PRODUCT MONOGRAPH

PrGENERESS ™

norethindrone and ethinyl estradiol chewable tablets
0.8 mg / 0.025 mg

ferrous fumarate chewable tablets

Oral Contraceptive

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Date of Revision:
January 31, 2020

Submission Control No.: 234951

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	**Active tablet** chewable tablets/ 0.8 mg norethindrone and 0.025 mg ethinyl estradiol	**Active tablet** chewable tablets/ Lactose monohydrate **Non-hormonal tablet** chewable tablets/ 75 mg ferrous fumarate, from which no therapeutic benefits have been established *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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

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

Each non-hormonal chewable tablet contains 75 mg of ferrous fumarate. No therapeutic benefits from the ferrous fumarate in the non-hormonal chewable tablets have been established.

CONTRAINDICATIONS

GENERESS 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
- a history of or actual prodromi of a thrombosis (e.g., transient ischemic attack, angina pectoris)
- presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
    - severe hypertension (persistent values of ≥160/100 mmHg)
    - hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia (e.g., due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
    - severe dyslipoproteinemia
    - smoking, if over age 35
    - diabetes mellitus with vascular involvement
    - major surgery associated with an increased risk of postoperative thromboembolism
    - prolonged immobilization
- 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 in 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 hypertriglyceridemia
- hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **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 from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, GENERESS, should not be used by women who are over 35 years of age and smoke (see **Cardiovascular** section below).

Oral contraceptives **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** oral contraceptives.

General

Discontinue medication at the earliest manifestation of:

A. **Thromboembolic and Cardiovascular Disorders** such as thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.
B. **Conditions that Predispose to Venous Stasis and to Vascular Thrombosis** (e.g. immobilization after accidents or confinement to bed during long-term illness). Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of combination hormonal contraceptives when surgery is contemplated, see **Peri-Operative Considerations.**
C. **Visual Defects – Partial or Complete**
D. **Papilledema, or Ophthalmic Vascular Lesions**
E. **Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache**
F. **Increase in Epileptic Seizures**

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 GENERESS because breast cancer is a hormonally-sensitive tumour (see **CONTRAINDICATIONS**).

The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age, the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.

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

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

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. For this reason, combination oral contraceptives, including GENERESS, should not be used by women who are over 35 years of age and 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

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

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

Unscheduled (breakthrough or intracyclic) bleeding and spotting sometimes occur in patients on COCs, especially during the first three months of use. If bleeding persists or occurs after previously regular cycles, check for causes such as pregnancy or malignancy. If pathology and pregnancy are excluded, bleeding irregularities may resolve over time or with a change to a different COC.

If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), consider the possibility of pregnancy at the time of the first missed period and take appropriate diagnostic measures. If the patient has adhered to the prescribed regimen and misses two consecutive periods, rule out pregnancy.

Some women may encounter amenorrhea or oligomenorrhea after stopping COCs, especially when such a condition was pre-existent.

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.

VTE, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs.

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

Symptoms of deep venous thrombosis (DVT) can include: unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg, which may be felt only when standing or walking; increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (e.g., “shortness of breath”, “coughing”) are nonspecific and might be misinterpreted as more common or less severe events (e.g., respiratory tract infections).

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). Symptoms of a cerebrovascular accident can include: sudden numbness or weakness of the face, arm, or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling, and slight blue discolouration of an extremity; acute abdomen.

Symptoms of MI can include: pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting, or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

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 (e.g,, 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 <50 µg 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, unexplained partial or complete loss of vision, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, GENERESS 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 1 month prior to **MAJOR** elective surgery. Oral contraceptive use 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 1 normal spontaneous menstrual cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time.

Amenorrhea

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

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

Amenorrhea, especially if associated with breast secretion that continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

Reduced Efficacy

The efficacy of GENERESS may be reduced in the event of non-compliance (missed tablets), gastrointestinal disturbances or concomitant medication (see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS).

Skin

Chloasma may occasionally occur, 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 GENERESS, 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.

Women who do not breastfeed may start COCs no earlier than four weeks postpartum.

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 GENERESS in nursing women.

Pediatrics:

Safety and efficacy of GENERESS have been established in women 18 – 46 years of age. Use of this product before menarche is not indicated.

