailability study of QUATERNA (Mylan Pharmaceuticals ULC) and Seasonique® (TEVA WOMEN'S HEALTH INC.) was conducted in healthy, adult, female human subjects under fasting conditions. A summary of the data from the 26 subjects that were included in the statistical analysis are presented in the tables below.

SUMMARY TABLES OF THE COMPARATIVE BIOAVAILABILTY DATA

Levonorgestrel (2 x levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72h} (ng·h/mL)	88.1 98.2 (45.4)	85.1 96.6 (48.6)	103.5	98.1 – 109.2
C_{max} (ng/mL)	6.5 7.2 (45.6)	6.9 7.5 (41.9)	94.3	87.9 – 101.2
T_{max}[3] (h)	1.8 (1.0 – 4.0)	1.5 (1.0 – 3.5)		

[1] QUATERNA (levonorgestrel /ethinyl estradiol) tablets 0.15 mg/0.03 mg (Mylan Pharmaceuticals ULC)
[2] Seasonique® (levonorgestrel /ethinyl estradiol) tablets 0.15 mg/0.03 mg (TEVA WOMEN'S HEALTH INC., Canada)
[3] Expressed as the median (range) only

Due to the long elimination half-life of levonorgestrel AUC_I and $T_{1/2}$ could not be accurately calculated from the data obtained in this study.

Ethinyl Estradiol (2 x levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg·h/mL)	1587.7 1754.2 (47.9)	1602.4 1757.6 (43.7)	99.1	95.6 – 102.7
AUC_I[3] (pg·h/mL)	1755.9 1965.8 (43.7)	1768.7 1925.5 (41.4)	99.3	96.0 – 102.7
C_{max} (pg/mL)	148.6 158.8 (37.6)	156.2 168.3 (38.7)	95.2	90.9 – 99.6
T_{max}[4] (h)	1.5 (1.5 – 2.5)	1.5 (1.5 – 2.5)		
$T_{½}$[5] (h)	1.7 (20.4)	1.7 (16.9)		

[1] QUATERNA (levonorgestrel /ethinyl estradiol) tablets 0.15 mg/0.03 mg (Mylan Pharmaceuticals ULC)
[2] Seasonique® (levonorgestrel /ethinyl estradiol) tablets 0.15 mg/0.03 mg (TEVA WOMEN'S HEALTH INC., Canada)
[3] n=25
[4] Expressed as the median (range) only
[5] Expressed as the arithmetic mean (range) only

A randomized, single dose (2 x ethinyl estradiol 0.01 mg), crossover comparative bioavailability study of QUATERNA (Mylan Pharmaceuticals ULC) and Seasonique® (TEVA WOMEN'S HEALTH INC.) was conducted in healthy, adult, female human subjects under fasting conditions. A summary of the data from the 26 subjects that were included in the statistical analysis are presented in the table below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILTY DATA

Ethinyl Estradiol (2 x 0.01 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg·h/mL)	1587.7 1754.2 (47.9)	1602.4 1757.6 (43.7)	99.1	95.6 – 102.7
AUC_I (pg·h/mL)	1755.9 1965.8 (43.7)	1768.7 1925.5 (41.4)	99.3	96.0 – 102.7
C_{max} (pg/mL)	148.6 158.8 (37.6)	156.2 168.3 (38.7)	95.2	90.9 – 99.6

Ethinyl Estradiol (2 x 0.01 mg) Geometric Mean Arithmetic Mean (CV%)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg·h/mL)	1587.7 1754.2 (47.9)	1602.4 1757.6 (43.7)	99.1	95.6 – 102.7
T_{max}[3] (h)	2.0 (1.5 – 2.0)	1.5 (1.0 – 2.5)		
$T_{½}$[4] (h)	1.7 (20.4)	1.7 (16.9)		

[1] QUATERNA (ethinyl estradiol) tablets 0.01 mg (Mylan Pharmaceuticals ULC)
[2] Seasonique® (ethinyl estradiol) tablets 0.01 mg (TEVA WOMEN'S HEALTH INC., Canada)
[3] Expressed as the median (range) only
[4] Expressed as the arithmetic mean (range) only

Study demographics and trial design

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

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

Patient Cohorts Analyzed in study PSE-301

Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=1024)		
	N	**%**
Randomized	1024	100.0
Treated Patients (Safety)	1006	98.2
Treated at Least 1 Complete Cycle (ITT)	799	78.0
ITT, 18-35 Years of Age (PITT)	708	69.1

The discontinuation rate was 50.3% in the levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets arm (506/1006 patients discontinued the study early). Among all treated patients, the most common reasons for discontinuation were adverse events (16.3% in the levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets arm). The most commonly reported adverse events (AEs) leading to study discontinuation were intermenstrual bleeding and menorrhagia. In the levonorgestrel

/ ethinyl estradiol tablets and ethinyl estradiol tablets arm, 62 of 164 (37.8%) AEs that lead to study discontinuation were related to bleeding and/or spotting.

