PRODUCT MONOGRAPH

PrLINESSA® 21 and PrLINESSA® 28

desogestrel and ethinyl estradiol tablets, USP

0.100 mg, 0.025 mg
0.125 mg, 0.025 mg
0.150 mg, 0.025 mg

Oral Contraceptive

Aspen Pharmacare Canada Inc.
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M5C 1S2

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets/ 0.100 mg desogestrel and 0.025 mg ethinyl estradiol 0.125 mg desogestrel and0.025 mg ethinyl estradiol 0.150 mg desogestrel and 0.025 mg ethinyl estradiol	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

LINESSA® (desogestrel and ethinyl estradiol tablets, USP) is indicated for:

- prevention of pregnancy

CONTRAINDICATIONS

Combined hormonal contraceptives (CHCs) should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during CHC use, the product should be stopped immediately.

- LINESSA® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Presence or history of venous thrombosis (deep vein thrombosis, pulmonary embolism);
- A history of actual cerebrovascular disorders;
- Presence or history of arterial thrombosis (myocardial infarction, cerebrovascular accident) or prodromal conditions (e.g., transient ischaemic attack, angina

pectoris);

- valvular heart disease with complications
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Presence or history of liver tumours (benign or malignant);
- known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or of the breast);
- undiagnosed abnormal vaginal bleeding;
- Steroid-dependent jaundice, cholestatic jaundice, history of jaundice of pregnancy;
- 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;
- current or history of migraine with focal aura;
- history of actual pancreatitis if associated with severe hypertriglyceridemia.
- Known predisposition for arterial or venous or thrombosis:
  - severe hypertension (persistent values of ≥160/100 mmHg)
  - 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, hyperhomocysteinemia (eg, due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - severe dyslipoproteinemia
  - smoking and over age 35
  - diabetes mellitus with vascular involvement
  - major surgery associated with an increased risk of postoperative thromboembolism (see **WARNINGS AND PRECAUTIONS**)
  - prolonged immobilization (see **WARNINGS AND PRECAUTIONS**)
- Major surgery with prolonged immobilisation
- LINESSA® is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir with or without dasabuvir (see section **WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS**).

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, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including LINESSA®, should not be used by women who are over 35 years of age and smoke (see **Cardiovascular** section below).

Patients should be counseled that birth control pills **DO NOT PROTECT** against sexually

transmitted infections including HIV/AIDS. For protection against STIs, patients should be counseled to use condoms **IN COMBINATION WITH** birth control pills.

General

Discontinue Medication at the Earliest Manifestation of:

A. Thromboembolic and cardiovascular disorders, such asthrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.
B. Conditions which predispose to venous stasis and to 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.
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

Throughout this section the general term combined hormonal contraceptives (CHC) is used when data exist for oral and non-oral contraceptives. The term combined oral contraceptives (COC) is used when data exist only for oral contraceptives.

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, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), sickle cell disease, valvular heart disease and atrial fibrillation.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COC's has not been firmly established:: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria, systemic lupus erythematosus, hemolytic uremic syndrome, Sydenham's chorea, herpes gestationis, and otosclerosis-related hearing loss, (hereditary) angioedema

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 oral contraceptives with lower doses of both estrogen and progestogen 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 at 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, estrogen-containing drugs 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 Combination Oral Contraceptives (COCs) may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to the confounding effects, e.g., 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.

Cardiovascular

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 in 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.

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.

Lactose Intolerance
LINESSA® contains < 65 mg lactose per tablet. Patients with lactase deficiency including Lapp lactase deficiency or glucose-galactose malabsorption on lactose-free diet, should consider this excipient when considering LINESSA® for contraception.

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.

Genitourinary

Vaginal Bleeding
Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

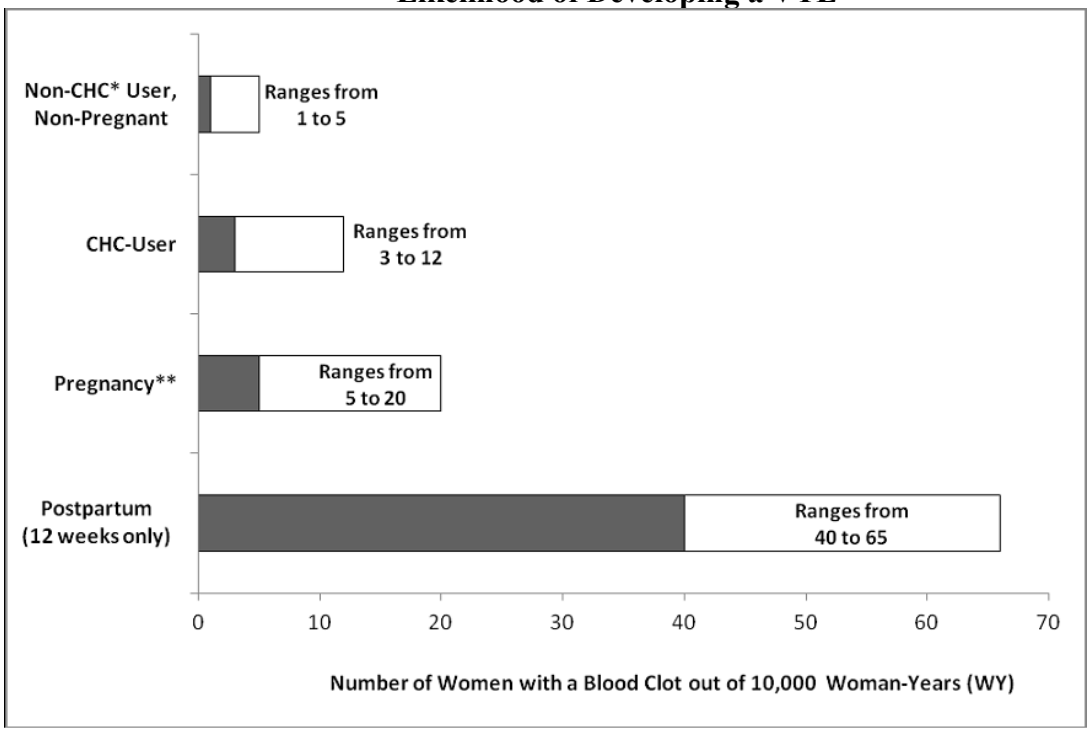
Fibroids
Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness requires discontinuation of the use of oral contraceptives.

Hematologic
Epidemiological studies have shown an association between the use of CHCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism.

Epidemiological studies have shown that the incidence of venous thromboembolism (VTE) in users of CHC with low estrogen content (<50 mcg ethinyl estradiol) ranges from about 3 to 12 cases per 10,000 women-years, but this risk estimate varies according to the progestogen. This compares with 1 to 5 cases per 10,000 women-years for non-CHC users.

The use of CHC 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 CHC. The risk is also increased when patients initially start a CHC or restart the same or different CHC after a break in use of 4 weeks or more. The increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 5 to 20 cases per 10,000 women-years or the risk in the postpartum period which is estimated as 40-65 cases per 10,000 women-years. VTE is fatal in 1-2% of cases. The figure below shows the risk of developing a VTE for women who are not pregnant and do not use CHCs, for women who use CHCs, for pregnant women, and for women in the postpartum period.

Likelihood of Developing a VTE



*CHC=combined hormonal contraception

**Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10 000 WY.

Several epidemiological studies indicate that third generation oral contraceptives, including those containing desogestrel, are associated with a higher risk of venous thromboembolism than certain second generation oral contraceptives. These studies indicate an approximate 2-fold difference in risk, which corresponds to 1-2 cases of venous thromboembolism per 10,000

women-years of use. However, data from additional studies have not shown this difference in risk.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g., hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in CHC users.

Symptoms of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident can include: unilateral leg pain and/ or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen.

Other Risk Factors for Venous Thromboembolism
risk of venous thromboembolism increases with:

- increasing age;
- a personal history,
- a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary or acquired predisposition for venous thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any CHC use.
- obesity (body mass index >30 kg/m^2)
- smoking
- systemic lupus erythematosus.
- and possibly also with superficial thrombophlebitis and varicose veins and;

- The risk of VTE may be temporarily increased with prolonged immobilization, major surgery, any surgery to the legs or major trauma. In these situations, it is advisable to discontinue CHC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation (see **CONTRAINDICATIONS**).

Patients with superficial thrombophlebitis and varicose veins and leg cast should be closely supervised.

Other Risk Factors for Arterial Thromboembolism

The risk of arterial thromboembolic complications increases with:

- increasing age;
- smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- dyslipoproteinaemia;
- obesity (body mass index over 30 kg/m^2);
- hypertension;
- migraine;

- valvular heart disease;
- atrial fibrillation;
- a positive family history (i.e. arterial thrombosis ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use.

The increased risk of thromboembolism in the puerperium must be considered when LINESSA® is being considered for contraception.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the healthcare professional should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis. Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

Hepatic/Biliary/Pancreatic

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal.

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 hormonal contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir /paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations greater than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs) (see section CONTRAINDICATIONS and

DRUG INTERACTIONS). LINESSA® should be discontinued prior to starting therapy with the combination drug regimen ombitsavir/partaprevir/ritonavir and dasabuvir with or without ribavirin. LINESSA® can be restarted 2 weeks following completion of therapy for HCV. The contraceptive efficacy of LINESSA® may be reduced in patients taking HCV or other hepatically cleared medication.

Gallbladder Disease
Patients taking 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.

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.

Immune

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

Neurologic

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

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

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

Psychiatric
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 cases of a serious recurrence, a trial of an alternate method of contraception should be made which may help to

clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

Renal

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

Sexual Function/Reproduction

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

Amenorrhea
In some women, withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to directions, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to directions prior to the first missed withdrawal bleed, or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued. Women having 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 that 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).**

Skin
Chloasma may occasionally occur with use of COCs, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

Special Populations

Pregnant Women:
Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with LINESSA®, further intake should be stopped. 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 breastfeeding women, the use of oral 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 and 0.02% of the daily maternal dose of ethinyl estradiol could be transferred to the newborn via milk. Adverse effects on the child have been reported, including jaundice and breast enlargement. The nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

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

Use of this product before menarche is not indicated.

Geriatrics
LINESSA® is not indicated for use in postmenopausal women.

Monitoring and Laboratory Tests

Physical Examination and Follow-up
, Prior to the initiation or reinstitution of LINESSA® a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and if clinically indicated physical examination should be performed, guided by the contra-indications and warnings.

