PRODUCT MONOGRAPH

[Pr] ESME 21 and [Pr] ESME 28

Levonorgestrel and Ethinyl Estradiol Tablets, USP

100 mcg levonorgestrel and 20 mcg ethinyl estradiol tablets

Oral Contraceptive

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Date of Revision: August 16, 2018

Submission Control No.: 218551

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[Pr] ESME 21 and [Pr] ESME 28

Levonorgestrel and Ethinyl Estradiol Tablets, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-Medicinal Ingredients
Oral	Tablet, 100 mcg levonorgestrel and 20 mcg ethinyl estradiol	Each pink tablet contains croscarmellose sodium, ferric oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium lauryl sulfate. Each inactive green tablet contains croscarmellose sodium, FD&C Blue No. 1 aluminum lake (aluminium chloride, aluminium hydroxide, brilliant blue), ferric oxide (yellow), lactose monohydrate, magnesium stearate, microcrystalline cellulose and povidone.

INDICATIONS AND CLINICAL USE

ESME Tablets are indicated for:

- Conception control.
- Treatment of moderate acne vulgaris in women ≥14 years of age who, have no known contraindications to oral contraceptive therapy, desire contraception, and have achieved menarche.

Geriatrics (> 65 years of age):
ESME is not indicated for use in postmenopausal women.

Pediatrics (< 16 years of age):
Safety and efficacy of ESME tablets have been established in women of reproductive age. Use of this product before menarche is not indicated.

CONTRAINDICATIONS

Combination Oral Contraceptives (COCs) are contraindicated in the following:

- History of or actual thrombophlebitis or thromboembolic disorders.
- History of or actual cerebrovascular disorders.
- History of or actual myocardial infarction or coronary arterial disease.
- Deep vein thrombosis (current or history)
- Thrombogenic valvulopathies and Thrombogenic rhythm disorders
- Hereditary or acquired thrombophilias
- Migraine with focal neurological symptoms such as aura (current or history)
- Active liver disease or abnormal liver function testing.
- History of or actual benign or malignant liver tumours.
- Known or suspected carcinoma of the breast.
- Known or suspected estrogen-dependent neoplasia.
- 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.
- When pregnancy is suspected or diagnosed.
- Hypersensitivity to any of the components of ESME. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.
- Diabetes with vascular involvement
- Uncontrolled hypertension
- Pancreatitis associated with severe hypertriglyceridemia (current or history)
- Use with the anti-viral Hepatitis C Virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir and dasabuvir, with or without ribavirin (see WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic 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 hormonal contraceptive users older than 35 years of age who smoke. Women should be counselled not to smoke. (see WARNINGS AND PRECAUTIONS: Cardiovascular)

Patients should be counselled that birth control pills **DO NOT PROTECT** against sexually transmitted infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** birth control pills.

General

For any estrogen/progestin combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestin that is compatible with a low failure rate and the needs of the individual patient. New users of COCs should be started on preparations containing less than 50 mcg of estrogen.

Discontinue Medication at the Earliest Manifestation of the following:

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

B. **Conditions that 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 WARNINGS AND PRECAUTIONS: 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.**

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.

Carcinogenesis and Mutagenesis

Breast Cancer

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using COCs compared to never-users. The increased risk gradually disappears during the course of the

10 years after cessation of COC use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to an earlier detection of breast cancer in COC users, the biological effects of COCs or a combination of both. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

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

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

Cervical Cancer

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

Hepatocellular Carcinoma

ESME is contraindicated in patients with a history of or actual benign or malignant liver tumours.

Hepatocellular carcinoma may be associated with COC use. The risk appears to increase with duration of COC use. However, the attributable risk (the excess incidence) of liver cancer in OC users is extremely small.

Cardiovascular

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality from COC use. This risk increases with age and with the extent of smoking. 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, obesity or a family history of these. Whether COCs 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

COC use is contraindicated in women with uncontrolled hypertension (see CONTRAINDICATIONS)

Patients with essential hypertension whose blood pressure is well-controlled may be given COCs 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.

Increases in blood pressure have been reported in women taking COCs. Elevated blood pressure associated with COC use will generally return to baseline after stopping COCs, and there appears to be no difference in the occurrence of hypertension among ever- and never-users.

Endocrine and Metabolism

Diabetes

Glucose intolerance has been reported in COC users. Current low-dose COCs 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. Women who are predisposed to diabetes, with impaired glucose tolerance or who have diabetes mellitus should be carefully monitored if using COCs. 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 taking oral contraceptives. Nonhormonal contraception should be considered in women with uncontrolled dyslipidemias. Persistent hypertriglyceridemia may occur in a small population of combination oral contraceptive users. Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Women who are being treated for hyperlipidemias should be followed closely if they elect to use COCs.

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.

Absorption

Vomiting and/or diarrhea may reduce absorption of oral contraceptives resulting in decreased serum concentration and therefore may reduce contraceptive efficacy. Physicians should advise the patients of the need for a back-up contraceptive method in the case of such gastrointestinal symptoms.

Genitourinary

Vaginal Bleeding

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology. See also WARNINGS AND PRECAUTIONS: Sexual Function/Reproduction.

Fibroids

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

Hematologic

Venous and arterial thrombosis and thromboembolism

Use of COCs is associated with an increased risk of venous and arterial thrombotic and thromboembolic events.

Venous thrombosis and thromboembolism

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

The use of any combined oral contraceptive carries an increased risk of VTE compared with no use. Reported events include deep venous thrombosis, thrombophlebitis, pulmonary embolism and mesenteric thrombosis. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive. The increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 women-years. VTE is fatal in 1-2% of cases.

Other Risk Factors for Venous Thromboembolism

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

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 COC use.

Arterial thrombosis and thromboembolism

The use of COCs increases the risk of arterial thrombotic and thromboembolic events. Reported events include myocardial infarction and cerebrovascular events (ischemic and hemorrhagic stroke, transient ischemic attack). For information on retinal vascular thrombosis see WARNINGS AND PRECAUTIONS: Ophthalmologic.

The risk of arterial thrombotic and thromboembolic event is further increased in women with underlying risk factors. Examples of risk factors for arterial thrombotic and thromboembolic events are smoking, hypertension, hyperlipidemias, obesity and increasing age. Caution must be exercised when prescribing COCs for women with risk factors for arterial thrombotic and thromboembolic events.

Hepatic/Biliary/Pancreatic

Hepatic Function

ESME is contraindicated in patients with active liver disease or abnormal liver function testing (see CONTRAINDICATIONS and DRUG INTERACTIONS: Drug-Laboratory Test Interactions).

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

Hepatitis C

During clinical trials with patients treated for HCV infections with the combination of ombitasvir, paritaprevir, ritonavir and dasabuvir with or without ribavirin, it was found that transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinyl estradiol-containing medications such as COCs. Therefore ESME 21 and ESME 28 are contraindicated in hepatitis C patients during treatment with these drugs (see CONTRAINDICATIONS and DRUG INTERACTIONS).

Gallbladder Disease

For women with symptomatic gall bladder disease, consideration should be given to whether the benefits of COCs outweigh the risks. COC use these patients may worsen existing disease.

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, and in this instance, ESME should be discontinued.

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.

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.

Hepatocellular injury has been reported with COC use. Early identification of drug-related hepatocellular injury can decrease the severity of hepatotoxicity when the drug is discontinued. If hepatocellular injury is diagnosed, patients should stop their COC, use a non-hormonal form of contraception and consult their doctor.

Pancreatic Function

Please see WARNINGS AND PRECAUTIONS: Endocrine and Metabolism: Lipid and Other Metabolic Effects.

Immune

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, particularly 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 COCs and evaluation of the cause. **(**see CONTRAINDICATIONS**)**

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 COCs, 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.

With use of COCs, there have been reports of retinal vascular thrombosis which may lead to partial or complete loss of vision. If there are signs or symptoms such as visual changes, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, the COC should be discontinued and the cause immediately evaluated.

Peri-Operative Considerations

Thromboembolic Complications – Post-surgery

There is an increased risk of thromboembolic complications in COC users after major surgery. If feasible, COCs should be discontinued and an alternative method substituted at least one month prior to **major** elective surgery and during periods of prolonged immobilization. COC use should not be resumed for at least two weeks after major elective surgery, and only after the first menstrual period has occurred following hospital discharge.

Psychiatric

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking COCs. Women with a history of depression who use COCs should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking COCs should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related. 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.

Sexual Function/Reproduction

Return to Fertility

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

Vaginal Bleeding

Breakthrough bleeding/spotting may occur in women taking COCs, especially during the first three months of use. If this bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures may be indicated to rule out pregnancy, infection, malignancy, or other conditions. Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology. If pathology has been excluded (see WARNINGS AND PRECAUTIONS: Cervical Cancer), continued use of the COC or a change to another formulation may solve the problem.

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 consecutive withdrawal bleeds are missed, tablet taking should be discontinued and a non-hormonal back-up method of contraception should be used until the possibility of pregnancy is excluded. 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 hormonal contraceptives, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should protect the affected area from exposure to the sun or ultraviolet radiation while taking hormonal contraceptives.

