PRODUCT MONOGRAPH

Pr LOLO®

Norethindrone acetate and ethinyl estradiol tablets, Mfr Std
norethindrone acetate 1 mg
ethinyl estradiol 0.010 mg

Ethinyl estradiol tablets, Mfr Std
ethinyl estradiol 0.010 mg

Oral Contraceptive

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PrLOLO®

norethindrone acetate and ethinyl estradiol tablets
ethinyl estradiol tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets 1 mg norethindrone acetate and 0.010 mg ethinyl estradiol and 0.010 mg ethinyl estradiol	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

LOLO (norethindrone acetate and ethinyl estradiol) is indicated for the prevention of pregnancy.

In a one year (thirteen 28-day cycles) multicenter open-label clinical trial 1,582 women were studied to assess the safety and efficacy of LOLO. In this study 1,270 women 18 to 35 years of age were studied to assess the efficacy of LOLO,completing the equivalent of 12,482 28-day evaluable cycles of exposure. **The pregnancy rate (Pearl Index [PI]) in women 18-35 years of age was 2.92 pregnancies per 100 women-years of use** (see **CLINICAL TRIALS).**

The efficacy of LOLO in women with a body mass index >35 kg/m^2 has not been evaluated.

Exposure to exogenous estrogen with LOLO is less than with other combined oral contraceptives with similar synthetic estrogens. Any benefits from the lower estrogen exposure provided by LOLO have not been evaluated.

CONTRAINDICATIONS

LOLO should not be used in women with:

- a history of or actual thrombophlebitis or thromboembolic disorders (such as deep vein thrombosis or pulmonary embolism);
- a history of or actual cerebrovascular disorders;
- a history of or actual myocardial infarction or coronary artery disease;
- valvular heart disease with complications;
- history of or actual prodromi of a thrombosis (e.g., transient ischaemic attack, angina pectoris);
- active liver disease, or history of or actual benign or malignant liver tumours;
- known or suspected carcinoma of the breast;
- carcinoma of the endometrium or other 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;
- known or suspected pregnancy;
- current or history of migraine with focal aura;
- history of or actual pancreatitis if associated with severe hypertriglyceridaemia;
- presence of severe or multiple risk factor(s) for arterial or venous or thrombosis such as:
    - severe hypertension (persistent values of ≥160/100 mmHg)
    - uncontrolled hypertension
    - hereditary or acquired predisposition for venous or arterial thrombosis such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia (e.g., due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
    - severe dyslipoproteinemia
    - over age 35 and smoke
    - diabetes mellitus with vascular involvement
    - major surgery associated with an increased risk of postoperative thromboembolism
    - prolonged immobilization
- hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious cardiovascular events associated with the use of hormonal contraceptives. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, LOLO should not be used by women who are over 35 years of age and smoke (see **Cardiovascular** section below).

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

Discontinue medication at the earliest manifestation of:

A. **Thromboembolic and cardiovascular disorders,** such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, proptosis and retinal thrombosis.
B. **Conditions which predispose to venous stasis and to vascular thrombosis** (eg, 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 Perioperative Considerations, below.
C. **Visual defects- partial or complete**
D. **Papilledema or ophthalmic vascular lesions**
E. **Severe headache of unknown etiology or worsening of pre-existing migraine headache**
F. **Increase in epileptic seizures**

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

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes. Other medical conditions which have been associated with adverse circulatory events include systemic lupus erythematosus, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), sickle cell disease, valvular heart disease and atrial fibrillation.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COCs has not been firmly established: porphyria, systemic lupus erythematosus, hemolytic uremic syndrome, Sydenham's chorea, herpes

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

Carcinogenesis and Mutagenesis

Breast Cancer

Women who currently have or have had breast cancer should not use LOLO because breast cancer is a hormonally-sensitive tumour (see **CONTRAINDICATIONS**).

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

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

Cervical Cancer

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

Hepatocellular Carcinoma

Hepatocellular carcinoma may be associated with oral contraceptives. The risk appears to increase with duration of hormonal contraceptive use (>8 years). However, the attributable risk (the excess incidence) of liver cancers in oral contraceptive users is extremely small (<1 case/million users). A liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs (See also Hepatic/Biliary/Pancreatic: *Hepatic nodules*).

Cardiovascular

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular events and mortality. Birth control pills increase this risk, particularly in women over 35 years of age, and with the number of cigarettes smoked. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use by women who smoke.

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

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

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

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

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

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

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

Genitourinary
Vaginal Bleeding
Unscheduled (breakthrough or intra-cycle) bleeding and /or spotting (IB/S) sometimes occur in patients on COCs, especially during the first three months of use. In the pivotal trial for LOLO, a total of 1,257 women (85.9%) experienced IB/S at some time during Cycles 2-13 of this study. The incidence of IB/S was highest during Cycle 2 (53%) and lowest at Cycle 13 (36%). The

mean number of days per cycle of IB/S decreased from 3.2 days in Cycle 2 to 1.8 days during Cycle 13 (See **CLINICAL TRIALS** - Bleeding Profile).
Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over the one year study, with an average of less than 2 days per cycle when including all women and all cycles.

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

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

Venous Thromboembolism
The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive or restarts (following a 4-week or greater pill-free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months. VTE is fatal in 1% to 2% of cases.

A large, prospective 3-armed cohort study has shown that the frequency of VTE diagnosis ranges from about 8 to 10 per 10,000 woman-years in users of oral contraceptives with low estrogen content (<50 μg ethinyl estradiol). The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman-years in nonpregnant, non-COC users and ranges from 20 to 30 per 10,000 women-years in pregnant women or postpartum.

Overall the risk for VTE in users of COCs with low estrogen content (<50 μg ethinyl estradiol) is 2- to 3-fold higher than for nonusers of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

The risk of VTE with COCs has been shown to be related to the estrogen dose, as risk has decreased as doses have decreased from 100 μg to 50 μg to 30 μg. Whether doses as low as 10 μg are further protective is unknown. LOLO provides a daily dose of ethinyl estradiol of 10 μg, for 26 of 28 days each cycle.

Extremely rarely, thrombosis has been reported to occur in other blood vessels (eg, hepatic, mesenteric, renal, cerebral, or retinal veins and arteries) in COC users. There is no consensus as to whether the occurrence of these events is associated with the use of COCs.

Arterial Thromboembolism
The risk for arterial thromboembolism (ATE) in users of oral contraceptives with <50 μg ethinyl estradiol ranges from about 1 to 3 cases per 10,000 woman-years. An ATE can include cerebrovascular accident, vascular occlusion, or myocardial infarction (MI).

Arterial thromboembolic events may be fatal.

Other Risk Factors for Venous or Arterial Thromboembolism or of a Cerebrovascular Accident
Other generalized risk factors for venous or arterial thromboembolism include but are not limited to age, severe obesity (body mass index >30 kg/m^2), a personal history, a positive family history (the occurrence of VTE/ATE in a direct relative at a relatively early age may indicate genetic predisposition) and systemic lupus erythematosus. If a hereditary or acquired predisposition for venous or arterial thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any COC use. The risk of VTE/ATE may be temporarily increased with prolonged immobilization, major surgery, or trauma. In these situations, it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume COC use until two weeks after complete remobilization. Also, patients with varicose veins and leg cast should be closely supervised. Other risk factors may include smoking (with heavier smoking and increasing age, the risk further increases, especially in women over 35 years of age), dyslipoproteinemia, hypertension, migraine, valvular heart disease, and atrial fibrillation.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia (eg, due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with COCs containing <0.05 mg ethinyl estradiol).

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

Jaundice
Patients who have had jaundice should be given oral contraceptives only with great care and under close observation. Oral contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. Women with a history of cholestasis may have the condition recur with subsequent hormonal contraceptive use. The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved.

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

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

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

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

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

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

Ocular Lesions
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, LOLO should be discontinued and the cause immediately evaluated.

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

Psychiatric

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

Renal

Fluid Retention

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

Sexual Function/Reproduction

Return to Fertility

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

Amenorrhea

Women on LOLO may not get a period each month. In the clinical trial with LOLO, the incidence of amenorrhea increased from 32% in Cycle 1 to 49% by Cycle 13 (see **CLINICAL TRIALS** - Bleeding Profile). If LOLO has been taken according to directions, it is unlikely that the woman is pregnant. However, if LOLO has not been taken according to directions prior to the first missed withdrawal bleed, or if two withdrawal bleeds are missed, pregnancy must be ruled out before LOLO 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 6 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, gastrointestinal disturbances or concomitant medication (see **DRUG INTERACTIONS).**

Skin

Chloasma may occasionally occur with use of COCs, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs. Chloasma is often not fully reversible.

Special Populations

Pregnant Women:

Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with LOLO, further intake must be stopped. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child.

Nursing Women:

In breastfeeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk. There is no evidence that low-dose oral contraceptives are harmful to the nursing infant.

If possible, 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. There have been no formal studies of LOLO in nursing women.

Pediatrics

The safety and efficacy of LOLO have not been established in women under the age of 18 years. Use of this product before menarche is not indicated.

Geriatrics

LOLO is not indicated for use in postmenopausal women.

Body Mass Index (BMI)

The safety and efficacy of LOLO in women with a body mass index (BMI) > 35 kg/m^2 has not been evaluated.