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

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

Demographic Information at Screening: Patients 18-35 Years of Age with at Least One Complete Cycle on Treatment (PITT) in study PSE-301	
Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets (N=708)	
Race	
African-American	80 (11.3%)
Asian	16 (2.3%)
Caucasian	562 (79.4%)
Hispanic	34 (4.8%)
Other	16 (2.3%)
Smoking Status	
Non-Smoker	570 (80.5%)
Smoker	138 (19.5%)

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

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

N	707
Mean (Std)	25.9 (6.19)
Median	24.3
(Min, Max)	(17.1, 56.5)

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

Study results

As noted above, the PITT cohort was the primary cohort used for the efficacy analyses, and was comprised of patients 18-35 years of age with at least one complete cycle on treatment. Cycles in which another form of birth control was used (including condoms) were excluded from the assessment of the Pearl Index. The Pearl Index for levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets for the PITT cohort, excluding cycles in which another birth control method was used was 1.77 (95% CI 0.71-3.65), based on 7 pregnancies that occurred on-treatment over 5125.25 28-day equivalent patient months (1577 91- day cycles). The Pearl Index for levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets for the subset of the PITT cohort with compliant use, excluding cycles in which another birth control method was used 0.78 (95% CI 0.16-2.28), based on 3 pregnancies that occurred on-treatment over 4982.25 28-day equivalent patient months (1533 91-day cycles). In the compliant-use subset analysis, patient cycles that were deemed non-compliant (where non-compliance is defined as all cycles in which a patient skipped two or more consecutive pills or had a pattern of substantial non-compliance with study medication or used a prohibited concomitant medication that may interact with oral contraceptive therapy) were not used. Substantial non-compliance was defined as an overall pill compliance of less than 80%.

The cumulative failure rate for levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets at the end of one year of treatment, estimated by the life table method, was 0.89% (95% CI 0.37%, 2.18%).

See summary table of Pearl Indices and Life Table Analyses for levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets, below.

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

Treatment Group	Number of Cycles	Number of 28-Day Patient Months	Number of On-Drug Pregnancies	Pearl Index (95% CI)
Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets	1577	5125.25	7	1.77 (0.71,3.65)

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

Levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets			
Cycle	N	**Pregnancy Rate**	**95% C.I.**
1	709	0.0029	0.0007-0.0115
2	667	0.0045	0.0015-0.0140
3	530	0.0065	0.0024-0.0174
4	464	0.0089	0.0037-0.0218

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

General Information

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

Reported Pregnancies per 100 Women per Year:

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

DETAILED PHARMACOLOGY

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

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

estradiol, norgestrel tends to ameliorate the effects of the estrogen, while the estrogen will modify the effects of the progestogen. In rats, suppression of fertility with norgestrel/ethinyl estradiol combinations is followed by recovery of normal fertility and fecundity.

Additional experiments in laboratory animals were directed toward evaluating the endocrine effects and safety of the norgestrel and ethinyl estradiol formulation at dose levels approximating those employed clinically (on a milligram per kilogram basis). Metrotropic effect (uterine glandular development and growth) was most clearly demonstrated. Blockade of pituitary gonadotrophins can be produced by the estrogenic component alone at the clinical dose range; this pituitary effect does not appear to be modified by addition of the progestogen.

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

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

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

Endometrial biopsies taken during the course of therapy with 250 mcg *d*-norgestrel (as the *d1*-racemate) plus 50 mcg 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 mcg *d*-norgestrel (as the *dl*-racemate) plus 50 mcg ethinyl estradiol, and 37.5 mcg *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 mcg d-norgestrel (as the dl-racemate) plus 30 mcg ethinyl estradiol over a continuous period of three months indicated no clinically or statistically significant elevation or depression of hormone levels during the course of active drug ingestion, nor in the post-treatment cycle.