Special Populations

Pregnant Women

Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with ESME, 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 [10, 13, 18, 22, 23, 31]

In breast-feeding 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 (< 16 years of age)

Safety and efficacy of ESME tablets have been established in women of reproductive age. Use of this product before menarche is not indicated.

Geriatrics (> 65 years of age)

ESME is not indicated for use in postmenopausal women.

Monitoring and Laboratory Tests

Physical Examination and Follow-up

Before oral contraceptives are used, a thorough individual and family history and physical examination should be performed, including a blood pressure determination. 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 or if it is otherwise indicated.

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 Preventive Health Care.

Tissue Specimens

Pathologists should be advised of COC therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

An increased risk of the following serious adverse reactions has been associated with the use of Combined Oral Contraceptives:

- Arterial thromboembolism
- Being diagnosed with breast cancer
- Benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenomas)
- Cerebral hemorrhage
- Cerebral thrombosis
- Cervical cancer
- Cervical intraepithelial neoplasia
- Gallbladder disease, including gallstones*
- Hepatocellular carcinomas
- Hypertension
- Inflammatory bowel disease (Crohn's Disease, ulcerative colitis)
- Mesenteric thrombosis
- Myocardial infarction
- Neuro-ocular lesions (e.g. retinal thrombosis)
- Pulmonary embolism
- Stroke
- Transient ischemic attach
- Thrombophlebitis
- Venous thrombosis

* COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

The following adverse reactions also have been reported in patients receiving COCs: Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10 percent or

fewer of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally.

The following adverse reactions have been reported in patients receiving COC and are believed to be drug related:

- Amenorrhea
- Breakthrough bleeding
- Breast changes: pain, tenderness, enlargement, and secretion
- Change in cervical ectropion and secretion
- Change in corneal curvature (steepening)
- Change in menstrual flow
- Change in weight (increase or decrease)
- Chloasma (melasma) which may persist
- Cholestatic jaundice
- Diminution in lactation when given immediately postpartum
- Dysmenorrhea
- Fluid retention/Edema
- Gastrointestinal symptoms (such as abdominal pain, cramps and bloating)
- Headache, including migraines
- Hepatocellular injury (e.g., hepatitis, hepatic function abnormal)
- Intolerance to contact lenses
- Mood changes, including depression
- Rash (allergic)
- Reduced tolerance to carbohydrates
- Retinal vascular thrombosis
- Spotting
- Temporary infertility after discontinuance of treatment
- Vaginitis including candidiasis

The following adverse reactions have been reported in users of COCs and the association has been neither confirmed nor refuted:

- Acne
- Aggravation of varicose veins
- Anaphylactic (anaphylactoid reactions, including very rare cases of urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms)
- Budd-Chiari syndrome
- Cataracts
- Cerebrovascular disease with mitral valve prolapse
- Changes in appetite (increase or decrease)
- Changes in libido
- Changes in Serum Lipid levels, including hypertriglyceridemia
- Colitis
- Congenital anomalies
- Cystitis-like syndrome

- Decrease in serum folate levels**
- Dizziness
- Erythema multiforme
- Erythema nodosum
- Exacerbation of chorea
- Exacerbation of porphyria
- Exacerbation of systemic lupus erythematosus
- Hemolytic uremic syndrome
- Hemorrhagic eruption
- Hepatic adenomas
- Hepatocellular Carcinomas
- Hirsutism
- Impaired renal function
- Ischemic colitis
- Loss of scalp hair
- Lupus-like syndrome
- Nervousness
- Optic neuritis***
- Pancreatitis
- Premenstrual syndrome
- Sickle-cell disease
- Vaginitis

**Serum folate levels may be depressed by COC therapy.
***Optic neuritis may lead to partial or complete loss of vision.

Clinical Trial Adverse Drug Reactions

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

Oral Contraception

Treatment-emergent adverse events were analyzed for 1,477 subjects exposed to the study drug for 7,870 cycles. One or more treatment emergent adverse events were reported for 1,106 (75%) subjects. Table-1 lists the frequency of treatment emergent adverse events that were reported by ≥ 2% of subjects.

Table - 1
FREQUENCY OF TREATMENT EMERGENT ADVERSE EVENTS THAT OCCURRED IN ≥ 2% OF SUBJECTS

Event	Number (%) of Subjects (n=1,477)
Headache	400 (27%)
Dysmenorrhea	210 (14%)
Infection	200 (14%)
Pharyngitis	146 (10%)
Abdominal pain	134 (9%)
Nausea	134 (9%)
Metrorrhagia	123 (8%)
Sinusitis	90 (6%)
Flu syndrome	84 (6%)
Vaginal moniliasis	71 (5%)
Pain	71 (5%)
Back pain	66 (4%)
Breast pain	65 (4%)
Accidental injury	64 (4%)
Acne	62 (4%)
Rhinitis	54 (4%)
Emotional lability	50 (3%)
Vaginitis	48 (3%)
Urinary tract infection	41 (3%)
Dizziness	40 (3%)
Diarrhea	40 (3%)
Bronchitis	37 (3%)
Depression	36 (2%)
Asthenia	35 (2%)
Vomiting	34 (2%)
Allergic reaction other than to study drug	33 (2%)
Amenorrhea	30 (2%)

A total of 133 (9%) subjects stopped taking the study medication because of adverse events. Some of the study events that led to subject discontinuation were considered by the medical monitor to be potentially serious: headache (21), hypertension (7), migraine (3), phlebitis (1), palpitations (1), varicose veins (1), vascular disorder (1), hypercholesterolemia/hyperlipidemia (6), depression/emotional lability (16), hypesthesia (1), abnormal vision (2), visual field defect (1), amenorrhea (8), dysmenorrhea (4), menorrhagia (6), irregular bleeding (1), menstrual bloating (1), metrorrhagia (1), fibroid growth (1).

No deaths occurred during the multicentre study.

Acne

In the two acne studies (see CLINICAL TRIALS), the safety profile of Levonorgestrel and Ethinyl Estradiol Tablets was compared with that of placebo. Treatment-emergent adverse events that were reported by ≥ 2% of patients in either treatment group are presented in Table 2.

Table 2. Percentage of Patients (≥ 2%) Reporting Treatment-Emergent Adverse Events in Either Treatment Group in Studies 0858A1-900, 901		
Adverse event	**Number (%) of Subjects**	
	Levonorgestrel and Ethinyl Estradiol Tablets (n=349)	**Placebo (n=355)**
Headache	110 (31.5)	107 (30.1)
Metrorrhagia*	77 (21.8)	14 (3.9)
Nausea	49 (14.0)	40 (11.3)
Infection	48 (13.8)	49 (13.8)
Pharyngitis	46 (13.2)	58 (16.3)
Pain	31 (8.9)	36 (10.1)
Abdominal pain	27 (7.7)	24 (6.8)
Dysmenorrhea	27 (7.7)	39 (11.0)
Accidental injury	21 (6.0)	16 (4.5)
Menstrual disorder*	21 (6.0)	8 (2.3)
Flu syndrome	19 (5.4)	20 (5.6)
Allergic reaction*	16 (4.6)	6 (1.7)
Breast pain	16 (4.6)	11 (3.1)
Rhinitis	15 (4.0)	13 (3.7)
Sinusitis	14 (4.0)	2.0 (8)
Asthenia	13 (3.7)	5 (1.4)
Back pain	12 (3.4)	12 (3.4)
Dyspepsia	12 (3.4)	2.3 (8)
Weight gain	17 (3.4)	12 (2.3)
Emotional lability*	12 (3.4)	4 (1.1)
Acne	13 (3.4)	6 (1.4)
Migraine	11 (3.2)	8 (2.3)
Dizziness	11 (3.2)	10 (2.8)
Cough increased	10 (2.9)	8 (2.3)
Vomiting	10 (2.6)	6 (1.7)
Depression	9 (2.6)	11 (2.5)
Moniliasis	7 (2.0)	8 (2.3)
Myalgia	7 (2.0)	5 (1.4)
Bronchitis	7 (2.0)	7 (2.0)
Rash	7 (2.0)	7 (2.0)
Urticaria*	7 (2.0)	0
Allergic reaction other than drug	7 (2.0)	7 (2.0)
Diarrhea	6 (1.7)	10 (2.8)
Unintended pregnancy*	2 (0.6)	12 (3.1)
* Statistically significantly different between treatment groups ($p<0.05$).		

As expected, menstrual-related events were more frequent in women treated with Levonorgestrel and Ethinyl Estradiol Tablets than with placebo. However, other adverse events often associated with oral contraceptive use, including nausea, vomiting, breast pain, headache, migraine, and weight gain, occurred at similar rates in women treated with placebo or Levonorgestrel and Ethinyl Estradiol Tablets.