Monitoring and Laboratory Tests

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

The first follow-up visit should be done three months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on the Periodic Health Examination.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

- arterial and venous thromboembolism
- being diagnosed with breast cancer
- benign and malignant hepatic tumours
- cerebral hemorrhage
- cerebral thrombosis
- congenital anomalies
- gallbladder disease
- hypertension
- mesenteric thrombosis
- myocardial infarction
- neuro-ocular lesions (e.g., retinal thrombosis)
- pulmonary embolism
- thrombophlebitis

The following adverse reactions also have been reported in patients receiving oral contraceptives:

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

Blood and lymphatic system: hemolytic uremic syndrome

Ear and labyrinth: auditory disturbances, otosclerosis-related hearing loss[a]

Eye: cataracts, change in corneal curvature (steepening), intolerance to contact lenses, retinal thrombosis

Gastrointestinal: abdominal pain, Crohn's disease[a], diarrhea, gastrointestinal symptoms (such as abdominal cramps and bloating), pancreatitis, ulcerative colitis[a]

General: edema

Hepatobiliary: cholestatic jaundice, gallstone formation[a], liver function disturbances[a]

Immune system: hypersensitivity

Infections and infestations: rhinitis, vaginal candidiasis, vaginitis,

Investigations: change in weight (increase or decrease), reduced tolerance to carbohydrates

Metabolism and nutrition: changes in appetite, hypertriglyceridemia (increased risk of pancreatitis when using COCs) [a], porphyria

Musculoskeletal and connective tissue: systemic lupus erythematosus[a]

Neoplasms benign, malignant and unspecified (incl cyst and polyps): increase in size of uterine leiomyomata

Nervous system: chorea, dizziness, headache, migraine, optic neuritis, Sydenham's chorea[a]

Psychiatric: changes in libido, mental depression, nervousness

Renal and urinary: cystitis-like syndrome, impaired renal function

Reproductive system and breast: amenorrhea during and after treatment, breakthrough bleeding, breast changes including tenderness, enlargement, and secretion, change in menstrual flow, dysmenorrhea, endocervical hyperplasias, possible diminution in lactation when given immediately post-partum, premenstrual-like syndrome, spotting, temporary infertility after discontinuance of treatment, vaginal discharge

Skin and subcutaneous tissue: chloasma or melasma which may persist, loss of scalp hair, hirsutism, erythema multiforme, erythema nodosum, hemorrhagic eruption, herpes gestationis[a], pruritis related to cholestasis[a], rash (allergic), urticaria

Vascular: hypertension[a], Raynaud's phenomenon

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

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse 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 approximate rates of occurrence.

A multicenter phase 3 clinical trial evaluated the safety and efficacy of LOLO for pregnancy prevention. The study was a one year, open-label, single-arm, uncontrolled study. A total of 1,660 women aged 18 to 45 were enrolled and took at least one dose of LOLO.

A list of adverse reactions experienced by ≥ 1% of the subjects is listed in Table 1.

Table 1
Treatment-related Adverse Reactions Reported in ≥1% of Subjects

MedDRA System Organ Class	Event	LOLO N= 1660 n (%)
Nervous System Disorders	Headache	79 (4.8)
Gastrointestinal Disorders	Nausea	53 (3.2)
Reproductive System and Brest Disorders	Metrorrhagia	54 (3.3)
	Breast Tenderness	50 (3.0)
	Dysmenorrhea	42 (2.5)
Metabolism & Nutrition Disorders	Weight Fluctuation	48 (2.9)
Skin and Subcutaneous Tissue Disorders	Acne	35 (2.1)
Psychiatric Disorders	Mood Swings	23 (1.4)

The mean weight gain on LOLO was 1.7 lb (SD ±9.8 lb).

Serious Adverse Events leading to discontinuation included: deep vein thrombosis, ovarian vein thrombosis and cholecystitis.

Adverse Events Leading to Study Discontinuation: 10.7% of the women discontinued from the clinical trial due to an adverse event. Adverse events occurring in ≥1% of subjects leading to discontinuation of treatment were, in decreasing order: menstrual irregularities (including metrorrhagia, irregular menstruation, menorrhagia and vaginal hemorrhage) (4%), headache/migraine (1%), mood disorder (including mood swings, depression, anxiety) (1%), and weight fluctuation (1%). Less than 1% of subjects discontinued because of amenorrhea.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Rare adverse reactions (<1%) which were observed in clinical trials and deemed to be at least possibly related to LOLO are as follows:

Gastrointestinal: abdominal pain, vomiting, diarrhea, abdominal distension, gastroesophageal reflux disease, constipation, dyspepsia, stomach discomfort, abdominal discomfort.

General: fatigue, irritability, peripheral edema, swelling, edema, drug intolerance

Hepatobiliary: cholycystitis, cholelithiasis

Investigations: abnormal cervical smear, abnormal lab test, blood pressure increased, AST increased, blood cholesterol increased

Infections and Infestations: HPV cervicitis, fungal infection, bronchitis

Metabolism and Nutrition: hypercholesterolemia, hypertriglyceridemia, increased appetite, fluid retention, food craving, impaired glucose tolerance, lack of satiety

Musculoskeletal and Connective Tissue: pain in extremity, muscle spasms

Nervous System: migraine, dizziness, tension headache, lethargy, loss of consciousness, somnolence.

Ophthalmologic: vision blurred, contact lens intolerance, dry eye

Psychiatric: anxiety, depression, insomnia, decreased libido, mood altered, affect liability, tearfulness, suicidal ideation.

Renal and Urinary: urinary tract infection,

Reproductive System and Breast: bacterial vaginitis, vulvovaginal mycotic infection, amenorrhea, irregular menstruation, ovarian cyst, vaginal candidiasis, vaginal discharge, breast pain, menorrhagia, pelvic pain, breast mass, vaginal inflammation, fibrocystic breast disease, premenstrual syndrome, dypareunia, vulvovaginal dryness, breast cyst, breast discharge, breast hypertrophy, vaginal hemorrhage, coital bleeding, vaginal pain, adnexa uteri pain, breast atrophy, breast swelling, cervical discharge, dysfunctional uterine bleeding, nipple pain.
Respiratory: upper respiratory tract infection, alveolar proteinosis

Skin and Subcutaneous Tissue: rash, alopecia, urticaria, hyperhidrosis, night sweats, eczema, prurius, generalized rash, hair texture abnormal, pigmentation disorder, lip pigmentation, generalized pruritis.

Vascular: hypertension, hot flush, deep vein thrombosis, hemorrhage, venous thrombosis.

Abnormal Hematologic and Clinical Chemistry Findings

In the pivotal trial, a total of 80 abnormal laboratory results (not including positive pregnancy tests) in 31 subjects in the All Treated population were considered clinically significant, consisting mostly of elevated cholesterol and triglycerides; moderately elevated AST, ALT and GGT. In most of these cases values elevated at the end of the study were actually lower than the initial values. Slightly reduced hemoglobin and hematocrit were also common.

Post-Market Adverse Drug Reactions

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

Congenital, Familial and Genetic Disorders: heart disease (congenital)

General Disorders and Administration Site Conditions: chest pain

Hepatobiliary Disorders: gallbladder disorder, liver disorder

Musculoskeletal and Connective Tissue Disorders: muscular weakness

Neoplasms Benign, Malignant and Unspecified (incl. cysts and polyps): benign breast neoplasm

Nervous System Disorders: cerebrovascular accident, convulsion, epilepsy, grand mal convulsion, hypoaesthesia, intracranial aneurysm, paralysis

Pregnancy, Puerperium and Perinatal Conditions: abortion spontaneous, premature delivery

Psychiatric Disorders: Suicidal ideation

Renal and urinary Disorders: Renal infarct

Reproductive System and Breast Disorders: menorrhagia

Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism

Vascular Disorders: deep vein thrombosis, thrombosis

DRUG INTERACTIONS

Overview

The concurrent administration of oral contraceptives with other drugs may lead to breakthrough bleeding and/or may result in an altered response to either agent (see Table 2 and Table 3). Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low-dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before oral contraceptives are prescribed.

No formal drug-drug interaction studies were conducted with LOLO.

Drug-Drug Interactions

Table 2
Drugs which may decrease the efficacy of oral contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry	For short course, use additional method or use another drug. For long course, use another method.
	Rifabutin Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of oral contraceptives, increasing the risk of cholestatic jaundice.	
Anticonvulsants	Carbamazepine Ethosuximide Felbamate Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone Topiramate	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose oral contraceptives (50 µg ethinyl estradiol), another drug or another method.
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy.	Use another method.
HCV Protease Inhibitors	Boceprevir Telaprevir	Uncertain, but may be due to an effect on GI transporters, leading to a decrease in the AUC of ethinyl estradiol.	Exposure to ethinyl estradiol was decreased when co-administered with telaprevir or boceprevir. Additional methods of non-hormonal contraception should be used when hormonal contraceptives are co-administered with telaprevir or boceprevir.
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.

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Sedatives and Hypnotics	Barbiturates Benzodiazepines Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose oral contraceptives.
Other Drugs	Antihistamines Analgesics Antimigraine preparations Phenylbutazone preparations Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	
	Bosentan	Induction of hepatic microsomal enzymes.	Consider switching to a non-hormonal contraceptive method or adding a barrier method to oral contraceptive therapy

Table 3
Modification of other drug action by oral contraceptives

Class of Compound	Drug	Modification of other drug action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II adrenoreceptor agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients.	Use another method
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another method.
	Lamotrigine	Decreased lamotrigine levels, may lead to breakthrough seizures.	Use another method.
Antidiabetic drugs	Oral hypoglycemics and insulin	Oral contraceptives may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin oral contraceptive or another method. Monitor blood glucose.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen oral contraceptive or use another method.
	Beta blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.