In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (e.g., 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 woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman.
The first follow-up visit should be done three months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per 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 combination hormonal contraceptives:

- arterial and venous thromboembolism

- benign and malignant 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 combination hormonal contraceptives: nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10% or less 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
- angioedema (exogenous estrogens may induce or exacerbate symptoms of angioedema in women with hereditary angioedema) [a]
- auditory disturbances
- breakthrough bleeding
- breast changes: tenderness, enlargement, and secretion
- cataracts
- changes in appetite
- change in corneal curvature (steepening)
- changes in glucose tolerance or effect on peripheral insulin resistance
- changes in libido
- change in menstrual flow
- change in weight (increase or decrease)
- chloasma or melasma which may persist
- cholestatic jaundice
- chorea
- Crohn's disease
- cystitis-like syndrome
- diarrhea
- dizziness
- dysmenorrhea
- edema
- endocervical hyperplasias
- erythema multiforme
- erythema nodosum
- gallstone formation[a]
- gastrointestinal symptoms (such as abdominal cramps and bloating)
- headache
- hemolytic uremic syndrome
- hemorrhagic eruption

- herpes gestationis[a]
- hirsutism
- hypersensitivity
- hypertension [a]
- hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- impaired renal function
- increase in size of uterine leiomyomata
- intolerance to contact lenses
- jaundice related to cholestasis[a]
- liver function disturbances
- loss of scalp hair
- mental depression
- migraine
- nervousness
- optic neuritis
- otosclerosis-related hearing loss[a]
- pancreatitis
- porphyria
- possible diminution in lactation when given immediately post-partum
- premenstrual-like syndrome
- pruritus related to cholestasis[a]
- rash (allergic)
- Raynaud's phenomenon
- reduced tolerance to carbohydrates
- retinal thrombosis
- rhinitis
- spotting
- Sydenham's chorea[a]
- Systemic lupus erythematosus[a]
- temporary infertility after discontinuance of treatment
- ulcerative colitis
- urticaria
- vaginal candidiasis
- vaginal discharge
- vaginitis

[a]Occurrence or deterioration of conditions for which association with COC use is not conclusive.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse drug 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.

Two multicenter 6-cycle controlled efficacy and safety studies were conducted in 5,552 women.

A list of adverse events experienced by > 1% of the subjects is listed in Table 1.

Table 1: Incidence of All Adverse Experiences (>1%) (All Subjects Treated Group) to LINESSA®

	Incidence During Study	
Preferred (WHOART) Term	**n**	**%**
LINESSA® (Number of Subjects)	**(n=2768)**	
Body as a Whole-General		
Influenza-like symptoms	97	3.5
Back pain	80	2.9
Allergy	59	2.1
Fatigue	48	1.7
Fever	29	1.0
Central & Peripheral Nervous System		
Headache	420	15.2
Migraine	34	1.2
Gastrointestinal System		
Nausea	225	8.1
Diarrhea	61	2.2
Flatulence	53	1.9
Dyspepsia	46	1.7
Vomiting	43	1.6
Abdominal pain	33	1.2
Metabolic & Nutritional		
Weight increase	64	2.3
Musculoskeletal system		
Myalgia	40	1.4
Arthralgia	37	1.3
Psychiatric	117	4.2
Emotional Lability	45	1.6
Depression	30	1.1
Insomnia	28	1.0
Nervousness		
Reproductive, Female	181	6.5
Intermenstrual bleeding	150	5.4
Dysmenorrhoea	139	5.0
Breast pain female	132	4.8
Moniliasis genital	57	2.1
Vaginitis	36	1.3
Pelvic cramping		
Resistance Mechanism	30	1.1
Herpes simplex		
Respiratory System	328	11.8

	Incidence During Study	
Preferred (WHOART) Term	**n**	**%**
LINESSA® (Number of Subjects)	**(n=2768)**	
Upper respiratory tract infection	227	8.2
Sinusitis	134	4.8
Pharyngitis	70	2.5
Bronchitis	50	1.8
Coughing	51	1.8
Rhinitis		
Secondary Terms-Events	51	1.8
Cervical smear test PAP II	47	1.7
Inflicted injury		
Skin & Appendages	80	2.9
Acne	35	1.3
Rash		
Urinary System	112	4.0
Urinary tract infection	30	1.1
Cystitis		

Notes: This table contains all adverse events which occurred during treatment, including those deemed to be not related or unlikely related, in addition to those which were deemed to be possibly related, probably related and related.

This table contains counts of subjects. Within each treatment group, percentages based on the number of subjects with an event or without an event divided by the total number of subjects in each demographic subgroup. Adverse experiences that stopped before first dose date or started after last dose date were excluded from this table.

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

Rare adverse events (<1%) which were observed in clinical trials and deemed to be at least possibly related to LINESSA® are as follows:

Body as a whole-general: Chest pain, crying abnormal, hot flushes, leg pain, edema, peripheral edema, pain, rigors, syncope, vertebral disk disorder.
Cardiovascular, general: Hypertension
Central & peripheral nervous system: leg Cramps, dizziness, involuntary muscle contractions, tremor
Gastrointestinal system: Constipation, eructation, irritable bowel syndrome
Hearing & vestibular: Ear disorder, earache, motion sickness
Liver & biliary system: Bilirubinaemia, cholecystitis, cholelithiasis, increased hepatic enzymes, abnormal hepatic function, SGOT increased, SGPT increased
Metabolic & nutritional: Hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia, LDH increased, generalised edema, edema of the legs, peripheral edema
Neoplasms: Breast fibroadenosis, female breast neoplasm, cervical uterine polyp, ovarian cyst, uterine fibroid
Platelet bleeding & clotting: Epistaxis, gingival bleeding, purpura
Psychiatric: Agitation, anorexia, anxiety, increased appetite, impaired concentration, confusion, dyspareunia, decreased libido, neurosis, somnolence, suicide attempt

Red blood cell: Anaemia
Female reproductive system: Amenorrhea, breast discharge, breast engorgement, breast enlargement, cervicitis, cervix lesion, non-puerperal lactation, leukorrhea, menorrhagia, menstrual disorder, ovarian pain, female perineal pain, premenstrual tension, uterine contractions, uterine haemorrhage, vaginal bleeding, vaginal discomfort, vaginal haemorrhage, vulva disorder
Resistance mechanism: Infection, viral infection
Secondary terms, events: Ectropion
Skin & appendages: Alopecia, chloasma, dermatitis, eczema, erythema nodosum, folliculitis, abnormal hair texture, hypertrichosis, melanosis, abnormal pigmentation, pruritus, genital pruritus, skin discolouration, dry skin, increased sweating
Urinary system: Dysuria, haematuria, micturition frequency, abnormal urine
Vascular: Flushing, thrombophlebitis, deep vein disorders
Vision: Photophobia, abnormal vision, xerophthalmia
White cell & reticular endothelial system: Lymphadenopathy

Post-Market Adverse Drug Reactions

Additional adverse events which have been reported occasionally since the introduction of LINESSA® to the market include: peripheral edema, cyst, hypoaesthesia, menorrhagia, metrorrhagia, mood swings, abdominal distention, bleeding tendency, angioneurotic edema, drug exposure during pregnancy, pruritic rash, emotional lability, back pain, pollakiuria, fluid retention, pruritis, frequent bowel movements**.** These adverse events are compiled from spontaneous reports and are listed regardless of whether or not there was a possible causal relation to LINESSA®**.**

The most serious undesirable effects associated with the use of COCs are listed in WARNINGS AND PRECAUTIONS. Other side effects that have been reported in users of COCs but for which the association has been neither confirmed nor refuted are found in Table 2.

Table 2: Post Market Adverse Events occurring with Combined Oral Contraceptives

Body system	Common (more than / equal to 1/100)	Common/Uncommon (more than/ equal to 1/1000 and less than 100)	Rare (less than 1/1000)
Immune system disorders			Hypersensitivity
Metabolism and nutrition disorders		Fluid retention	
Psychiatric disorders	HeadacheDepressed mood, mood altered, Libido decreased		Libido increased
Nervous system disorders	Headache, Migraine		
Eye disorders			Contact lens intolerance

Vascular disorders			Venous thromboembolism[2] Arterial thromboembolism[2]
Gastrointestinal disorders	Nausea, , abdominal pain, Vomiting, diarrhea		
Skin and subcutaneous tissue disorders		Rash, urticaria	Erythema nodosum, erythema multiforme
Reproductive system and breast disorders	Breast pain, breast tenderness,	Breast enlargement	Vaginal discharge, breast discharge
Investigations	Weight increased		Weight decreased

[1] The most appropriate MedDRA term (version 6.1) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed but should be taken into account as well.

[2] Incidence in observational cohort studies of $\geq$ 1/10000 to < 1/1000 women-years.

DRUG INTERACTIONS

Overview

Interactions between desogestrel/ethinyl estradiol and other medicinal products have been reported in the literature which may alter the response to either agent (see Drug-Drug Interactions). No formal drug-drug interaction studies were conducted with LINESSA®.

Hepatic metabolism: Interactions can occur with medicinal or herbal products that induce microsomal enzymes, specifically cytochrome P450 enzymes (CYP), which can result in increased clearance reducing plasma concentrations of sex hormones and may decrease the effectiveness of combined oral contraceptives, including LINESSA®.

Enzyme induction can occur after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 28 days.

A barrier contraceptive method should be used in addition to LINESSA® during administration of the hepatic enzyme-inducing medicinal product, and for 28 days after discontinuation of the hepatic enzyme-inducing medicinal product.
For women on long-term therapy with enzyme-inducing medicinal products an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

The prescribing information of concomitant medications should be consulted to identify potential interactions.

Drug-Drug Interactions

The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent (Table 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.

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 (30)	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifampicin	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.
HCV Protease Inhibitors	Boceprevir Telaprevir	Remains to be confirmed	Use another drug or another non-hormonal method of contraception.

Class of Compound	Drug	Proposed Mechanism	Suggested Management
HIV protease inhibitors	Ritonavir	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Non-nucleoside reverse transcriptase inhibitors	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 (e.g., cyclosporine) or decrease (e.g., lamotrigine).

Table 4 - Drugs Which May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Modification of Other Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution
Alpha-II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	oral contraceptives increase clotting factors, decrease efficacy. However oral contraceptives may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another method.
	Lamotrigine	Decrease lamotrigine levels, may lead to breakthrough seizures.	Use another method.
Antidiabetic drugs	Oral hypoglycemics 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 cause sodium retention, progestin has no effect.	Use low 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.
	Antipyridine	Impaired metabolism.	Decrease dose of drug.

Class of Compound	Drug	Modification of Other Drug Action	Suggested Management
	ASA	Effects of ASA may be decreased by the short-term use of oral contraceptives.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because oral contraceptives augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing oral contraceptives can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as oral contraceptives may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol Lowering Agents	Clofibrate	Their action may be antagonized by oral contraceptives. Oral contraceptives may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		oral contraceptives have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperedine		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/HCV protease inhibitors (e.g., ritonavir, telparevir, boceprevir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine) have been studied with coadministration of oral combination hormonal contraceptives; significant changes (increase and decrease) in the mean AUC of the estrogen and progestin 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/HCV protease inhibitors for further drug-drug interaction information.

Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of estrogens or progestins, including etonogestrel, the active metabolite of desogestrel.