Abnormal Hematologic and Clinical Chemistry Findings

See CLINICAL TRIALS

DRUG INTERACTIONS

Overview

The concurrent administration of COCs with other substances may result in an altered response to either agent. Decreased ethinyl estradiol (EE) serum concentration may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the COC. During concomitant use of EE containing products and substances that may lead to decreased EE serum concentration, it is recommended that a nonhormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of ESME. In the case of prolonged use of such substances, COCs should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased EE serum concentrations, use of a nonhormonal back-up method is recommended for at least 7 days. Longer use of a back-up method is advisable after discontinuation of substances that have led to induction of hepatic microsomal enzymes, resulting in decreased EE serum concentrations. It may sometimes take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use and rate of elimination of the inducing substance.

Reduced effectiveness of the COC, 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 COCs are prescribed.

Examples of substances that may decrease serum EE concentrations:

- Any substance that reduces gastrointestinal transit time
- *Hypericum perforatum*, also known as St. John's wort and ritonovir (possibly by induction of hepatic microsomal enzymes)
- Substances that induce hepatic microsomal enzymes, such as rifampicin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, modafinil

Examples of substances that may increase serum EE concentrations:

- Atorvastatin
- Competitive inhibitors for sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and acetaminophen (paracetamol).
- Substances that inhibit cytochrome P 450 3A4 isoenzymes such as indinavir, fluconazole and troleandomycin.
- Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with COCs.

EE may interfere with the metabolism of other drugs by inhibiting hepatic microsomal enzymes, or by inducing hepatic drug conjugation, particularly glucuronidation. Accordingly, plasma and tissue concentrations may either be increased (eg, cyclosporine, theophylline, corticosteroids) or decreased (eg, lamotrigine).

In patients treated with flunarizine, use of oral contraceptives has been reported to increase the risk of galactorrhea.

There have been reports of pregnancy when COCs were co-administered with certain antibiotics (e.g., ampicillin and other penicillins, tetracyclines).

Concomitant use with the combination drug regimen ombitasvir, paritaprevir, ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS: Hepatic/Biliary/Pancreatic). Therefore, COC users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with anti-viral HCV drug combinations such as ombitasvir, paritaprevir, ritonavir, and dasabuvir with or without ribavirin. COCs can be restarted 2 weeks following completion of treatment with an anti-viral HCV medicinal product.

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

For possible drug interactions with COCs, see DRUG INTERACTIONS: Drug-Drug Interactions: Tables 3 and 4.

Drug-Drug Interactions

Table 3*: Drugs That May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antibiotics	Ampicillin Penicillin	Intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Cotrimoxazole	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifabutin Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamide Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation, except for tetracyclines.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
Anticonvulsants	Carbamazepine	Induction of hepatic microsomal enzymes.	Use higher dose OCs (50

Table 3*: Drugs That May Decrease the Efficacy of Oral Contraceptives			
Class of Compound	**Drug**	**Proposed Mechanism**	**Suggested Management**
	Ethosuximide Felbamate Lamotrigine Oxcarbazine Phenobarbital Phenytoin Primidone Topiramate	Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	mcg ethinyl estradiol), another drug or another method.
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive sterioids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol.; this reduces OC efficacy	Use another method.
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	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart
Other Drugs	Phenylbutazone** Antihistamines** Analgesics** Antimigraine Preparations** Vitamin E	Reduced OC efficacy has been reported. Remains to be confirmed.	

*Adapted from Dickey, RP, ed.: Managing Contraceptive Pill Patients, 5th edition Creative Informatics Inc., Durant, OK, 1987
** Refer to Oral Contraceptives 1994, A Report by the Special Advisory Committee on Reproductive Physiology to the Drugs Directorate, Health Protection Branch, Health Canada

Table 4*: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Proposed Mechanism**	**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	OCs increase clotting factors, decrease efficacy. However, OCs 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	OCs may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin OC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen OC or use another method.
	Beta Blockers	Increased drug effect (decreased metabolism)	Adjust dose of drug if necessary. Monitor cardiovascular status.

Table 4*: Modification of Other Drug Action by Oral Contraceptives			
Class of Compound	**Drug**	**Proposed Mechanism**	**Suggested Management**
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of OCs.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Anti-viral hepatitis C virus	Ombitasvir Paritaprevir Ritonavir Dasabuvir	May increase the risk of ALT elevations	Concomitant use is contraindicated (see CONTRAINDICATIONS)
Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because OCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine	Use with caution.
Cholesterol-lowering Agents	Clofibrate	Their action may be antagonized by OCs. OCs may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increases serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		OCs have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All phenothiazines, Reserpine, and similar drugs.	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose OCs. 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. Increased serum levels due to decreased clearance.	Use with caution.
Vitamin B_{12}		OCs have been reported to reduce serum levels of Vitamin B_{12}.	May need to increase dietary intake, or supplement.

*Adapted from Dickey, RP, ed.: Managing Contraceptive Pill Patients, 5th edition Creative Informatics Inc., Durant, OK, 1987

Drug-Food Interactions

No data is available.

Drug-Herb Interactions

Hypericum perforatum, also known as St. John's wort causes decrease in serum EE concentration possibly by induction of hepatic microsomal enzymes.

Drug-Laboratory Interactions

Results of laboratory tests should be interpreted in the light that the patient is on COCs. The following laboratory tests are modified:

Liver Function Tests	
Bromsulphthalein Retention Test (BSP)	Moderate increase
AST (SGOT) and GGT	Minor increase
Alkaline Phosphatase	Variable increase
Serum Bilirubin	Increased, particularly in conditions predisposing to or associated with hyperbilirubinemia
Coagulation Tests	
Factors II, VII, IX, X, XII and XIII	Increased
Factor VIII	Mild increase
Platelet aggregation and adhesiveness	Mild increase in response to common aggregating agents
Fibrinogen	Increased
Plasminogen	Mild increase
Antithrombin III	Mild decrease
Prothrombin Time	Decreased
Thyroid Function Tests	
Protein-bound Iodine (PBI)	Increased
Total Serum Thyroxine (T3 andT4)	Increased
Thyroid Stimulating Hormone (TSH)	Unchanged
Free T3 Resin Uptake	Decreased
Adrenocortical Function Tests	
Plasma Cortisol	Increased

Cortisol Binding Globulin	Increased
Dehydroepiandrosterone sulfate (DHEAS)	Decreased
Miscellaneous Tests	
Serum Folate	Occasionally decreased
Glucose Tolerance Test	Variable decrease with return to normal after 6 to 12 months
Insulin Response	Mild to moderate decrease
c-Peptide Response	Mild to moderate decrease

Drug-Lifestyle Interactions

See WARNINGS AND PRECAUTIONS regarding cigarette smoking. The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine. Use with caution. There may be possible increased levels of ethanol or acetaldehyde when combined with alcohol. Use with caution.

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 may 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 reduce the incidence of ectopic pregnancy.
7. Oral contraceptives have potential effects on endometriosis.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

CONTRACEPTION:

ESME 21 TABLETS REGIMEN:
Each cycle consists of 21 days on medication and a 7-day interval without medication (three weeks on, one week off).

The dosage of ESME Tablets is one tablet daily for 21 consecutive days per menstrual cycle, according to prescribed schedule. For the first cycle of medication, the patient is instructed to take one ESME Tablet daily for 21 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1. The tablets are then discontinued for seven days (one week). Withdrawal bleeding should usually occur within three days following discontinuation of ESME.

The patient begins her next and all subsequent 21-day courses of ESME Tablets (following the same 21 days on, 7 days off) on the same day of the week that she began her first course. She begins taking her tablets seven days after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.

ESME 28 TABLETS REGIMEN:
Each cycle consists of 21 days of pink ESME Tablets (active tablets) followed by 7 days of green inert tablets (three weeks on ESME, one week on inert tablets).

The dosage of ESME Tablets is one tablet daily for 21 consecutive days per menstrual cycle, according to prescribed schedule, followed by one inert tablet daily for 7 consecutive days according to prescribed schedule. For the first cycle of medication, the patient is instructed to take one pink tablet daily for 21 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1). One green tablet is taken daily for the following seven consecutive days. Withdrawal bleeding should usually occur within three days following the discontinuation pink ESME Tablets, i.e., during the week the patient is taking the green inert tablets.

The patient begins her next and all subsequent 28-day courses of tablets on the same day of the week that she began her first course. She continues her next course of 28 tablets immediately after the last course, regardless of whether or not a period of withdrawal bleeding is still in progress. There is no need for the patient to count days between cycles because there are no "off-tablet days".

ACNE
The timing of initiation of ESME treatment for acne should follow the instructions for use of ESME for contraception (see the DOSAGE AND ADMINISTRATION information for oral contraception).

Missed Dose

The patient should be instructed to use the following chart if she misses one or more of her birth control pills. She should be told to match the number of pills with the appropriate starting time for her type of pill.

SUNDAY START	OTHER THAN SUNDAY 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 two 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 two pills in one day.
Miss Two Pills in a Row	**Miss Two Pills in a Row**
First two weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Keep taking one 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 nonhormonal back-up method of birth control if you have sex in the seven 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.**	**First two weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a nonhormonal back-up method of birth control if you have sex in the seven 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 one 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 nonhormonal back-up method of birth control if you have sex in the seven 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 nonhormonal back-up method of birth control if you have sex in the seven 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.**

Contraceptive reliability may be reduced if active tablets are missed and particularly if the missed tablets extend the tablet-free interval. If active tablets were missed and intercourse took

place in the week before the tablets were missed, the possibility of pregnancy should be considered.