Class of Compound	Drug	Modification of other drug action	Suggested Management
	ASA	Effects of ASA may be decreased by the short-term use of oral contraceptives.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic acid		Theoretically, a hypercoagulable state may occur because oral contraceptives augment clotting factors.	Avoid concomitant use.
Betamimetic agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing oral contraceptives can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as oral contraceptives may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol lowering agents	Clofibrate	Their action may be antagonized by oral contraceptives. Oral contraceptives may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic acid		Oral contraceptives have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine tranquilizers	All phenothiazines, reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose oral contraceptives. If galactorrhea or hyperprolactinemia occurs, use other method.
Sedatives and hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic antidepressants	Clomipramine (possibly others)	Increased side effects: eg, depression	Use with caution.
Vitamin B_{12}		Oral contraceptives have been reported to reduce serum levels of Vitamin B_{12}	May need to increase dietary intake, or supplement.

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

Drug-Food Interactions
LOLO tablets may be administered without regard to meals.

Administration of food with a single-dose of a LOLO combination tablet did not affect the maximum concentration of norethindrone and increased the extent of absorption by 24%; it decreased the maximum concentration of ethinyl estradiol by 23% and did not affect the extent of absorption.

Administration of food with a single-dose of a LOLO ethinyl estradiol alone tablet decreased the maximum concentration of ethinyl estradiol by 31% and did not affect the extent of absorption.

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

Drug-Laboratory Test Interactions
Results of laboratory tests should be interpreted with the knowledge that the patient is taking an oral contraceptive. The following laboratory tests are modified:

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

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

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

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

Gonadotropins
LH and FSH levels are suppressed by the use of oral contraceptives. Wait 2 weeks after discontinuing the use of oral contraceptives before measurements are made.

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

Tissue Specimens
Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures and PAP smears are submitted for examination.

Drug-Lifestyle Interactions
No studies on the effects of LOLO on the ability to drive or use machines have been performed.

Noncontraceptive Benefits of Oral Contraceptives
Several health advantages other than contraception have been reported:

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

DOSAGE AND ADMINISTRATION

Dosing Considerations
To achieve maximum contraceptive effectiveness, LOLO should be taken exactly as directed and at intervals not exceeding 24 hours.

LOLO tablets may be administered without regard to meals.

LOLO provides a regimen consisting of 24 blue estrogen-progestin tablets, 2 white estrogen-only tablets, and 2 lilac placebo tablets.

Recommended Dose
During the first cycle of use:
The possibility of ovulation and conception prior to initiation of medication should be considered. The patient is instructed to begin taking LOLO on either Day 1 of menstruation (Day 1 Start) or the first Sunday after the onset of menstruation (Sunday Start). If menstruation begins on a Sunday, the first tablet (blue) is taken that day. One blue tablet should be taken daily for 24 consecutive days followed by one white tablet for 2 consecutive days, followed by one lilac

tablet daily for 2 consecutive days. During the first cycle with a Sunday start, contraceptive reliance should not be placed on LOLO until a blue tablet has been taken daily for 7 consecutive days and a non-hormonal back-up method of birth control (such as latex or polyurethane condoms or spermicide) should be used during those 7 days. LOLO is effective from the first day of therapy if the tablets are begun on the first day of the menstrual cycle.

The patient begins her next and all subsequent 28-day courses of tablets on the same day of the week on which she began her first course, following the same schedule: 24 days on blue tablets – 2 days on white tablets - 2 days on lilac tablets. If in any cycle the patient starts tablets later than the proper day, she should protect herself against pregnancy by using a non-hormonal back-up method of birth control until she has taken a blue tablet daily for 7 consecutive days.

Special Notes on Administration

Switching from another hormonal method of contraception:

When the patient is switching to LOLO after completing a 21-day regimen of oral contraceptive tablets, transdermal patches, or a vaginal ring, she should wait 7 days after her last tablet, patch, or ring before she starts LOLO. She will probably experience withdrawal bleeding during that week. She should be sure that no more than 7 days pass after her previous 21-day regimen. When the patient is switching to LOLO after completing a 28-day regimen of oral contraceptive tablets, she should start her first pack of LOLO on the day after her last tablet. She should not wait any days between packs. The patient may switch any day from a progestin-only pill and should begin LOLO the next day. If switching from an implant or injection, the patient should start LOLO on the day of implant removal or, if using an injection, the day the next injection would be due. If switching from an IUD, depending on the timing of removal, back-up contraception may be needed.

If spotting or breakthrough bleeding occurs:

Breakthrough bleeding or spotting may occur in women taking COCs, especially during the first 3 months of use. The patient is instructed to continue on the same regimen. This type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her healthcare provider.

If withdrawal bleeding does not occur:

Although pregnancy is unlikely if LOLO is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed schedule (missed one or more tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken. If the patient has adhered to the prescribed regimen and misses two consecutive periods, pregnancy should be ruled out. Hormonal contraceptives should be discontinued if pregnancy is confirmed.

Use after pregnancy, abortion or miscarriage:

LOLO should be initiated no earlier than 28 days postpartum in the nonlactating mother due to the increased risk for thromboembolism. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (see **CONTRAINDICATIONS**, and **WARNINGS AND PRECAUTIONS**

concerning thromboembolic disease). The patient should be advised to use a non-hormonal back-up method for the first 7 days of tablet taking. However, if intercourse has already occurred, the possibility of ovulation and conception prior to initiation of medication should be considered.

LOLO may be initiated immediately after a first-trimester abortion or miscarriage; if the patient starts LOLO immediately, additional contraceptive measures are not needed.

Missed Dose

The possibility of follicular growth, ovulation, and risk of pregnancy increases with each successive day that scheduled blue or white tablets are missed. If the patient misses one or more lilac tablets, she is still protected against pregnancy provided she begins taking the active blue tablets again on the proper day. Delayed restarting of active pills may result in reduction of contraceptive reliability.

Missing pills can cause spotting or light bleeding, even if the missed pills are made up. If breakthrough bleeding occurs following missed blue or white tablets, it will usually be transient and of no consequence. Nausea may also occur on the days two pills are taken to make up for missed pills.

The patient should be instructed to use the following chart if she misses 1 or more of her birth control pills. She should be told to match the number of pills missed with the appropriate starting time for her dosing regimen.

<table>
<tr><th>Sunday Start</th><th>Day 1 Start</th></tr>
<tr><td>Miss 1 blue Pill</td><td>Miss 1 blue Pill</td></tr>
<tr><td colspan="2">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.</td></tr>
<tr><td>Miss 2 blue pills in a row in Week 1 or Week 2</td><td>Miss 2 blue pills in a row in Week 1 or Week 2</td></tr>
<tr><td colspan="2">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 back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.</td></tr>
<tr><td>Miss 2 pills (blue or white) in a row in Week 3 or Week4</td><td>Miss 2 pills (blue or white) in a row in Week 3 or Week 4</td></tr>
<tr><td>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 back-up (barrier) 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.</td><td>1. Safely dispose of the rest of the pill pack and start a new pack that same day.
2. Use a back-up (barrier) 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.</td></tr>
<tr><td colspan="2">If you miss two periods in a row, call your doctor or clinic.</td></tr>
</table>

Sunday Start	Day 1 Start
Miss 3 or more (blue or white) pills in a row at any time	**Miss 3 or more pills (blue or white) in a row at any time**
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 back-up (barrier) 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	1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) 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.	

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

OVERDOSAGE

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

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Like other combination oral contraceptives, LOLO acts by suppression of gonadotropins. These actions include: suppression of follicular development and inhibition of ovulation, other alterations include changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).

Pharmacodynamics

No pharmacodynamic studies were conducted with LOLO.

Pharmacokinetics

Table 4
Summary of Pharmacokinetic Parameters LOLO (n=15)

Regimen	Study Day	Analyte	Arithmetic Mean[a] (%CV) by Pharmacokinetic Parameter				
			C_{max} (pg/mL)	t_{max} (h)	$AUC_{0–24h}$ (pg/mL·h)	C_{min} (pg/mL)	C_{avg} (pg/mL)
Single Dose LOLO combination tablet[c]	1	NE	7360 (21)	1.7 (1.3–6.0)	33280 (33)	--	--
		EE	50.9 (27)	1.3 (1.0-6.0)	389.9 (27)	--	--
		SHBG	--	--	--	54.8 (33) [b]	--
Multiple Dose LOLO combination tablet[d] x 24 days	24	NE	13900 (34)	1.3 (0.7–3.0)	84160 (41)	917 (84)	3510 (41)
		EE	71.3 (33)	1.3 (0.3–2.0)	621.3 (41)	10.0 (92)	25.9 (41)
		SHBG	--	--	--	109 (38)	--
Multiple Dose LOLO combination tablet x 24 days and EE alone tablet[d] x 2 days	26	EE	49.9 (34)	1.3 (0.7–3.0)	403.6 (50)	--	--

EE: ethinyl estradiol; NE: norethindrone; SHBG = Sex hormone binding globulin (nmol/L)
Cmax = Maximum plasma concentration (pg/mL); tmax = Time of Cmax (h); AUC0–24h = Area under plasma concentration versus time curve from 0 to 24 hours (pg·h/mL); Cmin = Minimum plasma concentration (pg/mL); Cavg = Average plasma concentration = AUC0–24h/24 (pg/mL);
%CV = Coefficient of Variation (%);
[a] The median (range) is reported for tmax
[b] The Cmin concentration reported for SHBG is the pre-dose concentration
[c] LOLO combination tablets contain 1 mg norethindrone acetate and 10 mcg ethinyl estradiol
[d] LOLO EE alone tablets contain 10 mcg ethinyl estradiol

Absorption: Norethindrone acetate is completely and rapidly deacetylated to norethindrone after oral administration, and the disposition of norethindrone acetate is indistinguishable from that of orally administered norethindrone. Norethindrone acetate and ethinyl estradiol are rapidly absorbed from LOLO, with maximum plasma concentrations of norethindrone and ethinyl estradiol generally occurring 1 to 2 hours postdose. Both are subject to first-pass metabolism after oral dosing, resulting in an absolute bioavailability of approximately 64% for norethindrone and 55% for ethinyl estradiol.