Pharmacodynamic interactions

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see section **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).
Therefore, LINESSA® users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. LINESSA® can be restarted 2 weeks following completion of treatment with this combination drug regimen.

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. Physicians and other health care providers should be made aware of the non-prescription products concomitantly used by the patient, including herbal and natural products.

Drug Laboratory Test Interactions
Results of laboratory tests should be interpreted in the light that the patient is on oral contraceptives. The following laboratory tests are modified.

Enzyme induction:
Enzyme induction can occur after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 28 days.

When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g., nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine), and/or combinations with Hepatitis C virus (HCV) medicinal products (e.g., boceprevir,

telaprevir), can increase or decrease plasma concentrations of progestins, including etonogestrel, the active metabolite of desogestrel, or oestrogens. The net effect of these changes may be clinically relevant.

Women receiving any of the above mentioned hepatic enzyme-inducing medicinal or herbal products should be advised that the efficacy of LINESSA® may be reduced. A barrier contraceptive method should be used in addition to LINESSA® during administration of the hepatic enzyme-inducing medicinal product and for 28 days after discontinuation of the hepatic enzyme-inducing medicinal product.

For women on long-term therapy with enzyme-inducing medicinal products an alternative method of contraception unaffected by enzyme-inducing medicinal products should be considered.

Concomitant administration of strong (e.g., ketoconazole, itraconazole, clarithromycin) or moderate (e.g., fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of oestrogens or progestins, including etonogestrel, the active metabolite of desogestrel.

Liver function tests
Aspartate Serum Aminotransferase (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
Thyroxin-binding Protein is increased as indicated by increased total serum thyroxine concentrations and decreased T_3 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 oral contraceptive therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

Non-Contraceptive Benefits of Oral Contraceptives

Several health advantages other than contraception have been reported.

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

DOSAGE AND ADMINISTRATION

Patients should be instructed to read the package insert prior to starting LINESSA® and any time they are unsure of administration. If they have additional questions they should call their doctor or clinic.

LINESSA® tablets are prescribed as a 21-day or 28-day regimen. LINESSA® tablets must be taken at approximately the same time every day until the pack is empty. The patient may begin taking LINESSA® on Day 1 of her menstrual cycle (i.e. the first day of menstrual flow) or on the first Sunday after her period begins. If the period starts on Sunday, she should start that same day.

Dosage

LINESSA® 21 (21-Day Regimen): One coloured tablet is to be taken as follows for 21 consecutive days (three weeks): light yellow for 7 days; orange for 7 days and red for 7 days. Tablets are then discontinued for one week. The patient must not be off the pill for more than seven consecutive days. A new pack will be started on the eighth day. The patient will have a period during the seven days off the pill (the bleeding may be lighter and shorter than their usual period).

LINESSA® 28 (28-Day Regimen): Tablets are taken sequentially following the arrows marked on the dispenser. One light yellow tablet is taken daily for 7 days; followed by one orange tablet for 7 days then one red tablet daily for 7 days. On the fourth week the patient will take one "inactive" green pill daily for the next seven consecutive days. A new pack will be started on the eighth day following completion of the green tablets. The patient will have a period during the seven days on the green pill. On this regimen the patient must not go a day without taking a pill.

Management of Missed Tablets

The patient should be instructed to use the following chart if she misses one or more birth control pill (light yellow, orange, or red). She should be told to match the number of pills missed with the appropriate starting time for her dosing regimen.

Sunday Start	Day One Start
Miss One Pill	**Miss One Pill**
Take it as soon as you remember and take the next pill at the usual time. This means that you might take 2 pills in one day.	Take it as soon as you remember and take the next pill at the usual time. This means that you might take 2 pills in one day.
Miss Two Pills in a Row	**Miss Two Pills in a Row**
First Two Weeks: 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills.	**First Two Weeks**: 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills.
Third Week: 1. Keep taking 1 pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Third Week**: 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**
Miss Three or More Pills in a Row	**Miss Three or More Pills in a Row**
Anytime in the Cycle: 1. Keep taking 1 pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Anytime in the Cycle**: 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**

Missing pills can cause spotting or light bleeding, even if the missed pills are made up. The woman may also feel a little sick to her stomach on the days she takes two pills to make up for missed pills.

If a woman misses pills at any time she could get pregnant. The greatest risks for pregnancy are starting a pack late or missing a pill(s) at the beginning or at the very end of the pack.

The patient should be counseled to always have another kind of birth control (such as condoms and spermicidal foam or gel) to use as a back-up in case they miss pills, and an extra full pack of pills available.
If the patient forgets more thanone pill, two months in a row, they should be instructed to talk to their doctor or clinic. The patient may require further counseling about ways to make pill-taking easier or about using another method of birth control.

NOTE to patients on the 28-day regimen (LINESSA® 28): If the patient forgets any of the 7 green pills (inactive pills) in Week 4, she should be advised to safely dispose of the pills she missed and then keep taking one pill each day until the pack is empty. A back-up method is not needed.

Administration
It is recommended that LINESSA® be taken at the same time each day. The patient should be counseled to associate the pill with some regular activity like eating a meal or going to bed.

The first-time user may wish to use a second method of birth control (e.g. condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back-up in case pills are forgotten while they are getting used to taking them.

If spotting, light bleeding or feeling sick to their stomach occurs during the first three months the woman should be counseled to not stop taking the pill. The problem will usually go away. If it does not subside, the patient should consult with her doctor or clinic.

The dosage regimen should not be altered (i.e. the pill should not be stopped) even if the woman does not have sex very often.

When receiving any medical treatment, patients should tell their doctor that they are using birth control pills.

Advice in case of vomiting
In case of severe gastro-intestinal disturbance, absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, the advice concerning missed tablets (DOSAGE AND ADMINISTRATION – Missed Dose) is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

Special Notes on Administration

When to start LINESSA®
No hormonal contraceptive use in the precedingcycle: Tablet taking should start on Day 1 of the woman's menstrual cycle or on the first Sunday after her period begins.

Switching from another combination hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch): The woman should start LINESSA® preferably on the day after the last active tablet of her previous COC, but at the latest on the day following

the usual tablet-free or inactive tablet of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using LINESSA® 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, implant) or from a progestogen-releasing intrauterine system (IUS): The woman may switch from the mini-pill to LINESSA® on any day of her cycle. Patients using a progestogen injection should start LINESSA® on the day the next injection is due. Patients using an implant or an IUS should start LINESSA® on the day it is removed. In all cases, the woman should be advised to use an additional barrier method for the first 7 days of LINESSA® use.

Following first-trimester abortion: The woman may start LINESSA® immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion: Women should be advised to start LINESSA® at day 21 to 28 after delivery or second trimester abortion, after consulting with their physician. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. 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 first menstrual period prior to starting LINESSA®.

The increased risk of VTE during the postpartum period should be considered when restarting **LINESSA®** (see **WARNINGS AND PRECAUTIONS**).

For breastfeeding women see **WARNINGS AND** PRECAUTIONS - Nursing Women.

OVERDOSAGE

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Combination oral contraceptives act by the suppression of gonadotropins. The primary mechanism of action is inhibition of ovulation, but other alterations include impaired sperm penetration and "spinnbarkeit" of the cervical mucus, and changes to the endometrium to reduce the likelihood of implantation. Receptor binding studies, as well as studies in animals and humans, have shown etonogestrel, the biologically active metabolite of desogestrel, combines high progestational activity with minimal intrinsic androgenicity. DSG in combination with EE, does not counteract the estrogen-induced increase in SHBG resulting in lower serum levels of free

testosterone.

Pharmacodynamics

The contraceptive effect of COCs is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion.

Desogestrel, the progestogen component of LINESSA®, displays low androgenic activity in relation to its progestogenic effects and may increase the HDL/LDL ratio. Like other oral contraceptives, these changes in lipid profile are associated with an increase in triglycerides.

Pharmacokinetics

Absorption

Desogestrel (DSG) is rapidly and almost completely absorbed and converted into etonogestrel, (ENG), its biologically active metabolite. Following oral administration, the relative bioavailability of desogestrel, based on the lowest and highest tablet strengths, 0.100 mg desogestrel/0.025 mg ethinyl estradiol and 0.150 mg desogestrel/0.025 mg ethinyl estradiol, compared to solution, as measured by serum levels of etonogestrel, is approximately 100%. Ethinyl estradiol is rapidly and almost completely absorbed. When the lowest and highest tablet strengths, 0.100 mg desogestrel/0.025 ethinyl estradiol and 0.150 mg desogestrel/0.025 mg ethinyl estradiol, were compared to solution, the relative bioavailability of ethinyl estradiol was 92% and 98% respectively. The effect of food on the bioavailability of LINESSA® tablets following oral administration has not been evaluated.

The pharmacokinetics of etonogestrel and ethinyl estradiol following multiple dose administration of LINESSA® tablets was determined during the third cycle in 21 subjects. After multiple dosing with LINESSA®, plasma concentrations of etonogestrel reached steady-state after four days of treatment during dosing Phases 1 and 3. During dosing Phase 2, steady-state was reached after five days of treatment. The dose-normalized AUC_{0-24} for etonogestrel was increased approximately 20% from Phase 1 to Phase 2 and approximately 10% from Phase 2 to Phase 3, indicating a possibility of time-dependent kinetics. Time dependency may be explained by a decreased clearance presumably due to increased binding of etonogestrel to sex hormone-binding globulin (SHBG). SHBG concentrations were shown to be induced by the daily administration of ethinyl estradiol. Steady state for ethinyl estradiol was reached after four days of dosing in all dosing phases. The pharmacokinetic parameters of etonogestrel and ethinyl estradiol during the third cycle following multiple dose administration of LINESSA® tablets are summarized in Table 5.

Table 5: Mean (SD) Pharmacokinetic Parameters of LINESSA® Over a 28-Day Dosing Period in the Third Cycle (n=21)

Etonogestrel					
Phase (days)	Dose[H] mg	C_{max} pg/mL	t_{max} hr	n-AUC $_{0-24}$ pgxhr/mL/mg	CL/F L/hr
1(1-7)	0.1	2163.3 (856.4)	1.6 (0.7)	196.0 (75.4)	6.1 (2.3)
2(8-14)	0.125	3241.5 (1296.5)[a]	1.1 (0.3)[a]	234.4 (85.0)[a]	5.1 (1.9)[a]
3(15-21)	0.15	3855.7 (1273.1)	1.5 (0.8)	256.6 (104.0)	4.6 (1.6)
Ethinyl Estradiol					
1(1-7)	0.025	85.4 (51.7)	1.5 (0.8)	26.4 (11.5)	43.5 (15.0)
2(8-14)	0.025	91.3 (52.2)[a]	1.2 (1.2)[a]	29.0 (15.5)[a]	41.7 (15.5)[a]
3(15-21)	0.025	90.1 (48.2)	1.2 (0.7)	28.3 (13.2)	42.5 (18.7)

[H]= Desogestrel
[a]= n=20
C_{max}= maximum serum drug concentration
t_{max}= time at which maximum serum drug concentration occurs
n-AUC_{0-2}[4]= area under the concentration-vs time curve -0 to 24 hours normalized to 1 mcg administered
CL/F- apparent clearance
Note: for information on $t_{1/2}$ for Day 21, see the ***Excretion***.