Administration

Tablets for oral use.

SPECIAL NOTES ON ADMINISTRATION

Administration
It is recommended that ESME Tablets be taken at the same time each day, preferably after the evening meal or at bedtime.

ESME is effective from the first day of therapy if the tablets are begun on the first day of the menstrual cycle.

If ESME Tablets administration is initiated postpartum (no earlier than day 28 after delivery in the nonlactating mother) or after Day 1 of the first menstrual cycle, contraceptive reliance should not be placed on ESME until after the first seven consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered. Therefore, nonhormonal methods of contraception (such as condoms and spermicide) should be used for the first 7 days of tablet taking.

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

Advice in case of vomiting and/or diarrhea
If vomiting and/or diarrhea occurs within 4 hours after tablet-taking, tablet absorption may be incomplete. In such event, advice concerning the Management of Missed Tablet is outlined in the above chart. The woman must take the extra active tablet(s) needed from a backup pack.

No hormonal contraceptive use in the past month
Tablet-taking should start on day 1 of the woman's natural cycle (ie, the first day of her menstrual bleeding). Starting on days 2-7 is allowed, but for the first 7 days of tablet-taking during the first cycle, a nonhormonal back-up method of birth control (such as condoms and spermicide) is recommended.

Changing from another COC pill
The woman should start ESME 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 interval of her previous COC.

Changing from a progestin only method (progestin-only pill, implant, intrauterine device [IUD], injection)

The woman may switch any day from the progestin-only pill and should begin ESME the next day. She should start ESME on the day that a progestin-only implant or a progestin-only IUD is removed. ESME use should begin on the day that the next progestin-only injection is scheduled. In all of these situations, the woman should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking.

Following first-trimester abortion
The woman may start ESME immediately. Additional contraceptive measures are not needed.

Following delivery or second-trimester abortion
Since the immediate post-partum period is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than day 28 after delivery in the nonlactating mother or after second-trimester abortion. The woman should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking. However, if intercourse has already occurred, the possibility of pregnancy should be ruled out before the actual start of COC use or the woman must wait for her first menstrual period.

OVERDOSAGE

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

Symptoms of COC overdosage in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Oral Contraception:
Although the primary mechanism of action is inhibition of ovulation, the effectiveness of ESME Tablets may also result from other mechanisms of action, such as hostility of the cervical mucus to sperm penetration and migration.

Acne:
Acne is a disease of the pilosebaceous apparatus characterized by abnormal keratinization, increased sebum production, and bacterial colonization. While the etiology of acne is multifactorial, there is evidence that androgenic action, including stimulation of sebaceous glands, is necessary for the development of acne. The suppression of gonadotropins by

levonorgestrel and ethinyl estradiol leads to decreased ovarian production of the androgens, including androstenedione. Levonorgestrel and ethinyl estradiol also significantly reduces bioavailable serum testosterone by preserving the estrogen-induced increases in sex hormone binding globulin (SHBG).[14,30] In addition, levonorgestrel and ethinyl estradiol decreases serum levels of 3β-androstanediol glucuronide (a marker of peripheral 5 β-reductase activity).[14,30] These biochemical changes produced by the coadministration of levonorgestrel and ethinyl estradiol are consistent with improvement of acne in otherwise healthy women.

Special Populations and Conditions

Geriatrics (> 65 years of age):
ESME is not indicated for use in postmenopausal women.

Pediatrics (< 16 years of age):
Safety and efficacy of ESME tablets have been established in women of reproductive age. Use of this product before menarche is not indicated.

STORAGE AND STABILITY

Store in original packaging between 15°C and 30°C. Keep out of reach of children and pets.

ESME 21 and ESME 28 Tablets should be protected from light once opened using the protective covering provided.

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

SPECIAL HANDLING INSTRUCTIONS

None

DOSAGE FORMS, COMPOSITION AND PACKAGING

Pr ESME Tablets are available in 21-day regimen (ESME 21) and 28-day regimen (ESME 28) in blister packs.

Each package consists of 21 pink ESME Tablets, each tablet containing 100 mcg of levonorgestrel and 20 mcg ethinyl estradiol. In the 28-day regimen package, there are, in addition, 7 green tablets containing inert ingredients.

Each pink, round flat tablet with beveled edges, debossed with “405” on one side and plain on the other side contains croscarmellose sodium, ferric oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium lauryl sulfate.

Each inactive green, round, flat tablet with beveled edges, debossed with “471” on one side and plain on the other side (in ESME 28) contains croscarmellose sodium, FD&C Blue No. 1 aluminum lake (aluminium chloride, aluminium hydroxide, brilliant blue), ferric oxide (yellow), lactose monohydrate, magnesium stearate, microcrystalline cellulose and povidone.

PART II: SCIENTIFIC INFORMATION

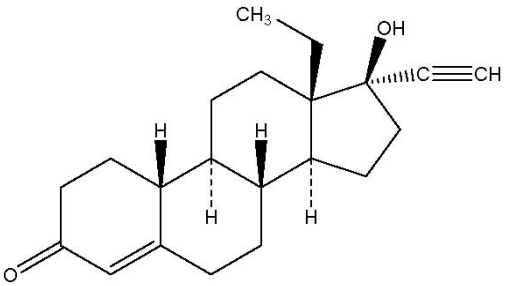
PHARMACEUTICAL INFORMATION

Drug Substance

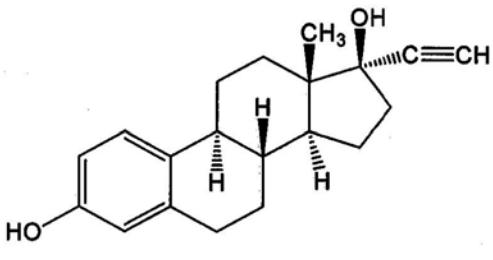
Proper name:	Levonorgestrel Ethinyl Estradiol	
Chemical name (Index):	Levonorgestrel:	18,19-Dinorpregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-,(17α)-(-)-
	Ethinyl Estradiol:	19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17 α)-
Molecular formula and molecular mass:	Levonorgestrel:	$C_{21}H_{28}O_2$
	Ethinyl Estradiol:	$C_{20}H_{24}O_2$
	Levonorgestrel:	312.45 g/mol
	Ethinyl Estradiol:	296.40 g/mol

Structural formulae:

Levonorgestrel



Ethinyl Estradiol



Physicochemical properties:

Description	Levonorgestrel:	A white or almost white, crystalline powder
	Ethinyl Estradiol:	White or slightly yellowish-white crystalline powder
Solubility:	Levonorgestrel:	Practically insoluble in water and n-hexane, slightly soluble in acetone and ethanol, sparingly soluble in dichloromethane and soluble in chloroform.
	Ethinyl Estradiol:	Freely soluble in ether, ethanol, acetone, dioxane, soluble in alkali hydroxide solutions, sparingly soluble in chloroform and practically insoluble in water.
Melting Point:	Levonorgestrel:	Between 232° C and 239°C (range should not exceed 4°C)
	Ethinyl Estradiol:	Ethinylestradiol is found to exist in an anhydrated form and a hemihydrate. The anhydrated form melts between 180°C and 185°C (according to USP: 180°C to 186°C). The hemihydrate melts between 145°C and 152°C. (In the USP monograph the melting range 142 to 146°C is assigned to a second polymorphic form, which corresponds to the melting range of the hemihydrate).

Biological Properties:	Levonorgestrel:	A unique, totally synthetic progestogen. Levonorgestrel is the International Nonproprietary Name for this biologically active enantiomer of norgestrel.
	Ethinyl Estradiol:	A semisynthetic estrogen. The presence of the ethinyl group at C 17 on ring D of the steroid nucleus prevents enzymatic degradation of the estradiol molecule and results in an orally active compound.

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY STUDY

A two-way blinded, single-dose, randomized, two-period, two-treatment, crossover, fasting bioequivalence study of ESME™ (100 mcg levonorgestrel and 20 mcg ethinyl estradiol) tablets versus Alesse® tablets (100 mcg levonorgestrel and 20 mcg ethinyl estradiol) was conducted in 34 healthy, adult female subjects. Thirty one subjects completed the study. One subject withdrew from the study for personal reasons and two subjects were discontinued due to an adverse event (vomiting).

Results from a randomized, two-way, cross-over comparative bioavailability study in which the rate and extent of absorption of levonorgestrel and ethinyl estradiol were determined and compared following the oral administration of either Mylan Pharmaceuticals ULC's levonorgestrel and ethinyl estradiol tablets, 0.1 mg/0.02 mg or Wyeth's Alesse® Tablets, 0.1 mg/0.02 mg to healthy female volunteers under fasting conditions.