A human study of the metabolism of ^{14}C-labelled norgestrel, revealed that most of the urinary excretion of norgestrel occurred on the first day. There was no difference in the rate of excretion of norgestrel whether administered orally or intravenously. The amount of radioactivity in plasma fell

rapidly within the first few hours and at the end of two days only small amounts were present. The foregoing and other studies with ^{14}C-labelled and unlabelled norgestrel have shown that saturation of the 4,5-double bond with and without concomitant reduction of the 3-carbonyl to a 3-hydroxyl group are important reactions during metabolism.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

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

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

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

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PART III: CONSUMER INFORMATION

PrQUATERNA™

levonorgestrel and ethinyl estradiol tablets,
Mfr. Std.,
0.15 mg and 0.03 mg
and
ethinyl estradiol tablets, Mfr. Std.,
0.01 mg

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

ABOUT THIS MEDICATION

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

What it does:
QUATERNA™ 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 QUATERNA™

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

Effectiveness of Birth Control Pills

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

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

The chance of becoming pregnant increases with incorrect use.

Other Ways to Prevent Pregnancy

Other methods of birth control are available to you. They are usually less effective than birth control pills. When used properly,

however, other methods of birth control are effective enough for many women.

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

Reported Pregnancies per 100 Women per Year:	
Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1to 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 QUATERNA™ 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 QUATERNA™ (see **What the medicinal ingredients are** and **What the non medicinal ingredients are**)

You should not be taking QUATERNA™ with hepatitis C drug combinations containing, glecaprevir / pibrentasvir and

sofosbuvir / velpatasvir / voxilaprevir. This may increase levels of the liver enzyme "alanine aminotransferase" (ALT) in the blood.

What the medicinal ingredients are:

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

What the non medicinal ingredients are:

Each bluish-green tablet contains the following non medicinal ingredients: lactose monohydrate, polacrilin potassium, D&C Yellow No. 10, FD&C Blue No. 1 aluminum lake, FD&C Yellow No. 6, magnesium stearate.

Each yellow tablet contains the following non medicinal ingredients: anhydrous and monohydrate lactose, microcrystalline cellulose, polacrilin potassium, D&C Yellow No. 10 aluminum, FD&C Yellow No. 6/Sunset yellow FCF aluminum lake, povidone, dl-α-tocopherol, magnesium stearate and isopropyl alcohol (in traces).

What dosage forms it comes in:

QUATERNA™ (levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg combination and ethinyl estradiol 0.01 mg) tablets are available in Extended-Cycle Tablet Blister Card. Altogether, the Tablet Blister Card holds 91 tablets consisting of 84 bluish-green tablets (each containing 0.15 mg of levonorgestrel and 0.03 mg ethinyl estradiol) and 7 yellow tablets (each containing 0.01 mg ethinyl estradiol).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

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

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

QUATERNA™ Oral Contraceptive

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

BEFORE you use QUATERNA™ talk to your doctor or pharmacist if you:

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

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

Skin pigmentation (brown patches on the skin) may occur with combination oral contraceptives including QUATERNA™. Women developing brown patches should avoid exposure to the sun or ultraviolet radiation while taking QUATERNA™.

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 QUATERNA™.

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

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

THE RISKS OF USING QUATERNA™

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

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

- sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung.
- pain and/or swelling in the calf. These symptoms could indicate a possible blood clot in the leg.

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

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

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

2. Breast cancer

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

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

ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF EXAMINATION OF YOUR BREASTS.

3. Cervical cancer

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

4. Liver tumours

The short and long-term use of birth control pills have also been linked with the growth of liver tumours. Such tumours are **extremely** rare.

Contact your doctor immediately if you experience severe pain or a lump in the abdomen.

5. Gallbladder disease

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

6. Use in pregnancy

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

7. Use after pregnancy, miscarriage or an abortion

Your doctor will advise you of the appropriate time to start the use of QUATERNA™ after childbirth, miscarriage, or therapeutic abortion.