Distribution
Etonogestrel, the active metabolite of desogestrel, was found to be 98% protein bound, primarily to sex hormone-binding globulin (SHBG). Ethinyl estradiol is primarily bound to plasma albumin. Ethinyl estradiol does not bind to SHBG, but induces SHBG synthesis. Desogestrel, in combination with ethinyl estradiol, does not counteract the estrogen-induced increase in SHBG, resulting in lower serum levels of free testosterone.

Metabolism
Desogestrel: Desogestrel is rapidly and completely metabolized by hydroxylation in the intestinal mucosa and on first pass through the liver to etonogestrel. *In vitro* data suggest an important role for the cytochrome P450 CYP2C9 in the bioactivation of desogestrel. Further metabolism of etonogestrel into 6β-hydroxy, etonogestrel and 6β-13ethyl-dihydroxylated as major metabolites is catalyzed by CYP3A4. Other metabolites (i.e. 3α-OH-desogestrel, 3β-OH-desogestrel, and 3α-OH-5α-H-desogestrel) also have been identified and these metabolites may undergo glucuronide and sulfate conjugation.

Ethinyl estradiol: Ethinyl estradiol is subject to a significant degree of presystemic conjugation (phase II metabolism). Ethinyl estradiol, escaping gut wall conjugation, undergoes phase I metabolism and hepatic conjugation (phase II metabolism). Major phase I metabolites are 2-OH-ethinyl estradiol and 2-methoxy-ethinyl estradiol. Sulfate and glucuronide conjugates of both ethinyl estradiol and phase I metabolites, which are excreted in bile, can undergo enterohepatic circulation.

Excretion
Etonogestrel and ethinyl estradiol are primarily eliminated in urine, bile and feces. At steady state, on Day 21, the elimination half-lives of etonogestrel and ethinyl estradiol are 37.1±14.8 hours and 28.2±10.5 hours, respectively.

Special Populations and Conditions

Race
There is no information to determine the effect of race on the pharmacokinetics of LINESSA® tablets.

Hepatic Insufficiency
No formal studies were conducted to evaluate the effect of hepatic disease on the disposition of LINESSA®. However, steroid hormones may be poorly metabolized in patients with impaired liver function (see WARNINGS & PRECAUTIONS – Hepatic/Biliary/Pancreatic).

Renal Insufficiency
No formal studies were conducted to evaluate the effect of renal disease on the disposition of LINESSA®.

STORAGE AND STABILITY
Store between 15-30°C.

Keep in a safe place out of the reach of children and pets.

SPECIAL HANDLING INSTRUCTIONS
Any unused portion or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Dosage Forms
LINESSA® 21: Each sachet contains a blister card dispenser with 21 round film coated tablets:
- 7 light yellow containing 0.100 mg desogestrel and 0.025 mg ethinyl estradiol;
- 7 orange, containing 0.125 mg desogestrel and 0.025 mg ethinyl estradiol;
- 7 red, containing 0.150 mg desogestrel and 0.025 mg ethinyl estradiol.

LINESSA® 28: Each sachet contains a blister card dispenser with 28 round film coated tablets consistingof the same three dosing phases as the 21–day pack and an additional seven (7) green tablets which do not contain any active ingredients.

Composition
LINESSA® is a triphasic oral contraceptive containing two active components, desogestrel and ethinyl estradiol.

Each treatment cycle pack consists of three active dosing phases:
- light yellow tablets containing 0.100 mg desogestrel and 0.025 mg ethinyl estradiol
- orange tablets containing 0.125 mg desogestrel and 0.025 mg ethinyl estradiol, and
- red tablets containing 0.150 mg desogestrel and 0.025 mg ethinyl estradiol.

Inactive ingredients include vitamin E, pregelatinized starch, stearic acid, lactose monohydrate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, talc, yellow ferric oxide, (in light yellow and orange tablets), and red ferric oxide (in orange and red tablets).

The inactive green tablets contained in the 28-day treatment cycle pack contain the following inert ingredients: lactose monohydrate, corn starch, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, FD&C Blue No. 2 aluminum lake, yellow ferric oxide, and talc.

Packaging
LINESSA® 21: Push-through strips contain 21 (as listed below) round, biconvex, film coated tablets which are 5mm in diameter:
- Seven light yellow are coded TR above 0 on one side and "Organon*" on the reverse side
- Seven orange tablets are coded TR above 6 on one side and "Organon*" on the reverse side
- Seven red tablets are coded TR above 1 on one side and "Organon*" on the reverse side

LINESSA® 28: Push-through strips contain 28 (as listed below) round, biconvex, film coated tablets which are 5mm in diameter:
- Seven light yellow are coded TR above 0 on one side and "Organon*" on the reverse side
- Seven orange tablets are coded TR above 6 on one side and "Organon*" on the reverse side
- Seven red tablets are coded TR above 1 on one side and "Organon*" on the reverse side
- Seven green tablets are coded KH above 2 on one side and "Organon*" on the reverse side

The push-through strip is a polyvinylchloride (PVC)/aluminum blister consisting of PVC film backed by aluminum foil with a heat-seal coating. Each blisteris packed in a sealed aluminum laminated sachet. The sachets are packed in a printed cardboard box together with the package insert (1, 2 or 6 sachets per box).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

I. Progestogen

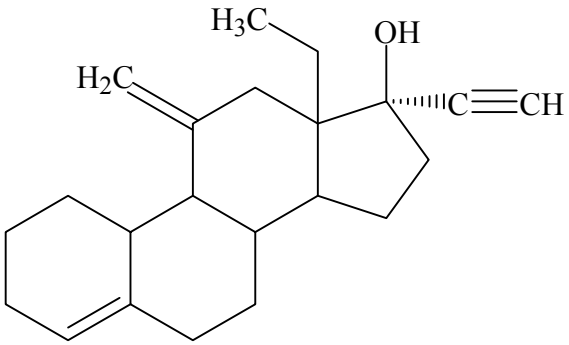
Common Name: Desogestrel

Chemical Name: 17 (α) –13- ethyl-11-methylene 18,19-dinor-pregn-4-en-20-yn-17-ol

Molecular Formula: $C_{22}H_{30}O$

Molecular Weight: 310.48

Structural Formula:



Physical Form: White, crystalline powder

Solubility: Solubility at 20°C: n-Hexane: 40 mg/mL
Ethanol (96%): > 200 mg/mL
Ethyl acetate:> 150 mg/mL
Water: Practically insoluble

Melting Point: 111 - 113 °C

II. Estrogen

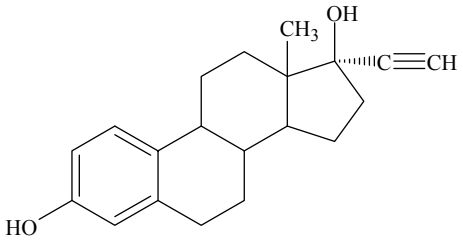
Common Name: Ethinyl Estradiol

Chemical Name: 19-nor-17α□-pregna-1,3,5(10)-trien-20-yne-3,17-diol

Molecular Formula: $C_{20}H_{24}O_2$

Molecular Weight: 296.4

Structural Formula:



Physical Form: White, crystalline powder

Solubility: Ethanol: Approximately 170 mg/mL
Acetone: Approximately 200 mg/mL
Chloroform: Approximately 50 mg/mL
Dioxane: Approximately 250 mg/mL
Diethyl ether: Approximately 250 mg/mL
Water: Practically insoluble.

Melting Point: 180-186°C

CLINICAL TRIALS

Data is provided from 2,768 subjects treated with LINESSA® who provided 14,526.8 cycles of exposure to LINESSA®, including 2,168 women who completed six cycles of exposure. The combined results of the two pivotal studies provide data to determine the Pearl Index and Life Table estimate values.

a) Pearl Index

The observed Pearl Index among LINESSA® users compares favourably to what has been reported for other low-dose oral contraceptives. Twelve of the 2,752 subjects using LINESSA® became pregnant. The Pearl Index for total pregnancies was 1.08 per 100 women-years calculated from 14,456 cycles and included 2,643 women.

b) Life Table Estimates

The six-cycle cumulative life-table pregnancy rate is estimated as 0.0051 women-years.

c) Cycle Control

Table 5 presents the incidence of intermenstrual breakthrough bleeding (IMB), early withdrawal bleeding (EWB) and absence of withdrawal bleeding (AWB), by treatment group

for all subjects in the Cycle Control Analysis Group. Breakthrough spotting occurred more frequently than breakthrough bleeding.

Table 6 summarizes the duration of withdrawal bleeding, which included early withdrawal bleeding and continued withdrawal bleeding, if any, by cycle and treatment group. The overall mean length of withdrawal bleeding, defined as "any bleeding-spotting episode that began during or continued into the active tablet-free interval" was 5.1 days for the LINESSA® Group and 4.8 days for the Triphasic Norethindrone/Ethinyl Estradiol (Net/EE) group.

Table 6: Incidence of Intermenstrual Bleeding, Early Withdrawal Bleeding and Absence of Withdrawal Bleeding by Cycle and Treatment Group

Total		**IMB**		**EWB**		**AWB**	
Cycle	N[a]	n[b]	%	n[b]	%	n[b]	%
LINESSA®							
1	2475	333	13.5	184	7.4	82	3.3
2	2401	275	11.5	156	6.2	70	2.9
3	2319	258	11.1	127	5.5	56	2.4
4	2257	210	9.3	108	4.8	52	2.3
5	2216	209	9.4	108	4.9	70	3.2
6	2093	234	11.2	108	5.2	67	3.2
Total	13761	1519	11	785	5.7	317	2.9
Triphasic Norethindrone/Ethinyl Estradiol (Net/EE)							
1	2525	567	22.5	210	8.3	133	5.3
2	2450	397	16.2	183	7.5	121	4.9
3	2358	361	15.3	149	6.4	127	5.4
4	2291	277	12.1	127	5.5	110	4.8
5	2228	253	11.4	103	4.6	114	5.1
6	2114	303	14.3	128	6.1	113	5.3
Total	13966	2158	15.5	900	6.4	718	5.1

[A] Number of subjects with a valid cycle

[b] Number of subjects with the event within each cycle

Notes: Absence of withdrawal bleeding is defined as no bleeding-spotting episode during the placebo tablet period. Early withdrawal bleeding (EWB) is defined as that portion of the withdrawal bleeding that occurred before the intake of placebo tablets.