Geometric Mean and Arithmetic Mean (%CV) Levonorgestrel Pharmacokinetic Parameters in Thirty-one Healthy Adult Female Subjects Following a Single Oral 0.2 mg/0.04 mg (2 x 0.1 mg/0.02 mg) Dose of Levonorgestrel and Ethinyl Estradiol Tablets under Fasting Conditions.

Levonorgestrel (2 x 0.1 mg/0.02 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng*hr/mL)	84.09 (51.75)	84.24 (66.28)	1.03	97.00% – 108.87%
AUC_I (ng*hr/mL)	120.6 (51.67)	122.4 (66.78)	1.01	95.13% – 107.54%
C_{max} (ng/mL)	5.945 (37.68)	5.758 (44.32)	1.05	98.23% – 113.21%
KEL (hr^{-1})	0.0169 (35.38)	0.0170 (34.85)		
$T_{½}$ (h)	46.07 (36.42)	48.37 (60.62)		
T_{max} (h)	1.597 (36.53)	1.825 (41.32)		

* Levonorgestrel and Ethinyl Estradiol 0.1 mg/0.02 mg tablets, Mylan Pharmaceuticals ULC
† Alesse® 0.1 mg/0.02 mg tablets, Wyeth Canada, were purchased in Canada.
Source: Module 5, Table 14.2, and Appendix 16.2.6.1

Geometric Mean and Arithmetic Mean (%CV) Ethinyl Estradiol Pharmacokinetic Parameters in Thirty-one Healthy Adult Female Subjects Following a Single Oral 0.2 mg/0.04 mg (2 x 0.1 mg/0.02 mg) Dose of Levonorgestrel and Ethinyl Estradiol Tablets under Fasting Conditions.

Ethinyl Estradiol (2 x 0.1 mg/0.02 mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg*hr/mL)	1518 (26.77)	1522 (28.70)	1.00	96.12% – 104.84%
AUC_I (pg*hr/mL)	1676 (25.25)	1709 (26.91)	0.99	95.20% – 102.51%
C_{max} (pg/mL)	147.3 (32.45)	153.1 (29.47)	0.96	90.76% – 101.04%
KEL (hr^{-1})	0.0408 (23.97)	0.0370 (22.04)		
$T_{½}$ (h)	17.98 (24.82)	19.98 (32.19)		
T_{max} (h)	1.694 (25.49)	1.605 (30.57)		

* Levonorgestrel and Ethinyl Estradiol 0.1 mg/0.02 mg tablets, Mylan Pharmaceuticals ULC
† Alesse® 0.1 mg/0.02 mg tablets, Wyeth Canada, were purchased in Canada.
Source: Module 5, Table 14.3, and Appendix 16.2.6

This study demonstrates that ESME™ (100 mcg levonorgestrel and 20 mcg ethinyl estradiol) tablets are bioequivalent to Wyeth's Alesse® tablets (100 mcg levonorgestrel and 20 mcg ethinyl estradiol) following a single, oral 0.2 mg/0.04 mg (2 x 0.1 mg/0.02 mg) dose administered under fasting conditions.

ORAL CONTRACEPTION

A total of 1477 patients completed 7,720 cycles with the drug over 15 months of use. In this study 5 pregnancies were reported which could be attributed to medication failure. Based on 13 cycles per year, the Pearl Index was 0.84. Four additional subjects were pregnant before receiving the study medication. Five other pregnancies occurred which were associated with omission of tablets for more than three consecutive days of study medication or stopped taking the study medication (return to fertility).

The mean cycle length, excluding cycle 1, was 29.1 days, and 90% of the cycles ranged in duration from 26 to 30 days. The withdrawal bleeding period during this monophasic regimen was between 3 and 7 days in 86% of cycles, and the mean bleeding intensity was light for the most common episode lengths (between 4 and 6 days).

Breakthrough bleeding alone and spotting alone occurred during 4.3% and 12.1% of cycles, respectively. Breakthrough bleeding and spotting occurred during 11.0% of the cycles, while breakthrough bleeding and/or spotting occurred during 27.3% of the cycles. The medication should not be halted during intermenstrual bleeding. If the bleeding persists, the usual diagnostic procedures should be undertaken to determine the cause of the vaginal bleeding.

The incidence of amenorrhea was low with the use of Levonorgestrel and Ethinyl Estradiol Tablets (see ADVERSE REACTIONS: Clinical Trials Adverse Drug Reactions: Table 1). If one period is missed, however, appropriate diagnostic procedures should be undertaken to rule out pregnancy and medication should be discontinued during this time, and an alternate method of contraception employed.

Clinical Laboratory Results:

Out-of-range clinical laboratory test values were flagged in the database and examined by the medical monitors to assess the clinical importance of these findings. Most of the abnormal values during therapy represented either transient or minimal changes from baseline and had no clinical importance.

Endometrial Biopsy: Endometrial biopsies were scheduled during the late luteal phase (last 7 days) of the pretreatment cycle and during days 15 to 21 of specified treatment cycles. Of the twenty-seven subjects who underwent a biopsy, twenty-four subjects had a secretory or proliferative endometrium before treatment. During treatment, most specimens were characterized as secretory, proliferative, or hypoplastic. None of the subjects had endometrial hyperplasia. The results of this study show that the effects of the monophasic regimen of

levonorgestrel/ethinyl estradiol 100 mcg/20 mcg on the endometrium were consistent with those seen with other low-dose oral contraceptives.

Results of Cervical Cytologic Studies: Of the 1,477 subjects, 1,240 (84%) subjects had normal Pap smears at baseline. During the study and at any later period (including poststudy), the percentage of subjects with normal smears was always greater than 75%. Epithelial abnormalities noted during the study were mostly atypical squamous cells of undetermined significance (ASCUS) smears, with a few indicating low-grade squamous intraepithelial lesion (SIL). Two subjects developed high-grade SIL during the study and were referred for further evaluation and treatment. These two subjects were withdrawn from the study because of protocol violation. One additional subject was listed as having a cervical neoplasm. Further examination 5 months later showed that her Pap smear was normal.

No microinvasive or invasive cancers were noted at any time throughout the study.

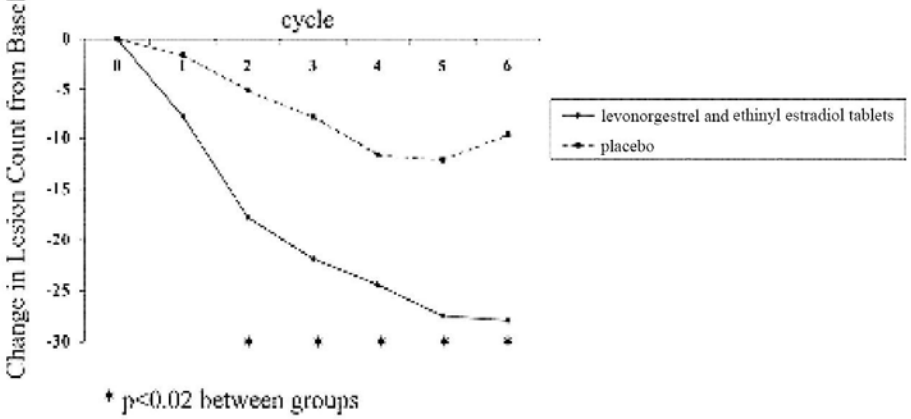
Vital Signs and Weight Gain: More than 97% of the subjects had normal BP (systolic BP ≤ 140 mm Hg; diastolic BP ≤ 90 mm Hg) at baseline and during treatment. Seven subjects (< 1%) withdrew because of elevated blood pressure.

Of the six subjects who discontinued because of weight gain, only one subject had an increase of more than 10% from her prestudy weight. Forty-one subjects gained more than 10% of their baseline weight and 17 subjects lost more than 10% of their baseline weight. These fluctuations in body weight were not considered clinically significant.

ACNE

In two randomized, placebo-controlled, 6-cycle, multicenter clinical trials in 721 women with moderate acne, treatment with Levonorgestrel and Ethinyl Estradiol Tablets in 359 women produced significant mean percent reductions in the number of inflammatory lesions, and in the overall total number of lesions compared with women treated with placebo (Figure 1).

FIGURE 1:REDUCTION IN TOTAL LESIONS
COMBINED INTENT-TO-TREAT POPULATION



In addition, improvement in the clinical global assessment of acne at the end of the study was also greater in patients treated with Levonorgestrel and Ethinyl Estradiol Tablets than with placebo (see CLINICAL TRIALS: Acne: Table 5).

Table 5: Clinician Global Assessment at Cycle-6 and End of Study Analyses for Combined Intent-To-Treat Population

Study Period	Levonorgestrel and Ethinyl Estradiol Tablets Clear/Almost Clear %	Total n	Placebo Clear/Almost Clear %	Total	p-Value
Cycle 6	56.90	239	46.28	242	0.0030
End of Study[a]	47.90	357	39.66	358	0.0118

a: Last observation carried forward (LOCF).

In these acne studies, [14, 15] the measured weight change and the incidence of some adverse events commonly attributed to OC use (such as nausea, breast tenderness, headache) were similar in women treated with Levonorgestrel and Ethinyl Estradiol Tablets and with placebo (see ADVERSE REACTIONS: Clinical Trials Adverse Drug Reactions: Table 2).