The rate of norethindrone and ethinyl estradiol absorption from LOLO tablets containing the combination of 1 mg norethindrone acetate and 10 mcg ethinyl estradiol is slower than that from a norethindrone suspension/ethinyl estradiol solution, but the extent of absorption is equivalent.

Ethinyl estradiol bioavailability from LOLO tablets containing 10 mcg ethinyl estradiol alone is equivalent to that from an ethinyl estradiol solution.

The plasma norethindrone and ethinyl estradiol pharmacokinetic profiles and serum sex hormone binding globulin (SHBG) concentrations following multiple-dose administration of LOLO were characterized in 15 healthy female volunteers. The mean plasma concentrations are shown below (Figures 1 and 2), and pharmacokinetic parameters are found in Table 4.

Ethinyl estradiol and norethindrone C_{max} values increase by a factor of 1.4 and 1.9, respectively, following 24 days administration of LOLO combination tablets as compared to single-dose administration. Ethinyl estradiol and norethindrone $AUC_{0–24h}$ values increase by a factor of 1.6 and 2.5, respectively, following 24 days administration of LOLO combination tablets as compared to single-dose administration. Norethindrone concentrations more than double by Day

24 due to both accumulation and increased SHBG concentration. Steady state with respect to ethinyl estradiol and norethindrone is reached by Day 5 and Day 13, respectively.

Figure 1
Mean plasma ethinyl estradiol concentration versus time profiles following single- and multiple-dose oral administration of LOLO to healthy female volunteers (n = 15)

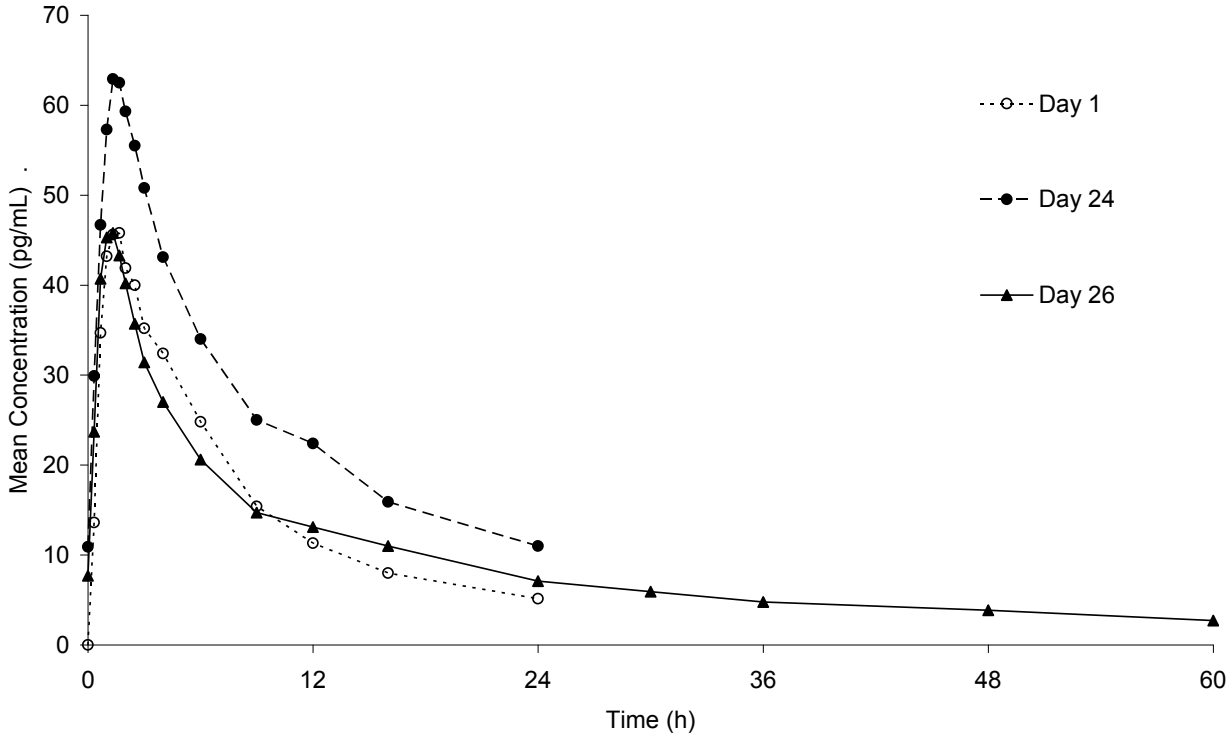
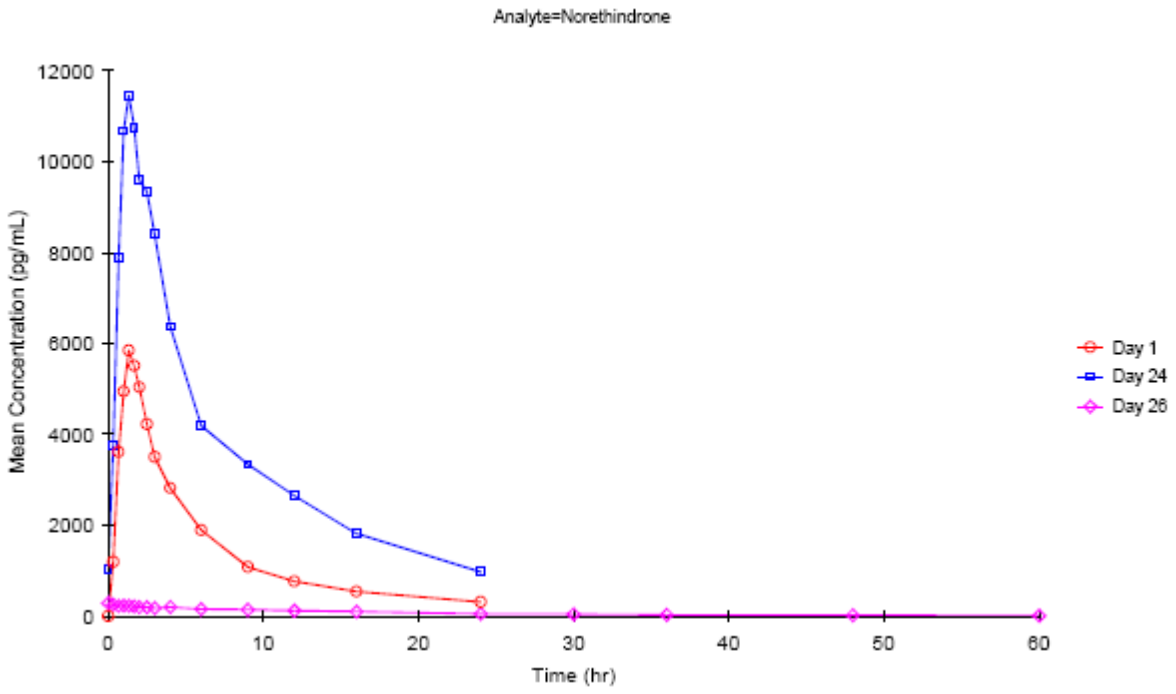


Figure 2
Mean plasma norethindrone concentration versus time profiles following single- and multiple-dose oral administration of LOLO to healthy female volunteers (n = 15)



Distribution: Volume of distribution of norethindrone and ethinyl estradiol ranges from 2 to 4 L/kg. Plasma protein binding of both steroids is extensive (>95%); norethindrone binds to both albumin and SHBG, whereas ethinyl estradiol binds only to albumin. Although ethinyl estradiol does not bind to SHBG, it induces SHBG synthesis.

Metabolism: Norethindrone undergoes extensive biotransformation, primarily via reduction, followed by sulfate and glucuronide conjugation. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites. A small amount of norethindrone acetate is metabolically converted to ethinyl estradiol.

Ethinyl estradiol is also extensively metabolized, both by oxidation and by conjugation with sulfate and glucuronide. Sulfates are the major circulating conjugates of ethinyl estradiol and glucuronides predominate in urine. The primary oxidative metabolite is 2-hydroxy ethinyl estradiol, formed by the CYP3A4 isoform of cytochrome P450. Part of the first-pass metabolism of ethinyl estradiol is believed to occur in gastrointestinal mucosa. Ethinyl estradiol may undergo enterohepatic circulation.

Excretion: Norethindrone and ethinyl estradiol are excreted in both urine and feces, primarily as metabolites. Plasma clearance values for norethindrone and ethinyl estradiol are similar (approximately 0.4 L/hr/kg). Elimination half-lives of norethindrone and ethinyl estradiol following administration of 1 mg norethindrone acetate/10 mcg ethinyl estradiol tablets are approximately 10 hours and 16 hours, respectively.

Special Populations and Conditions

Race: The effect of race on the disposition of norethindrone and ethinyl estradiol after LOLO administration has not been evaluated.