Intermenstrual bleeding (IMB) is defined as any bleeding-spotting event that occurred during the active tablet period that was neither part of an early nor continued withdrawal bleeding.

IMB consists of breakthrough bleeding and breakthrough spotting.

Table 7: Duration of Withdrawal Bleeding by Treatment Group and Cycle

Total			
n	Mean	SD	Median
LINESSA®			
2393	5.4	2.8	5
2331	5.2	2.3	5
2263	5.2	2.2	5
2205	5.1	2.1	5
2146	5.1	2	5
2026	4.4	2	4
13364	5.1	2.3	5
NET/EE			
2392	5.1	2.4	5
2329	4.9	2	5
2231	4.9	2	5
2181	4.8	1.8	5
2114	4.7	1.8	5
2001	4.6	1.7	5
13248	4.8	2	5

The results indicate that LINESSA® cycle control is generally excellent which was also reflected in the low number of dropouts due to irregular bleeding or absence of withdrawal bleeding. These results are very similar to those obtained with other oral contraceptives.

Based on these results LINESSA® demonstrated comparable cycle control to another triphasic preparation using a 7/7/7 regimen (Net/EE).

Tolerance

Among 2,768 LINESSA® subjects in the two pivotal studies 124 (4.4%) discontinued the study due to drug-related adverse experiences and 161 (5.8%) discontinued due to any adverse experience.

The most common system-organ class for which adverse experiences resulting in discontinuation were reported was the female reproductive (1.8%).

Table 8: Overall Assessment of Adverse Experiences by Treatment Period and Treatment Group-Pivotal Clinical Studies (All Subjects Treated Group)

	LINESSA® (n=2768)		(Net/EE) (N=2784)	
	n	**%**	**n**	**%**
Adverse Experiences that Occurred Prior to Start of Study Drug				
Total of all subjects treated group	2768	100.1	2784	100.0
Subjects with an AE	126	4.6	105	3.8
Subjects with a serious AE	4	0.1	2	0.1
Subjects with AE as a cause for discontinuation	0	0.0	0	0.0
Subjects with a drug-related AE[a]	N/A	N/A	N/A	N/A
Subjects with a severe AE	17	0.6	13	0.5
Adverse Experiences that Occurred During the Treatment Period				
Total of all subjects treated group	2768	100.0	2784	100.0
Subjects with an AE	1891	68.3	1830	65.7
Subjects with a serious AE	32	1.2	34	1.2
Subjects with AE as a cause for discontinuation	159	5.7	150	5.4
Subjects with a drug-related AE[a]	936	33.8	903	32.4
Subjects with a severe AE	329	11.9	302	10.8
Adverse Experiences that Occurred During the Post-Treatment Period				
Total of all subjects treated group	2768	100.0	2784	100.0
Subjects with an AE	353	12.8	322	11.6
Subjects with a serious AE	3	0.1	10	0.4
Subjects with AE as a cause for discontinuation	2	0.1	0	0.0
Subjects with a drug-related AE[a]	56	2.0	38	1.4
Subjects with a severe AE	38	1.4	39	1.4

[a] Adverse experiences classified as related were judged as possibly, probably or definitely related.

The incidence of discontinuations due to intermenstrual bleeding was 0.8% for LINESSA® and 0.7% for (Net/EE).

Vital Signs and Weight Gain

In the two controlled clinical studies, mean systolic and diastolic blood pressure remained relatively stable; there were no clinically significant differences at any time point between LINESSA® and Net/EE. Clinically significant high pulse rates and low respiratory rates were incidental in both treatment groups. There were minimal changes in body weight and Body Mass Index (BMI) over the course of the controlled clinical studies. Mean changes in body weight ranged between a mean loss of 0.1 kg to a mean gain of 0.4 kg in the LINESSA® group while in the Net/EE group, mean changes in body weight ranged between a mean loss of 0.2 kg and a mean gain of 0.4 kg. An increase in body weight was reported by 2.3% of subjects in the LINESSA® group and 1.8% of subjects in the Net/EE group. There was a slight decrease in the mean BMI from baseline to last measurement for subjects in the LINESSA® Group (-0.1 kg/m^2) and no change for subjects receiving Net/EE.

A total of 20 (0.7%) LINESSA® - treated subjects and 10 (0.4%) subjects who received Net/EE were reported to have mild to moderate hypertension, while one subject in the LINESSA® group showed severe hypertension. Eight subjects (0.8%) in the LINESSA® group and one subject (<0.10%) in the Net/EE group discontinued due to hypertension, each of these was considered to be drug-related by the investigator. These figures should be considered in light of the fact that mild to moderate hypertension is a common condition and its prevalence is 7-13 % among women aged 20-44 years, and 20 to 50% in women aged 30-65 years.

Lipid Metabolism
The analysis of lipids included data from 2026 subjects who received LINESSA®. The observed changes in total cholesterol and triglycerides were mostly within the normal range. Results of the six-cycles exposure showed statistically significant mean percent increases in triglycerides in subjects who received LINESSA® (29.5%) when compared to Net/EE (25.0%). The weighted mean difference between LINESSA® and Net/EE was 5.37 mg/dL which represented approximately 5% of the starting values of plasma triglyceride or 3% of the normal range. Potentially clinically significant increases in cholesterol and triglycerides were seen in 0.3% and 0.2% of LINESSA® subjects, respectively, and 0.2% and 0% of NET/EE subjects, respectively.

Other metabolic parameters were minimally affected (i.e. carbohydrate metabolism).

Clinical Laboratory Results
As a class, oral contraceptives are known to be associated with decreased glucose tolerance (in pre-diabetic and diabetic women).

Pooled data from two controlled clinical studies (over 2,000 women, 6 cycles) as well as the results of two smaller clinical pharmacology studies indicate that LINESSA® has no observable adverse effects on fasting serum glucose.

In addition, there were no observable adverse effects of LINESSA® on hepatic or renal parameters, red or white blood cell indices or urinalysis tests in the two controlled clinical studies, or in the smaller phase II and clinical pharmacology studies. The incidences of adverse events related to abnormalities of these analytes during the two major trials were, in general, low and similar between the two treatment groups. Data from the other studies support these conclusions.

DETAILED PHARMACOLOGY

Animal and <u>in vitro</u> pharmacology
Animal pharmacology and <u>in vitro</u> receptor binding studies indicate that etonogestrel, the biologically active metabolite of desogestrel, is a highly selective progestational agent (see Table 8) with no estrogenic effects, and only residual androgenicity.

Table 9: COMPARISON OF RELATIVE BINDING AFFINITY OF DESOGESTREL, ETONOGESTREL AND PROGESTERONE FOR THE PROGESTERONE RECEPTOR IN UTERINE CYTOSOL. *

	RABBIT MYOMETRIUM	HUMAN MYOMETRIUM
desogestrel	5	2
etonogestrel	111	113
progesterone	32	18

*Binding affinities were determined at 4°C using the reference standard 16∀ □-ethyl-21-hydroxy-9-nor-pregn-4-ene-3,20-dione.

Desogestrel and its metabolites, other than etonogestrel and 3-keto-5α-H-desogestrel, display minimal binding affinity for the androgen receptor with respect to dihydrotestosterone, as studied in intact MCF-7 cells. The binding affinity of both etonogestrel and 3-keto-5α-H-desogestrel is approximately 1/10 of 5 □-dihydrotestosterone; suggesting a low androgenic activity. The binding affinity for the androgen receptor in intact MCF-7 cells as displayed by etonogestrel was also significantly lower than that of other progestogens.

The "selectivity index" (progestogen/androgen receptor binding affinity ratio) for etonogestrel in intact MCF-7 cells is higher than any other oral progestagen used in contraceptives.

Oral desogestrel displays weak androgenic activity, approximately 0.05 the activity of 17α - methyl-testosterone, in orchidectomized rats, using the Herschberger test.

Human pharmacology
After oral administration of desogestrel, typical anti-gonadotropic and progestational effects are observed; these include suppression of the hypothalamic-pituitary-gonadal axis; secretory transformation of an estrogen primed endometrium; impaired sperm penetration and "spinnbarkeit" of the cervical mucus.

TOXICOLOGY

Acute Toxicity Studies
Acute single-dose studies were conducted in both rats and mice, with desogestrel + ethinyl estradiol and desogestrel alone, to determine the upper limits of tolerance and to assess specific signs of toxicity. Both compounds were dosed orally by gavage or intraperitoneal as aqueous suspensions. The oral dosage level of 2000 mg/kg was about 6×10^5 times the projected human clinical dose. The intraperitoneal dosage was 500 mg/kg. Groups of 10 males and 10 females were tested with desogestrel + ethinyl estradiol and groups of 6 males and 6 females with desogestrel alone. The animals were observed for 7 days and then necropsied.

None of the test animals died during the oral or intraperitoneal studies. The oral dosed mice and rats had temporary signs of reduced activity, some motor incoordination, diminished food consumption, and other nonspecific signs related to the large dose of the test material. Likewise,

mice and rats dosed intraperitoneal showed similar signs. Some evidence of serositis (localized peritoneal irritation) was associated with the test substances.

These data are consistent with published information on other contraceptive steroids which indicate that steroids in general have a low level of toxicity in single-dose acute animal studies.

Multidose Toxicity Studies

The objective of the multidose toxicity studies was to determine whether the chronic oral administration of either desogestrel + ethinyl estradiol or desogestrel alone to mice, rats, dogs, and monkeys would induce either reversible or irreversible systemic adverse effects or cause the development of benign or malignant neoplasms. Desogestrel + ethinyl estradiol, in a ratio of 2.5:1, was employed in most multidose toxicity and multidose tumorigenicity toxicity studies and in a ratio of 5:1 in 52-, 104-week and 3-year studies in dogs and monkeys. The test compounds were administered orally by gavage to mice and rats, orally by tablet or capsule to dogs, and orally by soft drink or by intubation to monkeys.

The protocol for each of these studies was typical of that used for multidose toxicity tests in general. The doses were multiples of the human dose and generally calculated to be 2, 20, and 200 times the expected human usage levels in most multidose and tumorigenicity studies in mouse, rat and dog. In shorter studies, the duration of treatment was 26 or 52 weeks with a 4 to 13-week recovery period incorporated into the study design. In the 52-, 104-week and 3-year dog and monkey studies dose levels were 1, 10, 25 and 2, 10, and 50 times the human dose respectively.