DETAILED PHARMACOLOGY

Animal Pharmacology

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

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

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

an exceedingly potent estrogen antagonist. When combined with ethinyl estradiol, norgestrel tends to ameliorate the effects of the estrogen, while the estrogen will modify the effects of the progestogen. In rats, suppression of fertility with norgestrel/ethinyl estradiol combinations is followed by recovery of normal fertility and fecundity. Additional experiments in laboratory animals were directed toward evaluating the endocrine effects and safety of the norgestrel and ethinyl estradiol formulation at dose levels approximating those employed clinically (on a milligram per kilogram basis). Metrotropic effects (uterine glandular development and growth) were most clearly demonstrated. Blockade of pituitary gonadotrophins can be produced by the estrogenic component alone at the clinical dose range; this pituitary effect does not appear to be modified by addition of the progestogen.

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

Human Pharmacology

Progestogens can have, in addition to progestational activity, estrogenic, anti-estrogenic and androgenic activity. When combined with estrogen, the progestogen will markedly affect the overall biological activity by producing a synergistic, summative or diminutional effect on activity. Comparisons of progestogen potency are not considered scientifically valid because the effects of one progestogen cannot be directly compared with those of another.[21]

A study of serum luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone and 17β-estradiol in patients taking low dose oral contraceptives indicated reduction or abolition of the mid-cycle ovulatory peak and post-ovulatory levels commonly associated with these hormones and gonadotrophins respectively.

Endometrial biopsies taken during the course of therapy with 250 mcg d-norgestrel (as 500 mcg of the dl-racemate) plus 50 mcg ethinyl estradiol revealed a histological sequence in the menstrual cycle of early glandular epithelial stimulation followed by later inhibition after the first half of the menstrual cycle.

Cervical mucus studies with 250 mcg d-norgestrel (as 500 mcg of the dl-racemate) plus 50 mcg ethinyl estradiol, and 37.5 mcg d-norgestrel (as 75 mcg of the dl-racemate) would suggest a similar action for Levonorgestrel and Ethinyl Estradiol Tablets on the cervical mucus, viz., absence of ferning and decreased spinnbarkeit, indicative of poor conditions for sperm penetration and migration.

The results of assays for prolactin in a group of 11 normally ovulating women given 150 mcg dnorgestrel (as 300 mcg of the dl-racemate) plus 30 mcg ethinyl estradiol over a continuous

period of three months indicated no clinically or statistically significant elevation or depression of hormone levels during the course of active drug ingestion, nor in the first post-treatment cycle.

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

MICROBIOLOGY

Not applicable.

TOXICOLOGY

Acute Toxicity

Acute oral toxicity studies have been carried out with oral, intraperitoneal and subcutaneous doses of levonorgestrel alone, ethinyl estradiol alone and in a combination of 5:1 ratio respectively. The following table represents the findings of these studies:

Table 6: - ACUTE TOXICITY

SPECIES	ROUTE OF ADMIN	LD_{50} LEVONORGESTREL	ETHINYL ESTRADIOL	LEVONORGESTREL + ETHINYL ESTRADIOL (5+1)
Mice	oral	> 4.0 g/kg	>2.5 g/kg	>2.5 g/kg
Mice	i.p.	> 3.9 g/kg	0.69 g/kg	1.32-1.65 g/kg
Mice	s.c.	> 4.0 g/kg	> 2.6 g/kg	> 2.5 g/kg
Rats	oral	> 4.0 g/kg	susp. > 5.0 g/kg solu. 1.5g/kg	> 2 g/kg
Rats	i.p.	> 5.0 g/kg	0.97 g/kg	approx. 2 g/kg
Rats	s.c.	> 4.0 g/kg hair loss		> 2 g/kg
Dogs	oral		> 1.0 g/kg	

Both compounds were found to be almost non-toxic in the acute toxicity studies.

Table 7 - CHRONIC TOXICITY				
SPECIES	**DRUGS DOSE AND ROUTE OF ADMINISTRATION**	**DURATION OF ADMINISTRATION**	**SYMPTOMS**	**HISTOPATHOLOGY**
RAT 16/sex/group	Norgestrel Oral - mg/kg 0.0001%, 0.0005%, 0.0025%	26 weeks	No signs and symptoms of toxicity.	No histopathological changes.
	Levonorgestrel Oral - mg/kg 0.00005%, 0.00025%, 0.00125%	26 weeks	Significant less weight gain in low dose females, no other signs of toxicity.	No abnormal histopathology.
DOG 6/sex/group	Levonorgestrel Oral - mg/kg 0.05, 0.1, 0.5	26 weeks	No estrus in any dog, mammary enlargement in all but 2 females and 8 males. Dose related clitoral reddening and enlargement. Significant decrease in cholesterol in all dosage groups.	No drug related effects on ophthalmology, ECG, hemostatic functions, urinalysis or organ weight.
DOG 16 females/dose	Norgestrel Oral - mg/kg 0.0, 0.003, 0.015,0.0375	Continuous 7 years	Estrus inhibited in all but low dosage group. Uterine enlargement and endometrial hyperplasia at 0.015 and 0.0375 mg/kg.	Norgestrel 0.0375 mg group - many dogs with cysts and absence of luteal phase. 1 dog mammary carcinoma (0.0375)
	Levonorgestrel Oral - mg/kg 0.5	cyclic - 7 years	Enlarged clitoris on majority of dogs. Hematocrit and hemoglobin low or SGPT Increased significantly. Fibrinogen increased.	Increase in benign mammary adenomas. 1 dog adenocarcinoma. Many vaginal cysts and absence of luteal phase.
DOG 16 females/dose	Levonorgestrel Oral - mg/kg 0.01, 0.05, 0.125	cyclic - 7 years	No unexpected findings. The only drug effects observed were at the higher dose levels, were endocrine related and were considered to be related to the desired pharmacological effects of a progestational agent.	No apparent drug-related changes during the post-mortem examination.

Table 7 - CHRONIC TOXICITY				
SPECIES	**DRUGS DOSE AND ROUTE OF ADMINISTRATION**	**DURATION OF ADMINISTRATION**	**SYMPTOMS**	**HISTOPATHOLOGY**
RHESUS MONKEY 16 females/dose	Norgestrel Oral - mg/kg 0.0, 0.003, 0.015, 0.075	Continuous 10 years (120 months)	Red vaginal discharge less frequent in 0.015 and 0.075 mg/kg group.	Mammary nodules in 3 animals at 0.075 mg/kg. 1 animal at 0.003 and 0.015 mg/kg.
	Levonorgestrel Oral - mg/kg 1.0	cyclic - (21 days) 10 years (120 months)	Red vaginal discharge more frequent in withdrawal period. Fibrinogen levels increased.	Mammary nodule in 1 animal.
MICE 40/sex/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol (10+1) Oral - mg/kg 0.02 + 0.002 0.7 + 0.07 2.0 + 0.2 3.0 + 0.3	80 weeks	Ethinyl Estradiol depressed weight gain in 3 highest dosage groups. Norgestrel + Ethinyl Estradiol-depressed weight gain in 3 highest dosage groups. Norgestrel-no effects.	Ethinyl Estradiol-significant increase in malignant tumours. Lymphocarcinoma-males interstitial tumours-females. Ethinyl Estradiol + Norgestrel-same. Norgestrel-no significant tumorigenic effect.

Table 7 - CHRONIC TOXICITY				
SPECIES	**DRUGS DOSE AND ROUTE OF ADMINISTRATION**	**DURATION OF ADMINISTRATION**	**SYMPTOMS**	**HISTOPATHOLOGY**
RAT 40/sex/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol (10+1) Oral - mg/kg 0.02 + 0.002 0.5 + 0.05 2.0 + 0.2	104 weeks	Norgestrel-no effects. Ethinyl Estradiol-dosage related decrease in body weight gain. Norgestrel +Ethinyl Estradiol-dosage related decrease in body weight gain.	Malignant and benign mammary tumours were significantly increased over controls in both male and females at the two highest dosage levels of Ethinyl Estradiol either alone or in combination with Norgestrel. Hematological changes included are one case of Leukemia in low dosage group of Norgestrel + Ethinyl Estradiol.
DOG 12 females/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol Oral - mg/kg I 0.1-0.25 II 0.01 III 0.1 + 0.025 0.1 + 0.01 0.25 + 0.025	7 years	Norgestrel-increase in body weight at 0.1 mg/kg. Slight to moderate increase SGPT values in treated groups also increase in fibrinogen in some animals. Norgestrel alone or in combination with Ethinyl Estradiol also suppressed estrus.	Dose related increase in mammary adenomas in the Norgestrel treated groups. Possible indication of an increase in benign adenomas and intraductal papillomas after high doses of Norgestrel.