8. Pregnancy after stopping QUATERNA™

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

- drugs used for the treatment of epilepsy (e.g. primidone, phenytoin, barbiturates,carbamazepine, lamotrigine, oxcarbazepine, topiramate, felbamate),
- drug used for the treatment of tuberculosis (e.g. rifampin, rifabutin)
- drugs used for the treatment of HIV infection (e.g. ritonavir, nevirapine)
- antibiotics (e.g. penicillins, tetracyclines) for infectious diseases; you may be at higher risk of a specific type of liver dysfunction if you take troleandomycin and oral contraceptives at the same time.
- Cyclosporine
- antifungals (griseofulvin)
- the herbal remedy St. John's Wort (primarily used for the treatment of depressive moods)
- cholesterol-lowering drugs (e.g. clofibrate)
- antihypertensive drugs (for high blood pressure)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (e.g. benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- pain medication (meperidine)
- antidepressants (e.g. clomipramine)
- some nutritional supplements (e.g. Vit. B_{12}, folic acid)
- antacids (use 2 hours before or after taking QUATERNA™
- hepatitis C drug combinations containing, glecaprevir / pibrentasvir and sofosbuvir / velpatasvir / voxilaprevir

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

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

PROPER USE OF THIS MEDICATION

1. BE SURE TO READ THESE DIRECTIONS:

- Before you start taking your pills.
- Anytime you are not sure what to do.

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

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

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

5. MISSING PILLS CAN ALSO CAUSE SPOTTING OR LIGHT BLEEDING, even when you make up these missed pills. On the days you take 2 pills to make up for missed pills, you could also feel a little sick to your stomach.

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

7. IF YOU HAVE TROUBLE REMEMBERING TO TAKE QUATERNA™, talk to your healthcare provider about how to make pill-taking easier or about using another method of birth control.

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

BEFORE YOU START TAKING QUATERNA™

1. DECIDE WHAT TIME OF DAY YOU WANT TO TAKE YOUR PILL. It is important to take it at about the same time every day.

LOOK AT YOUR EXTENDED-CYCLE TABLET BLISTER CARD. Your Blister Card 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 bluish-green pills (active pills with two hormones) and 7 yellow pills (pills with one hormone). Trays 1 and 2 each contain 28 bluish-green pills (4 rows of 7 pills). Tray 3 contains 35 pills consisting of 28 bluish-green pills (4 rows of 7 pills) and 7 yellow pills (1 row of 7 pills).

ALSO FIND:

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

2. BE SURE YOU HAVE READY AT ALL TIMES ANOTHER KIND OF BIRTH CONTROL (such as condoms or spermicides), to use as a back-up in case you miss pills.

WHEN TO START QUATERNA™

1. Take the first bluish-green pill on the *Sunday after your period starts*, even

if you are still bleeding. If your period begins on Sunday, start the first bluish-green pill that same day.

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

HOW TO TAKE QUATERNA™

1. **Take one pill at the same time every day until you have taken the last pill in the tablet blister card.**

   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 BLISTER CARD.**
   After taking the last yellow pill, start taking the first bluish-green pill from a new Extended-Cycle Tablet Blister Card **the very next day** regardless of when your period started. This should be on a Sunday.

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

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

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

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

Missed Dose:

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

If you **MISS two** bluish-green pills in a row:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You COULD BECOME PREGNANT if you have sex in the *7 days* after you restart your pills. You MUST use another birth control method (such as condoms or spermicide) as a back-up on the 7 days after you restart your pills.

If you **MISS 3 OR MORE** bluish-green pills in a row:
1. Do not remove the missed pills from the pack as they will not be taken. Keep taking 1 pill every day as indicated on the pack until you have completed all of the pills in the pack. For example: if you resume taking the pill on Thursday, take the pill under "Thursday" and do not take the previous missed pills. You may experience bleeding during the week following the missed pills.
2. You COULD BECOME PREGNANT if you have sex during the days of missed pills or during the first 7 days after you restart your pills.

3. You **must** use a non-hormonal birth control method (such as condoms or spermicide) as a back-up when you miss pills and for the first 7 days after you restart your pills. **If you miss your period when you are taking the yellow pills, call your healthcare professional because you may be pregnant.**

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

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

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED

1. Use a **BACK-UP METHOD** anytime you have sex.
2. **KEEP TAKING ONE PILL EACH DAY** until you can consult your healthcare professional.

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

Non-contraceptive Benefits of Birth Control Pills

Several health advantages have been linked to the use of birth control pills:

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects have been observed in studies of women taking levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets:

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

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

In the post-market period, there have been cases of stroke, deep vein thrombosis and pulmonary embolism (blood clots in the

brain, arms or legs and lungs) reported with the use of levonorgestrel / ethinyl estradiol tablets and ethinyl estradiol tablets.

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

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

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

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

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

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

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

HOW TO STORE IT

Store between 15°C to 30°C.

Keep out of reach of children and pets.

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

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document can be found at: www.mylan.ca.

The full Product Monograph prepared for health professionals can be obtained by contacting the sponsor, Mylan Pharmaceuticals ULC at: 1-844-596-9526.

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