The following table lists the study duration, species tested, and the test compounds:

Table 10: Multidose Toxicity Studies

Multidose Toxicity Studies				
Duration	Species	Drugs	Dose(mg/kg)	n
52 weeks	rat, dog	DSG + EE*	0.005+0.002[a] 0.05 +0.02 0.5 +0.2	70,14
	dog	DSG + EE	0.003+0.0006[b] 0.03 +0.006 0.075+0.015	20
	monkey	DSG + EE	0.006+0.0012[c] 0.03 +0.006 0.15 +0.03	20
80 weeks	mouse	DSG + EE	see [a]	112
104 weeks	rat	DSG + EE	see [a]	110
	dog	DSG + EE	see [b]	20
	monkey	DSG + EE	see [c]	20
3 years	dog	DSG + EE	see [b]	20
	monkey	DSG + EE	see [c]	20
26 weeks	rat, dog	DSG	0.00625 0.0625 0.625	64,14
52 weeks	rat, dog	DSG	0.005[d] 0.05 0.5	60,12
81 weeks	mouse	DSG	see [d]	112
104 weeks	rat	DSG	see [d]	110

*DSG = desogestrel EE = ethinyl estradiol

The 52-week study with desogestrel + ethinyl estradiol in rats revealed no direct treatment-associated effect on mortality. Clinical signs of treatment included alopecia and reduction of testicle size, primarily in high-dose animals, which were reversible on treatment cessation. Depressed weight gain and/or decreased food consumption was present in both sexes of the intermediate- and high-dose animals. There was an alteration in APTT, Hb, and PCV noted along with lowered neutrophil and lymphocyte counts. These changes are known to occur in these types of studies and were found to be reversible upon treatment cessation. No unusual changes were found in blood chemistry or urinalysis. Dose-related lower protein content of the urine in males may be attributed to the atrophic change in secondary sex organs.

Organ weight changes were consistent with those noted with other combination oral contraceptives. The liver weight was increased at 26 and 52 weeks in primarily intermediate-dose

(ID) and high-dose animals; testes, epididymides, prostate, seminal vesicles, ovaries, uterus, adrenals, and the pituitary gland were also affected by treatment.

Microscopic tissue changes included the following: Hepatocytic vacuolation and occasional foci of hepatocellular hyperplasia, especially in high-dose animals; a dose-related increase in yellowish pigment in the kidney cortical tubule epithelium, and increased mineralized concretions in high-dose males; atrophy of the testes, epididymides, prostate, and seminal vesicles; reduction or absence of corpora lutea in the ovaries; hyalinization or endometrial hyperplasia of the uterus; increased keratinization of the vagina in high-dose females; hypertrophy and hyperplasia of the adrenal cortex with sinusoidal telangiectasis; and hypertrophy/hyperplasia of the anterior lobe of the pituitary, especially at 52 weeks in high-dose animals.

The 8-week withdrawal period used in this study resulted in a partial reversal of the prior changes. All would have probably reverted to normal with a longer recovery period. There was an increased incidence of benign mammary neoplasms in all drug-treated groups.

The 52-week dog study was conducted with oral dosed desogestrel + ethinyl estradiol tablets in a ratio of 2.5:1. Three high-dose mortalities occurred during the study. Two females died and the other was killed in extremis. The cause of death or morbidity was peritonitis, secondary to perforating pyometra. Clinical signs included typical skin thickening and folding with alopecia, interruption of the estrous cycle with swelling of external genitalia in females, vaginal discharge in high-dose females, pendulous penile sheath in males with reduction in testicle size, enlarged and/or secretory mammary tissue in females, and 2 transients (1 intermediate-dose) and 1 transient and 1 persistent nodule (1 high-dose) of the mammary gland. The persistent nodule was an area of hyperplasia.

Changes in certain hematological, coagulation, blood chemistry and urinalysis parameters were neither unusual nor unexpected for this type of compound. Changes either in weight or histomorphological characteristics were noted in the primary and secondary sex organs and liver, primarily in high-dose animals. All were associated with the hormonal attributes of the drug.

The multidose toxicity study in the monkey was performed at a 5:1 ratio of desogestrel to ethinyl estradiol with dosing for 21 days followed by a 7-day drug-free period. The 12-month data revealed no unexpected clinical, clinicopathological, or histomorphological findings. Typical hormonal dose-related changes occurred, such as decreased corpora lutea, secretory mammary glands, increased endocervical mucus, decreased thickness of the endometrium with secretory changes, a dose-related decrease in the thickness of the vaginal epithelium and increased pituitary weight.

The multidose studies in rats and dogs with desogestrel alone resulted in fewer alterations in the primary and secondary sex organs and other peripheral hormonally sensitive tissues.

In rats, the absence of ethinyl estradiol in the test compound resulted in expected progestational changes at 26 and 52 weeks, such as secretory changes in the uterine endometrium, mucification of the vaginal epithelium, mild glandular hyperplasia of the mammary glands, and reduced

pituitary weights. In the 52-week portion of the study, a small number of benign or malignant neoplasms were observed, but none of these were causally related to the test compound.

The toxicity of multidoses of desogestrel alone in dogs resulted in no unusual or unexpected changes at 26 weeks. The liver weight in high-dose animals was increased but this was due primarily to the progestogenic effect of increased glycogen storage. The uterus was increased in both size and weight due to hormonal stimulation of the endometrium and the ovaries had a lack of mature follicles and an absence of corpora lutea. The prostate weight was slightly reduced in high-dose males. Lobular development of the mammary glands was increased in intermediate and high-dose females.

The 52-week segment of the dog study with desogestrel alone resulted in changes similar to those seen at 26 weeks; however, occasional small mammary nodules (5 mm or less) were present in 1 control (C), 1 low-dose (LD), 1 ID, and 4 high-dose animals. They disappeared in the 1 C and 2 high-dose animals. The remaining nodules were found to be nonneoplastic and proved to be either smaller superficial lymph nodes or dilated ducts. The uterine stimulation was increased at 52 weeks but did not result in the death of any animal.

Four multidose toxicity studies of up to 2 years in duration were conducted in rats, dogs, and monkeys. Desogestrel + ethinyl estradiol was studied in rats, monkeys, and dogs, and desogestrel alone was studied in rats.

In rats, there was no evidence of a neoplastic response when desogestrel was administered alone, however, increased evidence of benign mammary neoplasms was evident in all desogestrel + ethinyl estradiol-treated groups. Other clinical, clinicopathological, and histopathological changes were attributable to the hormonal influences of either desogestrel or its combination with ethinyl estradiol.

The 2-year dog study utilized a 5:1 desogestrel + ethinyl estradiol ratio. The test compound was dosed at 1, 10 and 25 times the human dosage levels for 21 days with a 7-day drug-free period. There was evidence of the following: suppression of the estrous cycle in intermediate- and high-dose animals, an increased incidence of mammary gland development and secretory activity similar to those observed in the normal metestrous phase of the cycle; decreased AP in high-dose dogs, and a single focus of ductal epithelial hyperplasia in 1 low-dose dog. No tumorigenic effect was present.

The 2-year study of desogestrel + ethinyl estradiol in monkeys caused the expected pattern of hormonally-mediated changes. Menstrual and ovarian activities were reduced in high-dose animals. Secretory activity of the mammary glands was increased in a dose-related manner in intermediate- and high-dose animals. Other hormonally-associated changes included: an increased fibrinogen and APTT; decreased PPT; reduced AP; increased triglycerides and cholesterol levels; and lowered albumen in intermediate- and high-dose animals; endometrium which was either stimulated (ID and HD) or lacked activity (some high-dose animals); and increased acidophils and decreased basophils in the pituitary in intermediate- and high-dose animals. All of these findings are consistent with contraceptive steroid effects in the monkey.

Multidose tumorigenicity studies were conducted in the mouse (80-81 months) and rat (2 years) with either desogestrel + ethinyl estradiol or desogestrel alone, respectively. Desogestrel + ethinyl estradiol in mice resulted in a higher mortality rate; this was primarily due to the increased incidence of pituitary tumors in treated mice, especially high-dose animals. Other nonneoplastic alterations occurred but were within expected limits for a compound of this type. Desogestrel alone in mice did not remarkedly affect the mortality rate and had no influence on tumorigenicity.

Desogestrel + ethinyl estradiol in the rat resulted in slightly increased mortality at the high-dose level and contributed to a dose-dependent increase in the number of pituitary and mammary neoplasms; this increase was largely attributable to the ethinyl estradiol component.

Desogestrel alone in the rat had no influence on mortality and possibly was responsible for a slight lowering effect. Incidences of mammary and pituitary tumors were slightly lessened at the high-dose level. This is in contrast to the 104-week rat study with desogestrel + ethinyl estradiol, where the differences noted were considered to have been attributable to the ethinyl estradiol component.

Three-year studies were conducted in both Beagle dogs and Rhesus monkeys with desogestrel + ethinyl estradiol with a 1- and 2-year interim sacrifice in monkey and a 2-year interim sacrifice in dogs. No tumorigenic response was noted. Mammary glands of dogs had lobulo-alveolar development with limited secretory change, an expected hormonal effect. Other tissue changes as described under the 2-year interim report, limited to the primary and secondary sex organs, were associated with the hormonal activities of the combination OC. The monkey study conducted for 3 years, with a 1- and 2- year interim sacrifice, revealed no evidence of a tumorigenic effect. The changes observed, as described at the 2-year interim studies, were typical of the hormonal activities of the combination OC and included effects on the menstrual cycle, cervical mucus and endometrial morphology.

Reproductive Toxicity Studies

Nonclinical reproductive toxicity studies included 11 studies conducted in rats and 2 studies conducted in rabbits. Desogestrel, both alone and in combination with ethinyl estradiol, was tested. These studies were conducted to assess what effect, if any, the test substance might have on the reproductive process, including; fertility and reproductive performance, teratogenicity and embryotoxicity, and perinatal and postnatal effects in the offspring.

Four segment I reproductive toxicity studies were conducted in rats; 1 study with desogestrel + ethinyl estradiol and 3 studies with desogestrel alone. The desogestrel + ethinyl estradiol study, conducted using doses of 0.5 mg desogestrel + 0.2 mg ethinyl estradiol/kg/day, demonstrated that the test compound had no adverse effect on mating and pregnancy performance in F_0 females or on the number, anatomical features, development and fertility of the offspring.

Desogestrel alone was studied in both Sprague Dawley and CFY rats. An additional study in Sprague Dawley rats was conducted after microphthalmia was increased in CFY offspring of the desogestrel -treated dams. No increase in microphthalmia was seen in the second Sprague Dawley study. The defect was thus thought to be strain-related. In all 3 studies the

contraceptive effect of desogestrel was reversible. Treatment at contraceptive and subcontraceptive dose levels did not cause any serious after-effects on the dams or their offspring.

A fertility and embryotoxicity study with desogestrel + ethinyl estradiol at levels causing complete infertility, slight infertility, and no infertility, were conducted in rats. Uninterrupted daily administration of desogestrel + ethinyl estradiol, at subcontraceptive doses before and during pregnancy, reduced the number of offspring but had no effect on the quality of the F_1 generation.

Segment II embryotoxicity studies following the classical design with dosage exclusively during pregnancy and organogenesis were performed in both the rat and rabbit. A total of 5 embryotoxicity studies were conducted; 3 studies with desogestrel alone and 2 studies with desogestrel + ethinyl estradiol.