Hepatic Insufficiency: The effect of hepatic disease on the disposition of norethindrone and ethinyl estradiol after LOLO administration has not been evaluated. However, ethinyl estradiol and norethindrone may be poorly metabolized in patients with impaired liver function.

Renal Insufficiency: The effect of renal disease on the disposition of norethindrone and ethinyl estradiol after LOLO administration has not been evaluated. In premenopausal women with chronic renal failure undergoing peritoneal dialysis who received multiple doses of an oral contraceptive containing ethinyl estradiol and norethindrone, plasma ethinyl estradiol concentrations were higher and norethindrone concentrations were unchanged compared to concentrations in premenopausal women with normal renal function.

STORAGE AND STABILITY

Keep this drug and all drugs out of the reach of children.
Store at controlled room temperature (20 - 25° C).

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

LOLO is available in blister cards (dispensers) containing 24 blue active tablets, 2 white active tablets and 2 lilac placebo tablets. Each blue, round tablet contains 1 mg of norethindrone acetate and 10 mcg of ethinyl estradiol and is imprinted with WC on one side and 421 on the other. Each white, hexagonal tablet contains 10 mcg of ethinyl estradiol and is imprinted with WC on one side and 422 on the other. Round, lilac placebo tablets are unmarked.

Non-medicinal ingredients for the blue tablets and white tablets include: Lactose monohydrate, mannitol, microcrystalline cellulose, magnesium stearate, povidone, sodium starch glycolate and vitamin E. The blue tablets also contain FD&C Blue No. 1 Aluminum Lake.

Ingredients for the lilac tablets include: Acacia, lactose monohydrate, magnesium stearate, corn starch, sugar talc and colours FD&C Blue No.1, FD&C Red No.3 and FD&C Red No. 40.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

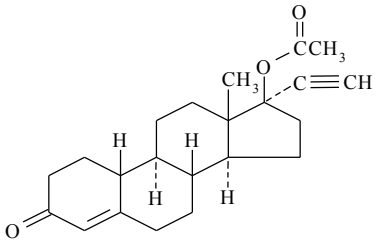
Drug Substance

Proper name: norethindrone acetate

Chemical name: [19-Norpregn-4-en-20-yn-3-one, 17-(acetyloxy)-, (17α)-]*[M2.3.S.1.1]*

Molecular formula and molecular mass: $C_{22}H_{28}O_3$ and 340.07

Structural formula:



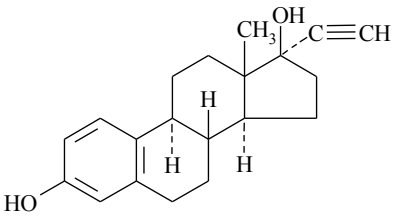
Physicochemical properties: A white solid with a melting point of 157º to 163ºC, freely soluble in dioxane, sparingly soluble in ether, and insoluble in water. Norethindrone acetate is a unique progestin synthesized from plant sterols, which may include soy. Soy is not present in the final drug product.

Proper name: ethinyl estradiol

Chemical name: 17-alpha-ethinyl-l,3,5(10)-estratriene-3,17-beta-diol

Molecular formula and molecular mass: $C_{20}H_{24}O_2$ and 296.41

Structural formula:



Physicochemical properties: A fine white, odorless crystalline powder, insoluble in water but soluble in vegetable oils and organic solvents. Ethinyl estradiol is synthesized from plant sterols, which may include soy. Soy is not present in the final drug product.

CLINICAL TRIALS

General Information

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

Reported Pregnancies per 100 Women per Year:

Combination pill	less than 1 to 3*
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

*Based on the results of one clinical study, about 3 out of 100 women may get pregnant during the first year they use LOLO.

Study demographics and trial design

In a one year (thirteen 28-day cycles) multicenter open-label clinical trial, 1,582 women 18 to 45 years of age, were studied to assess the safety and efficacy of LOLO, completing the equivalent of 15,591 28-day evaluable cycles of exposure. 1,270 women 18-35 years of age were studied to assess the efficacy of LOLO and completed the equivalent of 12,482 28-day evaluable cycles of exposure. The racial demographic of all enrolled women was: Caucasian (74.9%), African-American (11.8%), Hispanic (9.8%), Asian (1.3%), and Other (2.2%). Women with body mass index (BMI) greater than 35 kg/m^2 were excluded from the study. The weight range for those women treated was 89 to 260 lbs., with a mean weight of 150 lbs. Among the women in the trial, 51% had not used hormonal contraception immediately prior to enrolling in this study. Of treated women, 13.7% were lost to follow-up, 10.7% discontinued due to an adverse event, and 8.9% discontinued by withdrawing their consent.

Table 5
Patient Demographics

Study #	Trial design	Dosage, route of administration and duration	No. Study subjects	Mean age (Range)	Mean weight (Range)	Gender
RR-03108	Non-comparative, multicentre study	LOLO x 13 cycles	1582	28.6 years (18 – 45.9 years)	150.1 lb (89 – 260 lb)	Female

Study results

The pregnancy rate (Pearl Index [PI]) in women 18 to 35 years of age was 2. 92 (95% confidence interval 1.94-4.21) pregnancies per 100 women-years of use, based on 28 pregnancies that occurred after the onset of treatment and extending through the 7 days following the last dose of LOLO (See Table 6). Cycles in which conception did not occur, but which included the use of backup contraception, were not included in the calculation of the PI. The PI includes women who did not take the drug correctly.

Table 6
Study Results – Conception Control

	LOLO		
	All Ages N*=1555	**18-35 N*=1270**	**36-45 N*=285**
No. Pregnancies	28	**28**	0
No. 28 day treatment cycles	15591	**12482**	3109
Pearl Index	2.33 (95% CI: 1.55,3.37)	**2.92 (95% CI: 1.94, 4.21)**	0

* N= number of women with evaluable cycles.

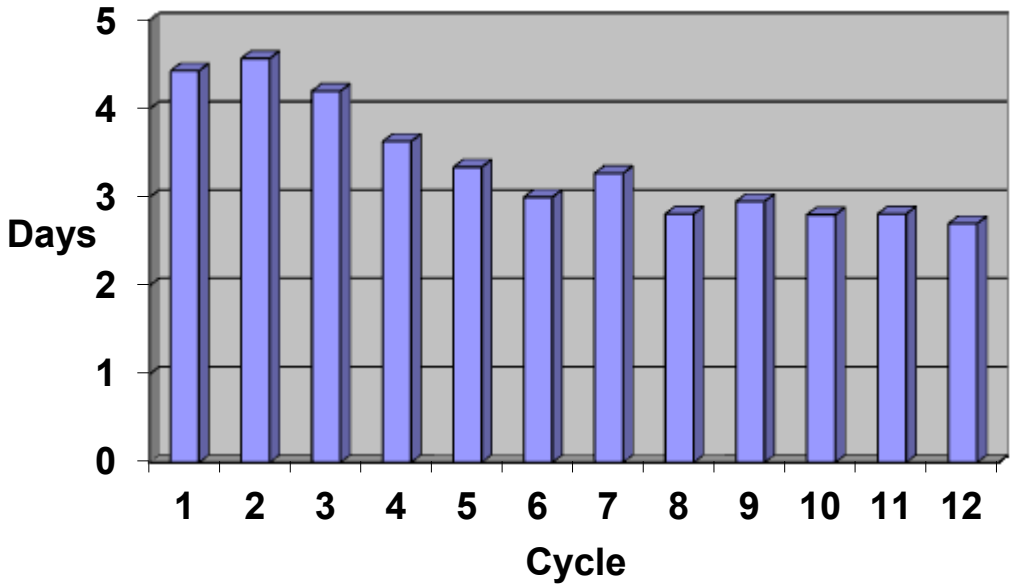
Bleeding Profile

The clinical trial that evaluated the efficacy of LOLO also assessed scheduled and unscheduled (intra-cycle) bleeding and/or spotting (IB/S). The participants in this 12-month clinical trial (N=1,582 who had at least one post-treatment evaluation) completed over 15,000 cycles of exposure.

Total Bleeding/Spotting (scheduled and unscheduled):

The mean number of total bleeding/spotting days (scheduled and unscheduled) was 3.8 days per cycle and tended to decrease throughout the study from Cycle 2 through Cycle 12 (See Figure 3).

Figure 3: Mean Number of Bleeding Days per Cycle (N=1582)



Scheduled (withdrawal) Bleeding/Spotting:

Scheduled (withdrawal) bleeding and/or spotting remained fairly constant over the one year study, with an average of less than 2 days per cycle when including all women and all cycles. The incidence of withdrawal bleeding decreased over the course of the study, from 43% of subjects during Cycle 1 to 22% during Cycle 13. Incidence and duration of withdrawal bleeds tended to be greater in new users than in switchers.

Intensity of a bleeding/spotting episode was defined by a score of 0-3 where 0 = none, 1=light; 2 = normal; and 3 = heavy. The overall mean median intensity of withdrawal bleeding / spotting was 1.53 for Cycle 2 through Cycle 13.

Unscheduled (intra-cycle) Bleeding and or Spotting (IB/S):

The mean number of days per cycle of IB/S decreased over the course of the study from 3.2 days during Cycle 2 to 1.8 days during Cycle 13. The mean duration throughout the study was 2.6 days/cycle.

A total of 1,257 women (85.9%) experienced IB/S at some time during Cycles 2-13 of this study. The incidence of IB/S was highest during Cycle 2 (53%) and lowest at Cycle 13 (36%).