Table 7 - CHRONIC TOXICITY				
SPECIES	**DRUGS DOSE AND ROUTE OF ADMINISTRATION**	**DURATION OF ADMINISTRATION**	**SYMPTOMS**	**HISTOPATHOLOGY**
RHESUS MONKEY 16 females/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol Oral - mg/kg I 0.02, 0.1, 0.5 II 0.002, 0.02, 0.05 III 0.02 + 0.002 0.1 + 0.01 0.5 + 0.05	10 years	Increase in body weight gain in the Norgestrel 0.5 mg/kg group. Fibrinogen levels increased in monkeys receiving Norgestrel alone or in combination with Ethinyl Estradiol. A higher rate with retinal depigmentation in the groups treated with Ethinyl Estradiol alone or in combination with Norgestrel.	No abnormal findings.

Reproduction and Teratology

At doses in the clinical range, norgestrel, ethinyl estradiol and their combinations have no demonstrable effects on pregnant rats, their pregnancies, their offspring or the reproductive potential of the young.

Also at doses approximating the clinical range, norgestrel and/or ethinyl estradiol have no observable effects on lactating rats, the lactation process or the nursing young.

At doses in the clinical range and above, a small dose-related increase in the number of abnormal fetuses is observed in mice treated during pregnancy with norgestrel/ethinyl estradiol combinations in a ratio of 5:1. Abnormalities include open eye, cleft palate, exencephaly and umbilical hernia. Rabbits treated during pregnancy with doses of norgestrel and ethinyl estradiol in the clinical range and above, failed to demonstrate any teratogenic potential for the drug.

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PART III: CONSUMER INFORMATION

Pr ESME 21 and Pr ESME 28

Levonorgestrel and Ethinyl Estradiol Tablets, USP

100 mcg Levonorgestrel and 20 mcg Ethinyl Estradiol Tablets

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

ABOUT THIS MEDICATION

What the medication is used for:

- To prevent pregnancy
- To treat moderate acne in women 14 years of age and older who are able to use birth control pills, desire birth control and have achieved menarche. Your first menstrual period is referred to as menarche.

What it does:

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

Birth control pills work in two ways:

1. They inhibit the monthly release of an egg by the ovaries.
2. They change the mucus produced by the cervix (narrow outer end of the womb). This slows the movement of the sperm through the mucus and through 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.

When it should not be used:

The birth control pill is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a risk to you. If you see a different doctor, inform him/her that you are taking birth control pills. Tell the doctor that your birth control pills are ESME. The use of the birth control pill should always be supervised by your doctor.

You should not use ESME if you have or have had any of the following conditions:

- History of or actual heart attack, chest pain (angina pectoris) or stroke;
- Blood clots in the legs (thrombophlebitis), lungs (pulmonary embolism), eyes or elsewhere;
- Hereditary or acquired blood clotting disorders;
- Known or suspected cancer of the breast, sex organs, or certain estrogen-dependent cancers;
- Unexplained vaginal bleeding (until a diagnosis is reached by your doctor);
- Partial or complete loss of vision or other vision problems caused by vascular disease (blood vessel disease of the eye);
- History of or actual liver disease or history of or actual benign or malignant liver tumor;
- Jaundice (yellowing of the skin and eyes) or liver disease if still present;
- Heart valve or heart rhythm disorders that may be associated with formation of blood clots;
- Diabetes affecting your circulation;
- Migraines (current or history) with neurological symptoms such as aura (visual or sensory disturbance);
- Uncontrolled high blood pressure;
- Hypersensitivity(allergy) to any of the components of ESME (levonorgestrel and ethinyl estradiol tablets) (see *What the nonmedicinal ingredients are);*
- Known or suspected pregnancy. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing. There is no conclusive evidence, however, that the pill can damage a developing child when taken inadvertently during early pregnancy.
- Pancreatitis associated with severe hypertriglyceridemia (current or history). Pancreatitis is the inflammation of the pancreas, marked by abdominal pain, whereas severe hypertriglyceridemia is a very high level of triglycerides in the blood, and may show no symptoms.
- Are using anti-viral medications to treat Hepatitis C Virus (HCV) which contain combination of ombitasvir, paritaprevir, ritonavir and dasabuvir with or without ribavirin.

What the medicinal ingredients are:
Levonorgestrel and Ethinyl Estradiol

What the nonmedicinal ingredients are:
Each pink, round flat tablet with beveled edges, debossed with "405" on one side and plain on the other side contains croscarmellose sodium, ferric oxide red, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone and sodium lauryl sulfate.

Each inactive green, round, flat tablet with beveled edges, debossed with "471" on one side and plain on the other side (in ESME 28) contains croscarmellose sodium, FD&C Blue No. 1 aluminum lake (aluminium chloride, aluminium hydroxide, brilliant blue), ferric oxide (yellow), lactose monohydrate, magnesium stearate, microcrystalline cellulose and povidone.

What dosage forms it comes in:
ESME (levonorgestrel and ethinyl estradiol tablets) are available in a 21-day regimen (ESME 21) and a 28-day regimen (ESME 28).

ESME 21: Each package contains 21 pink tablets. Each pink tablet contains 100 mcg levonorgestrel and 20 mcg ethinyl estradiol.

ESME 28: Each blister pack contains 21 pink and 7 green, tablets. Each pink tablet contains 100 mcg levonorgestrel and 20 mcg ethinyl estradiol. The green tablets are inactive (do not contain hormones).

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 birth control pill users over 35 years of age. Women who use birth control pills should not smoke.

Birth control pills DO NOT PROTECT against sexually transmitted infections (STIs), including HIV/AIDS.

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

There are also conditions that your doctor will want to watch closely or that might cause your doctor to recommend a method of contraception other than birth control pills.

BEFORE you use ESME talk to your doctor or pharmacist if the following apply to you:

- Breast conditions
  - A strong family history of breast cancer
  - Breast disorders including pain, discharge from the nipples, thickenings, or lumps. In some circumstances, benefit may be derived from taking the pill; in other cases, adverse effects may follow.
- Diabetes
- High blood pressure

- Abnormal levels of fats in the bloodstream (high cholesterol or triglycerides)
- Cigarette Smoking
- Heart or kidney disease
- Epilepsy/seizures
- History of Depression
- Fibroid tumours of the uterus
- Gallbladder or pancreatic disease
- History of liver disease or jaundice
- Family history of blood clots, heart attacks or strokes.
- May be pregnant or breast feeding
- Have systemic lupus erythmatosus
- 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 irregular heart rhythm
- Wear contact lenses
- Have Hepatitis C

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

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

Also tell your doctor if you are scheduled for **MAJOR** surgery, recent delivery, or second-trimester abortion. You should consult your doctor about stopping the use of ESME four weeks before major surgery and not using ESME for a time period after surgery or during prolonged bed rest.

ESME should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.

Use ESME only on the advice of your doctor and carefully follow all directions given to you. You must use the birth control pill exactly as prescribed. Otherwise, you may become pregnant. If you and your doctor decide that, for you, the benefits of ESME outweigh the risks, you should be aware of the following:

THE RISKS OF USING BIRTH CONTROL PILLS

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

Women who use hormonal contraceptives have a higher incidence of blood clots. Blood clots are the most common serious side effects of birth control pills. The risk of developing clots is especially high during the first year a woman ever uses a hormonal contraceptive. Clots can occur in many areas of the body.

Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:

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

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

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 accelerate the growth of an existing but undiagnosed breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to birth control pills seem to be small,

however; a yearly breast examination by a doctor is recommended for all women.

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

3. Cervical cancer

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

Chronic infection with the Human Papilloma Virus (HPV) is believed to be the most important risk factor for cervical cancer. In women who use COCs for a long time the chance of getting cervical cancer may be slightly higher. This finding may not be caused by the 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 have also been linked with the growth of liver tumors or liver injury (e.g., hepatitis, hepatic function abnormal). Such injury or tumors are extremely rare.

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

5. Gallbladder disease

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

6. Use in pregnancy

Birth control pills should not be taken by pregnant women. 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 doctor about risks to your unborn child from any medication taken during pregnancy.

7. Use after pregnancy, miscarriage or an abortion

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

8. Pregnancy after stopping ESME

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

9. Use while breast feeding

If you are breast-feeding, consult your doctor before starting the birth control pill. The hormones in birth control pills are known to appear in breast milk. Adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. You should use another method of contraception. The use of oral contraceptives is generally not recommended until the nursing mother has completely weaned her child.

INTERACTIONS WITH THIS MEDICATION

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. You may also need to use a nonhormonal method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective.

Drugs that may interact with ESME include:

- drugs used for epilepsy such as barbiturates (e.g. phenobarbital) and phenytoin, primidone, topiramate, carbamazepine
- certain drugs used in the treatment of tuberculosis (eg. rifampicin, rifabutin)
- drugs used for HIV or AIDS such as ritonavir
- herbal products containing St. John's Wort (Hypericum perforatum)
- antibiotics (e.g. penicillins, tetracyclines) for infectious diseases
- cyclosporine
- antifungals (griseofulvin)
- cholesterol-lowering drugs (eg. clofibrate)
- antihypertensive drugs (for high blood pressure)
- antidiabetic drugs and insulin (for diabetes)
- prednisone

- sedatives and hypnotics (eg, benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- antidepressants (e.g. clomipramine)
- other drugs such as phenylbutazone, analgesics, modafinil, troleandomycin**,** Vitamin E and Vitamin B_{12}.
- anti-viral hepatitis C virus (HCV) medicinal products such as ombitasvir, paritaprevir, ritonavir and dasabuvir, with or without ribavirin.