Desogestrel + ethinyl estradiol tested at high-dose levels in rats and rabbits caused maternal toxicity and embryolethality, but at lower doses had no untoward reaction in the dams and no detectable effect on the course of pregnancy, embryonic mortality, or fetal morphology.

Desogestrel alone was tested in both Sprague Dawley and CFY rats and in rabbits. High dosages of desogestrel caused maternal toxicity (2-8 mg/kg) in rats, while doses of 2 to 4 mg/kg caused abortion in rabbits. Lower dosages in rats and rabbits caused no discernible effect on the course of pregnancy, embryonic mortality, or on fetal morphology.

The effects of desogestrel alone, when dosed during late pregnancy, were assessed in rats. Dose levels up to 4 mg/kg/day from days 14-20 of pregnancy caused neither masculinization of female fetuses nor feminization of male fetuses.

Segment III studies, to evaluate the possible effects on peri- and postnatal development due to transfer of drug through the milk, were conducted with desogestrel, either alone or in combination with ethinyl estradiol. Desogestrel + ethinyl estradiol caused reduced food consumption in intermediate and high-dose dams. Retarded pup growth persisted until weaning in the high-dose group, but there was no effect on the pre- or post-weaning physical development. Fertility of the F_1 offspring was not affected. Desogestrel alone had no effect on the treated dams, weight gain in the pups, or physical development of the pups. Fertility of the F_1 treated animals was comparable to that of the F_1 control females.

Mutagenicity Studies

The Ames test and the rat Micronucleus test were conducted on desogestrel, either alone or in combination with ethinyl estradiol. Both assays demonstrated that neither desogestrel alone nor in combination with ethinyl estradiol exert any mutagenic effect.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

LINESSA® 21 and LINESSA® 28
desogestrel and ethinyl estradiol tablets

Read this carefully before you start taking **LINESSA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **LINESSA**.

Serious Warnings and Precautions

Smoking

Cigarette smoking increases the risk of serious heart and circulation problems. This risk increases with age and with the number of cigarettes smoked. It becomes important in women older than 35 years of age, who use hormonal birth control. For this reason, combination birth control pills, including LINESSA®, should not be used by women who are over 35 years of age and smoke.

Sexually Transmitted Infections

Combination birth control pills, including LINESSA, **DO NOT PROTECT** against sexually transmitted infections (STIs), including HIV/AIDS. For protection against STIs, you must use latex or polyurethane condoms **IN COMBINATION WITH** birth control pills.

What is LINESSA used for?
LINESSA is used to prevent pregnancy.

LINESSA is a tablet, therefore it is known as a birth control pill or oral contraceptive. It has been shown to be highly effective in preventing pregnancy when taken as prescribed by your healthcare professional. Pregnancy is always more risky than taking birth control pills, except in smokers over 35.

How does LINESSA work?
LINESSA is a combination birth control pill. It contains two female sex hormones; desogestrel and ethinyl estradiol. Combination birth control pills work in two ways:

- They stop the monthly release of an egg by the ovaries.
- They change the mucus produced by the cervix. This slows the movement of the sperm through the mucus and into the uterus (womb).

Effectiveness of Birth Control Pills
Combination birth control pills are more than 99 percent effective in preventing pregnancy when:

- the pill is **taken as directed**, and
- the amount of estrogen is 20 micrograms or more.

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

The chance of becoming pregnant increases with incorrect use.

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

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

Reported Pregnancies per 100 Women per Year:

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

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

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

Non-contraceptive benefits of Combined Birth Control Pills
Several health advantages have been linked to the use of hormonal birth control.

- Reduction in the incidence of cancer of the uterus and ovaries.
- Reduction in the likelihood of developing benign (non-cancerous) breast disease and ovarian cysts.
- Less menstrual blood loss and more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and 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.

What are the ingredients in LINESSA?
Medicinal ingredients: desogestrel and ethinyl estradiol
Non-medicinal ingredients: hydroxypropyl, lactose monohydrate, methylcellulose, polyethylene glycol, starch, stearic acid, titanium dioxide, talc and vitamin E.

The yellow and orange tablets also contain yellow ferric oxide. The orange and red tablets also contain red ferric oxide.

LINESSA 28 also contains 7 green tablets containing the following non-medicinal ingredients: corn starch, FD&C Blue No.2 aluminum lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, talc, titanium dioxide and yellow ferric oxide.

LINESSA comes in the following dosage forms:
Tablets available in a 21-day or 28-day packs.

LINESSA 21 (21-Day Pack: Each sachet contains a blister card with 21 tablets for oral administration. The 21 tablets are divided into three different dosing phases;

- Seven (7) light yellow tablets containing 0.100 mg desogestrel and 0.025 mg ethinyl estradiol
- Seven (7) orange tablets containing 0.125 mg desogestrel and 0.025 mg ethinyl estradiol
- Seven (7) red tablets containing 0.150 mg desogestrel and 0.025 mg ethinyl estradiol.

LINESSA 28 (28-Day Pack): Each sachet contains a blister card with 28 tablets for oral administration. The blister pack contains the same three dosing phases as LINESSA21 with an additional seven (7) green "reminder" tablets that do not contain hormones.

Do not use LINESSA if you have or have had any of the following conditions:

- allergy (hypersensitivity) to ethinyl estradiol, desogestrel or to any of the other ingredients in LINESSA (see **What are the ingredients in LINESSA?**)
- blood clot in the legs, lungs, eyes or elsewhere, or inflammation of the veins (thrombophlebitis)
- stroke, heart attack or coronary artery disease (e.g. angina or chest pain) or a condition that may be a first sign of stroke (such as transient ischemic attack or small reversible stroke)
- disease of the heart valves with complications
- severe high blood pressure
- diabetes with complications
- problems with blood clotting that increases your risk for developing blood clots
- very high blood cholesterol or triglyceride levels
- you smoke
- migraine headaches
- you are scheduled for major surgery
- prolonged bed rest
- jaundice (yellowing of the eyes or skin), severe liver disease and your liver is not working normally
- hepatitis C and are taking combination medication such as ombitasvir/paritaprevir/ritonavir with or without dasabuvir
- liver tumor(s)
- known or suspected cancer of the breast or uterus (womb) or other estrogen-dependant 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

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LINESSA. Talk about any health conditions or problems you may have, including if you:

- smoke
- are overweight
- have a history of breast disease (e.g. breast lumps) or 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 fibroid tumours (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 haemolytic uremic syndrome
- have sickle cell disease
- have 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
- have recently given birth
- if you are unable to digest lactose or milk products, are on a lactose-free diet or have any of the following rare hereditary diseases:
    - Galactose intolerance
    - Lapp lactase deficiency
    - Glucose-galactose malabsorption

  Because lactose is a non-medicinal ingredient in LINESSA.
- have a family history of blood clots, heart attacks or strokes

Other warnings you should know about:

If you see a different healthcare professional, inform him or her that you are using LINESSA.

Tell your healthcare professional if you are scheduled for any laboratory tests since certain blood tests may be affected by birth control pills, including LINESSA.

Tell your healthcare professional if you are scheduled for MAJOR surgery or if your ability to move around will be limited for a long period of time. In these cases, you should talk to your healthcare professional about stopping the use of LINESSA four weeks before surgery and not using LINESSA for a period of time after surgery or during bed rest.

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

If you and your healthcare professional decide that, for you, the benefits of LINESSA outweigh the risks, you should be aware of the following:

The Risks of Using Combination Birth Control Pills

1. **Circulatory problems (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 clots is high during the first year a woman uses a hormonal form of birth control. The risk is also higher if you restart a hormonal birth control (the same product or a different product) after a break of 4 weeks or more. Clots may occur in many areas of the body.

   Seek immediate medical help if any of the following symptoms 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, redness, skin feeling "warm to the touch" 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, disturbance of vision or speech, 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 possible 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 birth control have a higher risk of developing blood clots, but not as high as the risk during pregnancy. 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 birth control pills 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 speed up 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 is recommended for all women.

   Ask your healthcare professional for advice and instructions on how to perform regular breast self exams.

3. **Cervical cancer**
   Some studies have found an increase in cancer of the cervix in women who use hormonal birth control pills, however, there is not enough evidence to say for sure that hormonal birth control does not cause these cancers.

Chronic infection with the Human Papilloma Virus (HPV) is believed to be the most important risk factor for cervical cancer. In women who use combination birth control pills for a long time the chance of getting cervical cancer may be slightly higher. This may not be caused by the birth control pill itself but may be related to sexual behavior and other factors.

4. **Liver tumors**
   The short and long-term use of birth control pills has been linked with the growth of liver tumors or liver injury (e.g., hepatitis and problems with how the liver works). These tumors are **extremely** rare.

   Contact your ~~doctor~~ healthcare professional immediately if you experience yellowing of the skin or eyes, dark urine, nausea, vomiting, severe pain or a lump in the abdomen.

5. **Gallbladder disease**
   Users of hormonal birth control 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. They will not prevent the pregnancy from continuing. There is no evidence, however, that the birth control pill can damage a developing child. You should check with your healthcare professional about risks to your unborn child from any medication taken during pregnancy.

7. **Use after pregnancy, miscarriage or an abortion**
   You will be at increased risk for blood clots. Your healthcare professional will advise you of the appropriate time to start the use of **LINESSA** after childbirth, miscarriage or therapeutic abortion.

8. **Pregnancy after stopping LINESSA**
   You will have a menstrual period when you stop using LINESSA. You should not get pregnant until another menstrual period occurs within four to six weeks. In this way, the pregnancy can be more accurately dated. Contact your healthcare professional for recommendations on alternate methods of birth control during this time.

9. **Use while breast feeding**
   If you are breast-feeding, consult your healthcare professional before starting LINESSA Side effects in the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. You should use another method of birth control while you are breast-feeding. The use of birth control pills is generally not recommended until the breast-feeding mother has completely weaned her child.

Certain drugs may interact with combination birth control pills and prevent them from working properly making them less effective in preventing pregnancy or causing unexpected bleeding (spotting or breakthrough bleeding).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. Also tell any doctor or dentist (or the dispensing pharmacist) who prescribes another medicine that you use LINESSA. They can tell you if you need to use an additional method of birth control and if so, for how long.

The following may interact with LINESSA:

- medicines used for the treatment of epilepsy (e.g., primidone, phenytoin, barbiturates, carbamazepine,

oxcarbazepine, topiramate, felbamate);
- medicines used for the treatment of tuberculosis (e.g., rifampicin, rifabutin)
- medicines used for treatment of HIV infections (e.g., ritonavir) and Hepatitis C Virus (e.g. boceprevir, telaprevir, ombitsavir, paritaprevir, dasabuvir)
- antibiotics used to treat bacterial infections (e.g., penicillins, tetracyclines, metronidazole)
- antifungals used to treat fungal infections (e.g. griseofulvin)
- medicines used to lower cholesterol (e.g. clofibrate)
- blood thinners used to prevent blood clots
- the herbal remedy St. John's wort used to treat depression
- medicines used to lower high blood pressure
- insulin and other medicines used to treat diabetes
- prednisone and cyclosporin used to suppress the immune system
- sedatives and hypnotics (e.g. benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- antidepressants (e.g. clomipramine)
- other medicines such as phenylbutazone, antihistamines, pain medications and medicines used to treat migraines
- some nutritional supplements (e.g. Vitamin E and Vitamin B12)
- antacids (use 2 hours before or after taking LINESSA)

LINESSA may also interfere with how other medicines work, causing LINESSA and other drugs to become less effective. You may need to use another method of birth control if you are taking drugs that interfere with LINESSA.