Subjects in the study reported an average of 0.53 episodes per cycle of IB/S during the study. The mean maximum intensity score for IB/S episodes was 1.6 for Cycles 2 through Cycle 13. In all subgroups (new users, switchers, 18-35 and 36-45) the numbers of IB/S, spotting only and bleeding-only days per cycle decreased over the course of the study. The incidence of IB/S, the mean number of episodes and the mean intensity for IB/S were higher in younger patients 18-35 than those 36 to 45. Measures of IB/S such as incidence and number of episodes, and maximum

intensity tended to be higher in new users than in switchers, and decreased over the course of the study.

Amenorrhea:
The incidence of amenorrhea (absence of bleeding throughout the cycle) during Cycles 1 to 3 was approximately 30% to 32%, and increased to 49% for Cycle 13. In general the incidence of absence of bleeding was higher in older subjects (age 36-45), and in switchers vs. new users.

DETAILED PHARMACOLOGY

See **ACTION AND CLINCIAL PHARMACOLOGY, Mechanism of Action** for additional information.

Both norethindrone (NE) and ethinyl estradiol (EE) have been subject to extensive biological examination over the past four decades. Norethindrone, using the Clauberg assay with rabbits, has been variously estimated to possess an oral progestational activity at least 10 times that of injected progesterone. Only slight estrogenic activity along with some androgenic activity (9% that of methyl testosterone) has been evident. Ethinyl estradiol has been demonstrated to be slightly more active than 17R-estradiol using the vaginal cornification test in rats.

Norethindrone/ethinyl estradiol, in the ratio of 1.0/0.035, fed to female rats for 22 days at a daily dose of 0.15 mg/kg was effective in reducing the littering activity during a period of 15 days cohabitation with fertile males. Subsequent to the dosing period, these females regained their fertility.

Estrogenic, progestational and antigonadotropic characteristics are revealed for the endocrine profile of this combination. In female rats, a uterotropic effect is clearly demonstrated for a range of 0.1-0.4 mcg, total oral dose. In rabbits a McPhail index of 2.6 is recorded at a total oral dose of 0.8 mg of this progestin/estrogen combination. At a total dose of 450 mcg (based on EE content) compensatory ovarian hypertrophy is completely inhibited in hemicastrate female rats.

TOXICOLOGY

Toxicity Studies of Norethindrone Acetate (NA) in Animals

The LD_{50} value of NA (on intraperitoneal administration to rats was greater than 1000 mg per kg body weight. The drug produced no toxic effects or abnormalities when administered orally to dogs in a single 30 mg dose. Administration of NA by the drug-diet method in rats over a period of 41 weeks produced depression in food intake and weight gain comparable to that following the use of norethindrone. Animals received average daily doses of 6, 14, and 27 mg per kg body weight.

Hematocrit, hemoglobin and leukocyte counts were not noticeably affected. Cholesterol values were low in all drug-fed animals, but all other microchemical determinations (minerals, transaminase, proteins, bilirubin, glucose and urea nitrogen) revealed normal values. Histologic examination of tissues showed functional depression of testes and seminal vesicles and atrophy of pituitary and adrenal glands at the two higher dosage levels. Liver cell atrophy and several

deviations of a minor nature were also noted.
Results indicated that the acetate is as well tolerated as norethindrone in continuous long-term use.

Long-Term Use of Norethindrone in Monkeys
Long-term oral administration of norethindrone to female rhesus monkeys produced only temporary changes in ovarian function. Six monkeys were treated for two years and 12 monkeys for one year at a dosage of 2.5 mg daily for 21 days of each cycle. This is comparable to a dosage of 25 mg daily for eight-and four-year periods in humans. Extensive studies were conducted on the blood, bone marrow, and on the various other tissues and organs, particularly the ovaries. The only noteworthy differences between control and treated animals were found in the genital organs and the pituitary. The treated monkeys could not be differentiated from control on the basis of general health, alertness, and behaviour. Bleeding usually started on the third or fourth day after discontinuation of drug administration each month, lasted three or four days, and was never heavy.

Ovaries from animals treated for one or two years were small, whitish with only small follicles visible, and no sign of recent rupture or of corpora lutea. Germinal epithelium was intact, and the layer of primordial ovocytes and young follicles appeared normal. Inside this cortical layer were small and medium-sized vesicular follicles and many corpora atretica, remnants of old follicles. Follicles had developed normally until the vesicular stage and then degenerated before attaining their full preovulatory growth.

Ovocytes appeared normal in all stages of development until the last pre-ovulatory step when maturation was inhibited. Uteri of treated monkeys had proliferative endometria with no decidual changes in the stroma. The vaginal tracts exhibited moderate to considerable epithelial cornification. Mammary glands were in the resting stage. Pituitaries of treated monkeys showed a decrease of basophilic cells.

Normal ovulatory cycles resumed shortly after medication was stopped. The sexual skin increased in redness, the vaginal epithelium became highly carnified during ovulation, and corpora lutea developed in the ovaries. The number and appearance of ova were normal, as was the rate of atresia. Endometria were proliferative or secretory. The ability to conceive also returned. The conception rate in the treated group compared favourably with that in the control group. Babies of treated animals were all normal at birth, and the females developed normally.

In summary, it was concluded from these studies that continuous administration of norethindrone for periods of one and two years suppressed ovulation without permanent effects on ovarian function and fertility of monkeys.

Chronic Oral Toxicities in Monkeys
Chronic oral toxicity studies were conducted in 8 immature rhesus monkeys - 4 males and 4 females. Norethindrone was administered in the amount of 2.5 mg per kg daily, five days a week for 183 days. No gross or microscopic signs of drug toxicity were found from blood studies, biopsies or at autopsy. As might be anticipated, testicular atrophy occurred in the males. There was also evidence of hormonal stimulation of the sexual skin and mammary glands of both sexes

and of the uterine mucosa in females.

Long-Term Oral Studies of the Combination

Dogs

A combination of 50 parts NA to one part ethinyl estradiol was administered orally for 7 years at dosage levels of 0.051, 0.51, and 1.275 mg/kg/day (equivalent to 1, 10 and 25 times the human dose) in 28-day cycles (21 days of drug administration followed by 7 days of drug withdrawal). Sixteen dogs were initiated as controls and at each dosage level.

All dogs were observed daily. Body weights were recorded weekly. Mammary examinations were conducted once each month. Ophthalmoscopic examinations (indirect technique) were done every six months. Clotting studies were conducted for all dogs twice during the control period, six times during the first year, and semiannually thereafter. Urinary steroid outputs were done once during the control period and annually thereafter.

One control dog and 9 treated dogs died or were sacrificed in extremis during the study. At the end of 7 years of study, the number of dogs surviving in each group was 15, 15, 14 and 10 at the control, 0.051, 0.51, and 1.275 mg/kg/day dosage levels, respectively. One dog at the 0.051 and 0.51 mg/kg/day dosage levels, and 2 dogs at the 1.275 mg/kg/day dose levels were hysterectomized during the study. At the end of 7 years of study, nodules were palpated in the mammary tissue of 5 control dogs, 5 dogs at the 0.051 mg/kg/day dosage level, 6 dogs at the 0.51 mg/kg/day level and 6 dogs at the 1.275 mg/kg/day level. Frequently, nodules disappeared after variable periods of time. Only rarely did nodules reach or exceed 10 mm in diameter, and commonly the behaviour of these indicated that they were cystic in nature.

Alopecia was seen more frequently for treated dogs than for control dogs. Red or brown vaginal discharge was seen most frequently for control dogs and dogs at the 0.051 mg/kg/day dosage level. It was rarely noted for dogs at the 0.51 and 1.275 mg/kg/day dosage levels following 18 months of study. Treated dogs showed greater body weight gains than control dogs. No changes considered to be related to treatment were seen in the mammary development, behaviour or in urinary steroid output. Fibrinogen concentrations were somewhat greater for treated dogs than for control dogs during the 6th and 7th years of study. No other unusual changes were noted in clotting studies.

Ophthalmologic examinations revealed eye changes for several dogs in each group. No drug relationship was noted with respect to the occurrence of these changes. Drug related gross lesions consisting of alopecia and enlarged and/or cystic uteri were observed in a number of dogs at terminal sacrifice. Organ weight effects were limited to increase in uterine weights of individuals in most experimental groups. Microscopically, drug related changes included absence of ovulation in all dogs in the high-dose group and most dogs in the mid-dose group, and increased incidence and severity of cystic endometrial hyperplasia and uterine adenomyosis in dogs in the high dose group.

The occurrence of benign tumours in vaginas and uteri of several dogs in the high dose group was considered drug related. Hyperplastic nodules and benign tumours occurred in mammary

glands of dogs both in control and treated groups, but the incidence at the high-dose level was somewhat greater. No malignant mammary neoplasm occurred in any of the dogs in this study.

Monkeys

A combination of 50 parts of NA to one part ethinyl estradiol was administered orally to mature female rhesus monkeys in a long-term study for a period of 10 years at dosage levels of 0.051,0.51, and 2.55 mg/kg/day (1, 10, and 50 times the human dose). The dosing regimen consisted of consecutive cycles of 21 days of drug administration followed by 7 days of drug withdrawal. Sixteen monkeys were assigned to each treatment group; while an additional 16 animals received the food vehicle only. Daily observations of general health revealed no evidence of overt effects of drug treatment or significant changes in behaviour. The percent body weight gain of surviving animals was comparable, although the body weights of the treated groups were less than controls at some intervals.