Geriatrics:

GENERESS has not been studied in postmenopausal women and is not indicated in this population.

Body Mass Index (BMI):

The safety and efficacy of GENERESS in women with a BMI > 35 kg/m^2 have not been evaluated.

<u>Monitoring and Laboratory Tests</u>

Physical Examination and Follow-up

Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination and the family case history carefully noted. In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (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 3 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 serious adverse drug reactions identified with the use of GENERESS:

- depression
- cholelithiasis/acute cholecystitis
- angina pectoris
- hypertension
- headache
- deep vein thrombosis

In the GENERESS Phase 3 study, the most frequent AEs resulting in study discontinuation were those usually associated with COCs, including nausea (17 subjects, 1.0%), weight increased (14 subjects, 0.8%), acne (13 subjects, 0.8%), metrorrhagia (12 subjects, 0.7%), mood altered (6 subjects, 0.4%), and hypertension (6 subjects, 0.4%).

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.

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 gestationisa, 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 for approximating rates.

A Phase 3 clinical trial evaluated the safety and efficacy of GENERESS for pregnancy prevention. The study was a multicenter, non-comparative, open-label study with a treatment duration of 12 months (thirteen 28-day cycles). A total of 1,677 women aged 18-46 were

enrolled and took at least one dose of GENERESS.

The most commonly reported (i.e., by at least 1% of subjects) treatment-emergent adverse events (AEs); the incidence of treatment-emergent AEs by SOC (System Organ Class); is summarized in Table 1 below.

Table 1: Phase 3 Open-Label Efficacy and Safety Study: Most Commonly Reported (by ≥ 1% of subjects) Treatment-Emergent Adverse Drug Events (All Treated Population, N=1677)

System Organ Class	Adverse Reaction Preferred Term	Number (%) of Subjects
Gastrointestinal Disorders	Nausea	102 (6.1%)
	Vomiting	46 (2.7%)
	Diarrhoea	34 (2.0%)
	Gastroenteritis viral	34 (2.0%)
	Abdominal pain	26 (1.6%)
	Toothache	18 (1.1%)
General Disorders and Administration Site Conditions	Fatigue	22 (1.3%)
Infections and Infestations	Bronchitis	46 (2.7%)
	Fungal infection	35 (2.1%)
	Herpes simplex	21 (1.3%)
Investigations	Laboratory test abnormal	48 (2.9%)
	Weight increased	38 (2.3%)
	Smear cervix abnormal	36 (2.1%)
Musculoskeletal and Connective	Back pain	25 (1.5%)

Table 1: Phase 3 Open-Label Efficacy and Safety Study: Most Commonly Reported (by ≥ 1% of subjects) Treatment-Emergent Adverse Drug Events (All Treated Population, N=1677)

System Organ Class	Adverse Reaction Preferred Term	Number (%) of Subjects
Tissue Disorders		
Nervous System Disorders	Headache	80 (4.8%)
	Migraine	25 (1.5%)
	Dizziness	19 (1.1%)
Psychiatric Disorders	Anxiety	36 (2.1%)
	Depression	26 (1.6%)
	Insomnia	17 (1.0%)
	Mood swings	17 (1.0%)
Renal and Urinary Disorders	Urinary tract infection	80 (4.8%)
Reproductive System and Breast Disorders	Dysmenorrhoea	66 (3.9%)
	Vaginitis bacterial	58 (3.5%)
	Vulvovaginal mycotic infection	52 (3.1%)
	Breast tenderness	29 (1.7%)
	Cervical dysplasia	21 (1.3%)
	Metrorrhagia	19 (1.1%)
Respiratory, Thoracic and Mediastinal Disorders	Upper respiratory tract infection	122 (7.3%)
	Nasopharyngitis	121 (7.2%)
	Sinusitis	91 (5.4%)
	Influenza	32 (1.9%)

Table 1: Phase 3 Open-Label Efficacy and Safety Study: Most Commonly Reported (by ≥ 1% of subjects) Treatment-Emergent Adverse Drug Events (All Treated Population, N=1677)

System Organ Class	Adverse Reaction Preferred Term	Number (%) of Subjects
	Pharyngitis streptococcal	26 (1.6%)
	Pharyngolaryngeal pain	26 (1.6%)
	Cough	22 (1.3%)
	Sinus congestion	19 (1.1%)
Skin and Subcutaneous Tissue Disorders	Acne	54 (3.2%)
Vascular Disorders	Hypertension	19 (1.1%)

Note: A subject with multiple occurrences of an AE is counted once within that AE category or system organ class. An AE is treatment-emergent if its date of onset is Day 1 (first dose) or later.