This is not a complete list of possible drug interactions with LINESSA. Talk to your healthcare professional for more information about interactions with other medicines.

How to take LINESSA:

1. **Read these Instructions**
   - before you start taking LINESSA, and
   - any time you are not sure what to do.

2. **Look at your pill pack** to see if it has 21 or 28 pills:
   - 21-Day Pack: 21 active pills (with hormones) [7 light yellow, 7 orange and 7 red] taken daily for three weeks, and then no pills for one week;

or

   - 28-Day Pack: 21 active pills (with hormones) [7 light yellow, 7 orange and 7 red] taken daily for three weeks, and then seven (7) [green] "reminder" pills (without hormones) taken daily for one week.

3. You may wish to use a second method of birth control (e.g. condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.

4. When receiving any medical treatment, be sure to tell your healthcare professional that you are using birth control pills.

5. **Many women have spotting or light bleeding, or may feel sick to their stomach during the first three months taking birth control pills.** If you do feel sick, do not stop taking LINESSA. The problem will usually go away. If it does not go away, check with your doctor or clinic.

6. **Missing pills also can cause some spotting or light bleeding**, even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take two pills to make up for missed pills.

7. **Do NOT stop taking LINESSA or skip any pills even if you are sick to your stomach, have bleeding between your periods or do not have sex very often.**

8. **If you miss pills at any time, you could get pregnant. The greatest risks for pregnancy are:**
   - when you start a pack late
   - when you miss pills at the beginning or at the very end of the pack.

9. **Always be sure you have ready:**
   - **Another kind of birth control** (such as condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
   - **An extra full pack of pills.**

10. **If you have vomiting or diarrhea, or if you take certain medicines,** such as antibiotics, LINESSA may not work as well. Use a back-up method, such as condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

11. **If you forget more than one pill two months in a row,** talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

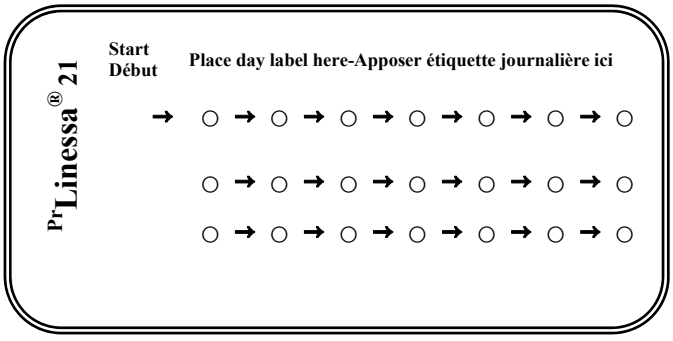
12. **If your questions are not answered here, call your healthcare professional or clinic.**

Usual Adult Dose:

Decide with your healthcare professional or clinic what day is best for you to start taking your first pack of pills. Your pills may be either a 21-day or a 28-day type.

Label the pill pack by selecting the appropriate day label strip: **Day 1** or **Sunday** start (see below for explanation). Place the day label strip in the space where you see the words "Place Day Label Here". Having the pill pack labelled with the days of the week will help remind you to take your pill every day.

A. LINESSA 21- Day Pack



With this type of birth control pill, you are on pills for 21 days and off pills for seven days. You must not be off the pill for more than seven days in a row.

If you have not used hormonal birth control in the past month:

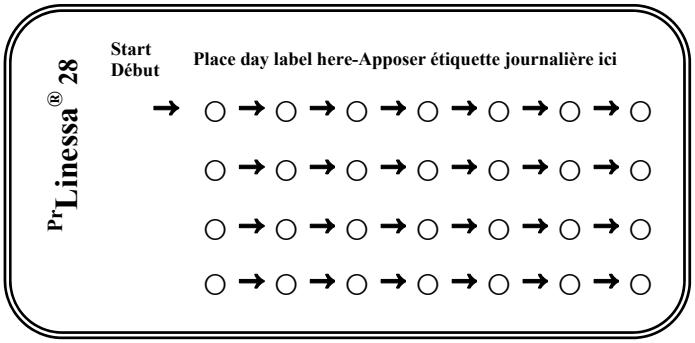
1. **The first day of your menstrual period (bleeding) is Day 1 of your cycle.** Your ~~doctor~~ healthcare professional may advise you to start taking LINESSA on Day 1 or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

2. Take one pill at approximately the same time every day for 21 days. Try to associate taking LINESSA with a regular activity such as eating a meal or going to bed. Follow the arrows marked on the pill pack (one light yellow tablet daily for 7 days, one orange tablet daily for 7 days, and one red tablet daily for 7 days).

3. **Then, do NOT take any pills for seven days**. You will probably have a period during the seven days you do not take LINESSA. This bleeding may be lighter and shorter than your usual period.

4. Start a new pack on the eighth day.

B. LINESSA 28- <u>Day Pack</u>



With this type of birth control pill, you take 21 pills that contain hormones and seven "reminder" pills that contain no hormones.

If you have not used hormonal birth control in the past month:

1. **The first day of your menstrual period (bleeding) is Day 1 of your cycle.** Your ~~doctor~~ healthcare professional may advise you to start taking LINESSA on Day 1 or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

2. Take one pill at approximately the same time every day for 28 days. Try to associate taking LINESSA with a regular activity such as eating a meal or going to bed. (Follow the arrows marked on the pill pack (one light yellow tablet daily for 7 days, one orange tablet daily for 7 days, one red tablet daily for 7 days, and one green "reminder" tablet daily for 7 days). Your period should occur during the last seven days of using the pill pack (i.e. while you are taking the green "reminder" pills).

3. Begin a new pack the next day. **DO NOT miss any days**.

If you are switching from another combined birth control (combined birth control pill, vaginal ring or transdermal patch):
Start LINESSA preferably on the day after the last active tablet (the last tablet containing hormones) of your previous combined birth control pill. If you cannot start immediately after the last active tablet of your previous birth control pill, the latest you should start is on the day following your usual tablet-free interval or following the last "reminder" tablet of your previous combined birth control pill. If a vaginal ring or transdermal patch has been used, start using LINESSA preferably on the day of removal, but at the latest when the next application would have been due.

If you are switching from a progestogen-only-method (mini-pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS):
You may switch any day from the mini-pill. From an implant or an IUS start on the day of its removal. From an injectable start when the next injection would be due. In all of these cases you should use a back-up (barrier) method for the first 7 days take LINESSA.

If you are starting following a first-trimester abortion:
You may start immediately. When doing so, you do not need to use any back-up birth control.

If you are starting following delivery of a baby or a second-trimester abortion:
You should start between days 21 and 28 after delivery or second trimester abortion. When starting later, you should use a back-up method for the first 7 days you take LINESSA. If intercourse has already occurred, you must make sure you are not pregnant or wait for your first menstrual period before starting LINESSA. If you are breastfeeding, or planning to breastfeed, talk to your healthcare professional about whether taking LINESSA is right for you.

Overdose:
Overdose may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain and fatigue/drowsiness. Withdrawal bleeding may occur.

If you think you have taken too much LINESSA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
The following chart explains what you should do if you miss one or more birth control pills. Match the number of pills missed with the appropriate starting time for your pill pack.

Sunday Start	**Day 1 Start**
Miss 1 Pill	**Miss 1 Pill**
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 pills in one day.	Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 pills in one day.
Miss 2 Pills in a Row	**Miss 2 Pills in a Row**

Sunday Start	Day 1 Start
First 2 weeks 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a non-hormonal back-up method of birth control if you have sex in the 7 days after you miss the pills.	**First 2 weeks** 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a non-hormonal back-up method of birth control if you have sex in the 7 days after you miss the pills.
Third Week: 1. Keep taking 1 pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a non-hormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **If you miss 2 periods in a row call your healthcare professional.**	**Third Week**: 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a non-hormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If you miss 2 periods in a row call your healthcare professional.**
Miss 3 or More Pills in a Row	**Miss 3 or More Pills in a Row**
Anytime in the Cycle: 1. Keep taking 1 pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a non-hormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **If you miss 2 periods in a row call your healthcare professional.**	**Anytime in the Cycle**: 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a non-hormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If you miss 2 periods in a row call your healthcare professional.**

28- Day Pack - If you forget any of the 7 green "reminder" pills in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

What are possible side effects from using LINESSA?

These are not all the possible side effects you may feel when taking LINESSA. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Side effects may include:

- headache
- painful menstrual cramps
- stomach pain
- nausea
- bronchitis, runny or stuffy nose, sore throat, common cold
- back pain
- breast tenderness
- diarrhea

- vomiting
- loss of strength, weakness, fatigue
- feeling of physical discomfort or uneasiness
- cough
- flu-like symptoms, fever
- migraine, severe headaches
- dizziness
- indigestion
- vaginal irritation or infections
- urinary tract infections or inflammation
- lack of a period or breakthrough bleeding, bleeding between menstrual periods
- weight gain
- difficulty wearing contact lenses
- acne
- insomnia, nervousness

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNCOMMON **Blood clot in the lung:** sharp pain in the chest, coughing blood, sudden shortness of breath			√
Blood clot in the leg: pain in the calf, swelling, redness, skin feeling "warm to the touch"			√
Heart attack: crushing chest pain or heaviness, heartburn, shortness of breath, nausea, cold sweat, dizziness			√
Stroke: sudden severe or worsening headache, vomiting, dizziness, fainting, vision or speech problems, weakness or numbness in the arm or leg			√
Blood clot on the eye: sudden partial or complete loss of vision or double vision			√
Liver problems including liver tumour: abnormal liver test, yellowing of the skin or eyes, dark urine, nausea, vomiting, severe pain or lump in the abdomen, loss of appetite			√
Depression: persistent sad			√

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
mood			
Edema: swelling of the arms or legs		√	
Breast changes (breast lumps/breast cancer): pain and tenderness, lumps, nipple discharge		√	
Unexpected (abnormal) vaginal bleeding		√	
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

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

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:
Store at room temperature – between 15°C - 30°C.

Keep in a safe place out of reach and sight of children and pets.

If you want more information about LINESSA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); or by contacting Aspen Pharmacare Canada Inc. at www.aspenpharma.ca or at 1-844-330-1213.

This leaflet was prepared by:

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