Red vaginal discharge occurred with greater frequency in control and low-dose groups and was usually observed in the withdrawal phase of the mid-and high-dose groups, reflecting the pharmacologic action of the drug combination. No drug related alterations were noted in vaginal cytology or mammary development.

A retinal macular granularity, with and without foci of altered reflectivity, was noted in both control and treated animals beginning at 6 years. Although the incidence and severity of these alterations appeared to be greater in treated animals, no definite relationship to drug administration was considered to have been established.

Reduced total platelet count and increased fibrinogen concentrations were noted more frequently for treated monkeys during the initial 90 months and 48 months of study, respectively. An occasional animal showed an elevated postprandial glucose concentration, but no treatment or dosage relationship was apparent. No drug related alteration in urinary steroid output was observed.

Small nodules were palpable in or near the mammary tissue of five, four, three, and two monkeys in the control, 0.051, 0.51, and 2.55 mg/kg/day dosage groups, respectively, at least at one examination. Detailed physical examinations also revealed an abdominal mass in 2 control monkeys, slight curvature of the spine in 2 low-dose animals, and a pulsating saphenous vein in a high-dose animal. No drug related gross lesions were seen in animals that died, were sacrificed *in extremi* during the study or were terminally sacrificed. A frequent cause of death in this study, which is a common occurrence in non-human primates, was acute gastric dilatation. The lesions observed at necropsy appeared spontaneous and unrelated to drug administration.

A statistically significant decrease ($p<0.05$) in the mean absolute uterine weight at the high-dose level was drug related. Microscopically, drug related lesions included uterine atrophy, slightly increased incidence of occurrence of mucus and inflammatory cells in the cervical canal, and dilatation of acini and ducts in mammary glands of monkeys from the high-dose group, were considered to be related to the pharmacologic effect of the test combination.
No drug related neoplasms were observed in the study. A low overall incidence of neoplasms was seen in all organs and tissues examined. A total of 6 neoplastic microscopic lesions were

noted during this entire study; an adenoma (pancreatic duct origin) in a low-dose animal; a granulosa cell carcinoma (ovary) in a control animal with metastasis to liver, lymph node, and lung; and a leiomyoma (uterus) and 2 papillomas (skin) in high-dose animals. With the exception of the granulosa cell carcinoma, no malignant neoplasms were identified.

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PART III: CONSUMER INFORMATION

PrLOLO®

norethindrone acetate and ethinyl estradiol tablets, Mfr Std, and ethinyl estradiol tablets, Mfr Std

This leaflet is part III of a three-part "Product Monograph" published when LOLO was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LOLO. 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

What it does:

LOLO is a birth control pill (combination oral contraceptive) that contains two female sex hormones: the progestin norethindrone acetate and the estrogen ethinyl estradiol. LOLO has been shown to be effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills, except in smokers over 35.

Combination hormonal contraceptives work in two ways:

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

The LOLO pill pack has 24 blue combination pills (with estrogen and progestin hormones) to be taken for 24 days, followed by 2 white estrogen-only pills, followed by 2 lilac placebo pills that do not contain hormone.

Effectiveness of LOLO

Based on the results of one clinical study, about 3 out of 100 women may get pregnant during the first year they use LOLO. The chance of becoming pregnant increases with incorrect use.

Women with a Body Mass Index (BMI) above 35 kg/m^2 were not studied in the clinical trial, so it is not known how well LOLO protects against pregnancy in such women. If you are overweight (obese) discuss with your healthcare provider whether LOLO is the best choice for you.

Other Ways to Prevent Pregnancy

Other methods of birth control are available to you. They are usually less effective than birth control pills. 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 3*
Intrauterine device (IUD)	less than 1 to 6
Condom & 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

*Based on the results of one clinical study, about 3 out of 100 women may get pregnant during the first year they use LOLO.

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

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

When it should not be used:

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

- blood clot in the legs, lungs, eyes or elsewhere, or thrombophlebitis (inflammation of the veins).
- stroke, heart attack or coronary artery disease (e.g. angina pectoris) or a condition that may be a first sign of stroke (such as transient ischemic attack or small reversible stroke).
- disease of the heart valves with complications
- severe high blood pressure
- diabetes with complications
- known abnormalities of the blood clotting system that increases your risk for developing blood clots
- very high blood cholesterol or triglyceride levels
- over age 35 and smoke
- migraine headaches
- you are scheduled for major surgery
- prolonged bed rest
- jaundice (yellowing of the eyes or skin), liver disease or liver tumour
- known or suspected cancer of the breast or uterus (womb) or other estrogen-dependant cancer
- unusual vaginal bleeding without a known reason
- loss of vision due to blood vessel disease of the eye
- you are pregnant or suspect you may be pregnant
- pancreatitis (inflammation of the pancreas) associated with high levels of fatty substances in your blood

- allergy (hypersensitivity) to ethinyl estradiol, norethindrone acetate or to any of the other ingredients in LOLO (see **What the medicinal ingredients are** and **What the non-medicinal ingredients are**).

Tell your doctor if you have ever had any of the above conditions (your doctor can recommend another method of birth control).

What the medicinal ingredients are:
Norethindrone acetate and ethinyl estradiol

What the non-medicinal ingredients are:
Non-medicinal ingredients for the blue tablets and white tablets include: Lactose monohydrate, mannitol, microcrystalline cellulose, magnesium stearate, povidone, sodium starch glycolate and vitamin E. The blue tablets also contain FD&C Blue No. 1 Aluminum Lake.

Ingredients for lilac placebo tablets include: Acacia, lactose monohydrate, magnesium stearate, corn starch, sugar, talc and colours (FD&C Blue No.1, FD&C Red No.3, FD&C Red No. 40).

What dosage forms it comes in:
LOLO (norethindrone acetate and ethinyl estradiol, and ethinyl estradiol) tablets are available in a 28-day regimen.

Each blister pack contains 24 blue, 2 white and 2 lilac tablets. Each blue tablet contains 1.0 mg norethindrone acetate, and 0.010 mg ethinyl estradiol. Each white tablet contains 0.010 mg ethinyl estradiol. The lilac placebo tablets do not contain any active ingredients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Cigarette smoking increases the risk of serious cardiovascular side effects (heart and blood vessels problems) associated with the use of hormonal contraceptives. This risk increases with age, particularly in women over 35 years of age, and the number of cigarettes smoked. For this reason, LOLO should not be used by women who are over 35 years of age and 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.

BEFORE you use LOLO, talk to your doctor or pharmacist if you:
- smoke
- are overweight
- have a history of breast disease (e.g. breast lumps) or family history of breast cancer
- have high blood pressure
- have high cholesterol
- have diabetes
- have heart or kidney disease
- have a history of seizures/epilepsy
- have a history of depression
- have a history of liver disease or jaundice
- wear contact lenses
- have uterine fibroid tumours (benign tumours of the uterus)
- may be pregnant or are breast feeding
- have systemic lupus erythematosus
- have inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- have haemolytic uremic syndrome
- have sickle cell disease
- have problems with the valves in your heart and/or have an irregular heart rhythm
- have been told that you have a condition called hereditary angioedema or if you have had episodes of swelling in body parts such as hands, feet, face or airway passages

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

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

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

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

LOLO 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 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 LOLO 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 LOLO outweigh the risks, you should be aware of the following:

THE RISKS OF USING LOLO

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

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 highest during the first year a woman uses a hormonal contraceptive. Clots may 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 blood clot in the leg.
- Crushing chest pain or heaviness. These symptoms could indicate a possible heart attack.
- Sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, 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 possible blood clot in the eye.
- Other signs of a blood clot can include sudden pain, swelling and slight blue discoloration of an extremity.

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.

If you have breast cancer now, or have had it in the past, do not use birth control pills because some breast cancers are sensitive to hormones.

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

ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS OF 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. Chronic infection with the Human Papilloma Virus (HPV) is believed to be the most important risk factor for cervical cancer. However, there is insufficient evidence to rule out the possibility that oral contraceptives may cause such cancers.

4. Liver tumours
The short and long-term use of birth control pills also has been linked with the growth of liver tumours or liver injury (e.g., hepatitis, abnormal hepatic function). Such injury or tumours are **extremely** rare.

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

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

6. Use in pregnancy
Birth control pills should not be taken by pregnant women. 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 LOLO after childbirth, miscarriage or therapeutic abortion.

8. Pregnancy after stopping LOLO
You will have a menstrual period when you stop using LOLO. 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. These hormones may decrease the flow of breast milk. If birth control pills are not resumed until nursing is established, however, the quantity and quality of breast milk does not seem to be affected. 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 and prevent them from working properly making them less effective in preventing pregnancy or causing unexpected bleeding (spotting or breakthrough bleeding). Please inform your doctor or pharmacist if you are taking or have recently taken any other medications or herbal products, even those without a prescription. Also tell any doctor or dentist (or the dispensing pharmacist) who prescribes another medicine that

you use LOLO. They can tell you if you need to use an additional method of contraception and if so, for how long.