Please inform your doctor and pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription. Also tell any other doctor or dentist who prescribes another drug (or the dispensing pharmacist) that you use ESME. They can tell you if you need to use an additional method of contraception and if so, for how long.

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

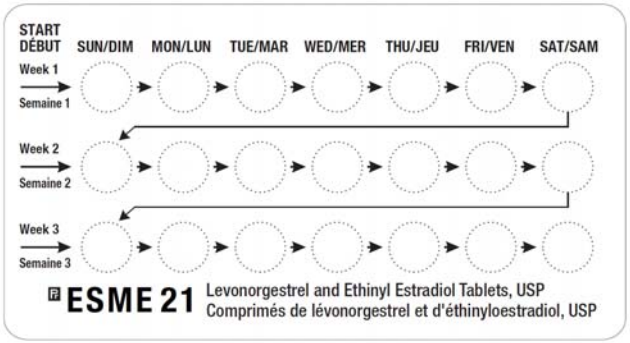
PROPER USE OF THIS MEDICATION

Usual dose:

HOW TO TAKE ESME:

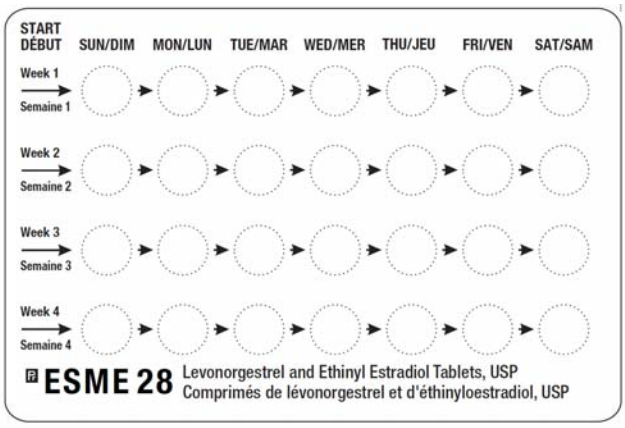
1. **READ THESE DIRECTIONS**
   - Before you start taking your pills, and
   - Any time you are not sure what to do.

2. **LOOK AT YOUR PILL PACK to see if it has 21 or 28 pills:**
   - 21-Pill Pack: 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week;



or

   - 28-Pill Pack: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.



3. You may wish to use a second method of birth control (e.g. latex 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 doctor 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 ON THE PILL. If you do feel sick, do not stop taking ESME. 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. IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:
   - when you start a pack late or
   - when you miss pills at the beginning or at the very end of the pack.

8. ALWAYS BE SURE YOU HAVE READY:
   - ANOTHER KIND OF BIRTH CONTROL (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
   - AN EXTRA PACK OF PILLS.

9. IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES, such as antibiotics, your pills may not

work as well. Use a back-up method, such as latex condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

10. IF YOU FORGOT 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.

11. IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.

WHEN TO START THE FIRST PACK OF PILLS

BE SURE TO READ THESE INSTRUCTIONS:

- before you start taking your pills, and
- any time you are not sure what to do.

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

A. 21-DAY COMBINATION

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 pills for more than seven days in a row.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day. If ESME tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on ESME until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet taking.

2. Take one pill at approximately the same time every day for 21 days, THEN TAKE NO PILLS FOR SEVEN DAYS. Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period).

TWO WAYS TO REMEMBER IN WHAT ORDER TO TAKE THE PILLS

1. Follow the days of the week (as shown above the pills).
2. Always finish the pink tablets before going on to the week when you are off pills.

B. 28-DAY COMBINATION

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

1. THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE. Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day. If ESME tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on ESME until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet taking.

2. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, NOT MISSING ANY DAYS. Your period should occur during the last seven days of using that pill pack.

TWO WAYS TO REMEMBER IN WHAT ORDER TO TAKE THE PILLS

1. Follow the days of the week (as shown above the pills).
2. Always finish the pink tablets before going on to the green pills in week 4 row.

INSTRUCTIONS FOR USING YOUR PACKAGE.

FOLLOW THESE INSTRUCTIONS CAREFULLY:

1.**For Day 1 or Day 5 start:** Label the Package by selecting the day label sticker that corresponds with Day 1 (or Day 5) of your menstrual period (the first day of menstruation is Day 1). For example, if your first day of menstruation is Tuesday, select and peel off the day label that begins with **TUE/MAR**.

OR

For Sunday start: No day label is required. The Package is printed for a Sunday start.

2.Place the day label sticker over the existing days of the week printed on the package. Having the Package labelled with the days of the week will help remind you to take your pill every day.

3.To begin taking your pills, start with the pill next to the word **START**. This pill should correspond to the day of the week that you are taking your first pill. To remove the pill, push through the back of the Package.

4.On the following day, take the next pill in the same row, always proceeding from left to right (→). Each row will always begin on the same day of the week.

WHAT TO DO DURING THE MONTH

1. TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
2. Try to associate taking your pill with some regular activity such as eating a meal or going to bed.
3. Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
4. Do not skip pills even if you do not have sex very often.
5. WHEN YOU FINISH A PACK
   - 21 PILLS
     WAIT SEVEN DAYS to start the next pack. You will have your period during that week.
   - 28 PILLS
     Start the next pack ON THE NEXT DAY. Take one pill every day. Do not wait any days between packs.

Overdose:

Overdosage may cause nausea, vomiting, breast tenderness, dizziness, abdominal pain, and fatigue/ drowsiness. Withdrawal bleeding may occur in females.

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

Missed Dose:

WHAT TO DO IF YOU MISS PILLS

Birth control pills may not be as effective if you miss pills. The following chart outlines the actions you should take if you miss one or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack.

SUNDAY START	**OTHER THAN SUNDAY 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 two 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 two pills in one day.
Miss Two Pills in a Row	**Miss Two Pills in a Row**
First two weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Keep taking one 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 nonhormonal back-up method of birth control if you have sex in the seven 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.**	**First two weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a nonhormonal back-up method of birth control if you have sex in the seven 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 one 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 nonhormonal back-up method of birth control if you have sex in the seven 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 nonhormonal back-up method of birth control if you have sex in the seven 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.**

NOTE: 28-DAY PACK - If you forget any of the seven "reminder" pills (without hormones) 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.

Always be sure you have on hand:

- a non-hormonal back-up method of birth control (such as latex condoms and spermicidal foam or gel) in case you miss pills, and

- an extra, full pack of pills.

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

Non-Contraceptive Benefits of Birth Control Pills:

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

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Some users of birth control pills have unpleasant side effects. Most side effects are temporary and are not hazardous to the health.

There may be tenderness of the breast, nausea, and vomiting. Some users will experience weight gain or loss. Many of these side effects occurred with high-dose combination birth control pills. These side effects are less common with the low-dose pills prescribed today.

Unexpected vaginal bleeding or spotting and changes in the usual menstrual period may also occur. These side effects usually disappear after the first few cycles. They are not an indication to stop taking birth control pills. Unless more significant complications occur, a decision to stop using the pill or to change the brand of pill should be made only after three consecutive months of use. Occasionally, users develop high blood pressure that may require stopping the use of birth control pills.

Other side effects may include

- growth of pre-existing fibroid tumours of the uterus;
- an increase or decrease in hair growth, sex drive and appetite;
- skin pigmentation;
- headaches;
- abnormal liver test, nausea, vomiting, severe pain or lump in the abdomen;
- rash; and/or
- vaginal infections.

Infrequently, there is a need to change contact lens prescription or an inability to use contact lenses.

A woman's menstrual period may be delayed after stopping birth control pills. There is no evidence that the use of the pill leads to a decrease in fertility. As mentioned, it is wise to delay starting a pregnancy for one menstrual period after stopping birth control pills.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN 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	Sharp pain in the chest, coughing blood, or sudden shortness of breath			√
	Pain or swelling in the leg			√
	Crushing chest pain or heaviness			√
	Sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg			√
	Sudden partial or complete loss of vision			√
	Abnormal liver test and/or, nausea, vomiting, severe pain or lump in the abdomen		√	
	Persistent sad mood			√
	Yellowing of the skin or eyes (jaundice)			√
	Unusual swelling of the extremities		√	

	Breast lumps		√	
	Unexpected (Abnormal) vaginal bleeding		√	

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

HOW TO STORE IT

Store at room temperature (15°C-30°C).
ESME 21 AND ESME 28 should be protected from light once opened using the protective covering provided. Keep out of reach of children and pets.

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.

MORE INFORMATION

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

The full product monograph prepared for health professionals can be obtained by contacting the Canadian distributor, Mylan Pharmaceuticals ULC, at: 1-844-596-9526.

This leaflet was prepared by Mylan Pharmaceuticals ULC, Etobicoke, Ontario M8Z 2S6

Revised on: August 16, 2018

Mylan

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