Drugs that may interact with LOLO include:

- drugs used for the treatment of epilepsy (e.g., primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate);
- drugs used for the treatment of tuberculosis (e.g., rifampicin, rifabutin)
- drugs used for treatment of HIV infections (e.g., ritonavir)
- drugs used for Hepatitis C virus (HCV) (e.g., boceprevir, telaprevir)
- antibiotics (e.g., penicillins, tetracyclines, metronidazole) for infectious diseases
- antifungals (e.g. griseofulvin)
- cholesterol lowering agents (e.g. clofibrate)
- anti-coagulants (blood thinners)
- the herbal remedy St. John's wort
- antihypertensive drugs (for high blood pressure)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (e.g. benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- pain medication (meperidine)
- antidepressants (e.g. clomipramine)
- other drugs such as phenylbutazone, antihistamines, analgesics, antimigraine preparations, Vitamin E and Vitamin B_{12}
- cyclosporine
- antacids (use 2 hours before or after taking LOLO)
- bosentan

LOLO may also interfere with the working of other drugs. *This is not a complete list of possible drug interactions with* LOLO. *Talk to your doctor for more information about drug interactions.*

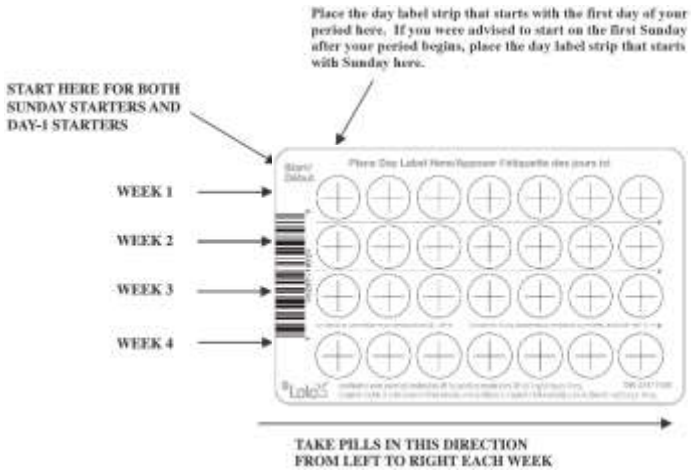
PROPER USE OF THIS MEDICATION

Usual dose:

BEFORE YOU START TAKING YOUR PILLS:

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

2. **LOOK AT YOUR PILL PACK:** LOLO contains 24 "active" BLUE pills (with progestin and estrogen hormones) for weeks 1, 2, 3 and the first part of week 4, 2 WHITE estrogen only pills, and 2 "reminder" LILAC pills (without hormones) for the last part of week 4.



Also, CHECK the pill pack for: 1) where to start taking pills and 2) in what order to take the pills (follow the arrows in the diagram).

3. You should use a second method of birth control (e.g. latex or polyurethane 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 WHILE TAKING THE FIRST 1 to 3 PACKS OF PILLS. If you have spotting or light bleeding or feel sick to your stomach, do not stop taking the pill. This type of bleeding is usually transient and without significance. The problem will usually go away. If it doesn't go away, check with your healthcare provider.

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

7. TAKE ONE PILL EVERY DAY AT THE SAME TIME. If you miss pills you could get pregnant. This includes starting the pack late. The more pills you miss, the more likely you are to get pregnant.

8. IF YOU HAVE VOMITING OR DIARRHEA (within 3 to 4 hours after you take your pill) or IF YOU TAKE CERTAIN MEDICINES, including some antibiotics, or the herbal supplement St. John's wort, your pills may not work as well. Use a back-up method of birth control (such as latex or polyurethane condoms or spermicide) until you check with your healthcare provider.

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

10. THERE IS NO NEED TO STOP TAKING BIRTH

CONTROL PILLS FOR A REST PERIOD

11. IF YOU HAVE ANY QUESTIONS OR ARE UNSURE ABOUT THE INFORMATION IN THIS LEAFLET**,** call your healthcare provider.

WHEN TO START THE FIRST PACK OF PILLS
You have a choice of which day to start taking your first pack of pills. Decide with your healthcare provider which is the best day for you to start. Pick a time of day that will be easy to remember. It is important to take it at about the same time every day.

1. Pick the day label strip that starts with the first day of your period. (This is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins.)

2. Place this day label strip on the top edge of the tablet dispenser over the area that has "Place Day Label Here" printed on the plastic. Having the dispenser labelled with the days of the week will help remind you to take your pill every day.

3. **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 or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

4. LOLO is effective from the first day of therapy if the tablets are begun on the first day of the menstrual cycle (1st day of period). If you start any day other than the day your period begins, use another method of birth control as a back-up method if you have sex anytime for the next 7 days. Latex or polyurethane condoms or spermicide are good back-up methods of birth control.

5. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS.**

WHEN YOU SWITCH FROM A DIFFERENT METHOD OF HORMONAL CONTRACEPTION

- When you switch from another birth control pill, start LOLO on the first day you would have started your previous birth control pack.

- When you switch from a vaginal ring or skin patch, finish the 21 days of use, and wait 7 days after removal of the ring or patch before starting LOLO.

- When you switch from a progestin-only pill, you should start LOLO the next day.

- When you switch from an implant or injectable contraceptive, you should start LOLO on the day of implant removal or, if using an injectable contraceptive, the day on which the next injection would be due.

- If you switch from an IUD, discuss with your healthcare provider when to start LOLO.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY. Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea). Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OF YOUR LOLO Start the next pack on the day after your last lilac "reminder" pill. Do not wait any days between packs. It is not uncommon to miss your period. However, if you have been having regular periods and then do not have a period for 2 cycles or longer, it is possible that you may be pregnant. You should speak to your doctor.

Overdose:

Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea, vomiting and withdrawal bleeding in women.

In case of overdosage, contact your healthcare provider, hospital emergency department, or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
Birth control pills may not be as effective if you miss any blue or white pills, and particularly if you miss the first few or the last few blue pills in a pack. The following chart outlines the actions you should take if you miss one or more birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack. If you miss one or more active pills and do not have a period that month, you may be pregnant, so you should speak to your doctor.

Sunday Start	Day 1 Start
Miss 1 blue Pill	**Miss 1 blue Pill**
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 pills in one day.	
Miss 2 blue pills in a row in Week 1 or Week 2 of your pack	**Miss 2 blue pills in a row in Week 1 or Week 2 of your pack**
1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.	
Miss 2 pills (blue or white) in a row in Week 3 or Week 4 of your pack	**Miss 2 pills (blue or white) in a row in Week 3 or Week 4 of your pack**
1. Keep taking 1 pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) 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 2 periods in a row, call your doctor or clinic.**	1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) 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 2 periods in a row, call your doctor or clinic.**
Miss 3 or more pills (blue or white) in a row at any time	**Miss 3 or more pills (blue or white) in a row at any time**
1. Keep taking 1 pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) 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	1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) 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 2 periods in a row, call your doctor or clinic.	

If you forget either of the 2 lilac "reminder" pills in Week 4, follow these steps:

- Throw away the pills you missed.
- Keep taking one pill each day until the pack is empty.
- You do not need to use a BACK-UP METHOD of birth control.

If you are not sure what to do about the pills you have missed:

- Use a BACK-UP METHOD of birth control anytime you have sex.
- KEEP TAKING ONE ACTIVE (blue or white, depending on the day) PILL EACH DAY until you can reach your healthcare provider.

Always be sure you have on hand:

- non-hormonal back-up method of birth control (e.g. latex or polyurethane 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 Combined Hormonal Contraceptives

Several health advantages have been linked to the use of hormonal contraceptives.

- Reduction in the incidence of cancer of the uterus and ovaries
- Reduction in the likelihood of developing benign (noncancerous) breast disease and ovarian cysts.
- Less menstrual blood loss and more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and premenstrual syndrome (PMS).
- Acne, excessive hair growth and male-hormone- related disorders also may be improved.
- Ectopic (tubal) pregnancy may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Most women do not develop serious and unpleasant side effects from using birth control pills. The most common side effects seen when using LOLO are similar to those seen with other birth control pills and include:

- headache
- nausea
- metrorrhagia (irregular menstrual bleeding)
- breast tenderness
- dysmenorrhea (painful menstrual cramps)
- weight change
- acne
- mood swings

In addition, the following side effects have been observed in women taking combination hormonal contraceptives in general, including LOLO:

- Upper respiratory tract infection (bronchitis, runny or stuffy nose, sore throat, etc.)
- Urinary tract infection
- HPV (Human papilloma virus)
- Abnormal cervical (Pap) smear
- Fungal infection
- Abdominal pain
- Influenza
- Vomiting
- Vaginal infection

- Anxiety
- Depression

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect	**Talk with your doctor or pharma-cist**	**Stop taking drug and call your doctor or pharmacist**
Uncommon		
Sharp chest pain, coughing of blood, or sudden shortness of breath		√
Pain in the calf		√
Crushing chest pain or heaviness in the chest		√
Sudden severe headache or vomiting, dizziness or fainting, disturbances of vision or speech, weakness, or numbness in an arm or leg		√
Sudden partial or complete loss of vision		√
Breast lumps	√	
Severe pain or tenderness in the stomach area		√
Difficulty in sleeping, weakness, lack of energy, fatigue, or change in mood		√
Jaundice or a yellowing of the skin or eyeballs, accompanied frequently by fever, fatigue, loss of appetite, dark-coloured urine, or light-coloured bowel movements		√
Unexpected (abnormal) vaginal bleeding	√	
Unusual swelling of the extremities	√	

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

HOW TO STORE IT

- Keep LOLO and all other medications out of the reach of children.
- Keep the tablets in their original package and store at controlled room temperature (20°-25°C).
- Do not keep medicine that is out of date or that you no longer need.

REPORTING SUSPECTED SIDE EFFECTS

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

Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html.

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.allergan.ca or by contacting the sponsor, Allergan Inc.., at: 1-800-668-6424.

This leaflet was prepared by Allergan Inc.

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