Less Common Clinical Trial Adverse Drug Reactions

The following adverse drug reactions were seen at a frequency of <1% and ≥0.1% in the Phase 3 clinical trial:

Cardiac Disorders: tachycardia, angina pectoris.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distension, constipation, abdominal pain upper, abdominal pain lower, gastritis.

General Disorders and Administration Site Conditions: irritability, oedema peripheral, chills.

Hepatobiliary Disorders: cholelithiasis.

Immune System Disorders: hypersensitivity.

Infections and Infestations: candidiasis.

Investigations: blood pressure increased, alanine aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased.

Metabolism and Nutrition Disorders: increased appetite, fluid retention, hypertriglyceridaemia.

Musculoskeletal and Connective Tissue Disorders: muscle spasms, pain in extremity.

Neoplasms Benign, Malignant, and Unspecified: uterine leiomyoma.

Nervous System Disorders: sinus headache, hypoaesthesia, paraesthesia, somnolence, tension headache, dysgeusia, burning sensation, lethargy.

Psychiatric Disorders: libido decreased, mood altered, affect lability, crying, tearfulness, abnormal dreams, panic disorder.

Reproductive System and Breast Disorders: vaginal infection, breast pain, genital pruritus female, vaginal candidiasis, vaginal discharge, breast mass, premenstrual syndrome, menorrhagia, ovarian cyst, hypertrophy breast, menstruation irregular, genital rash, vaginal odour, vulvovaginal dryness, nipple pain, vaginal haemorrhage, adnexa uteri pain, atrophic vulvovaginitis.

Respiratory, Thoracic, and Mediastinal Disorders: nasal congestion.

Skin and Subcutaneous Tissue Disorders: rash, dermatitis, night sweats, chloasma, hypotrichosis, rash generalized.

Surgical and Medical Procedures: cholecystectomy.

Vascuar Disorders: hot flush.

Post-Market Adverse Drug Reactions

The adverse events reported during post-marketing experience with GENERESS are listed below by system organ class. Causal relationships between the use of GENERESS and these events in post-marketing experience have not been established. The most frequently reported adverse events are presented in bold type.

Cardiac Disorders: **palpitations**

Ear and Labyrinth Disorders: ear disorder

Eye Disorders: vision blurred, pupils unequal, visual impairment

Gastrointestinal Disorders: **nausea, abdominal distension**, abdominal pain upper, vomiting, diarrhoea, abdominal pain, abdominal discomfort, constipation, dyspepsia, flatulence, gastrooesophageal reflux disease, stomatitis, frequent bowel movements, swollen tongue, tooth disorder, abdominal pain lower, dysphagia, eructation, oedema mouth

General Disorders and Administration Site Conditions: **drug ineffective**, fatigue, malaise, pain, irritability, crying, drug ineffective for unapproved indication, asthenia, chest pain, condition aggravated, non-cardiac chest pain, hunger, oedema peripheral, pyrexia

Infections and Infestations: fungal infection, nasopharyngitis, pharyngitis streptococcal

Injury, Poisoning and Procedural Complications: drug administration error, inappropriate schedule of drug administration, medication error, drug dose omission, wrong technique in drug

usage process, accidental exposure to product by child, incorrect drug administration duration, incorrect route of drug administration, fall, laceration, limb injury, incorrect dose administered

Investigations: weight increased, body temperature increased, weight decreased, blood glucose increased, blood follicle stimulating hormone increased

Metabolism and Nutrition Disorders: decreased appetite, increased appetite

Musculoskeletal and Connective Tissue Disorders: muscle spasms, pain in extremity, back pain, sensation of heaviness, muscle twitching, flank pain, neck pain, musculoskeletal chest pain

Nervous System Disorders: **headache**, dizziness, hypoaesthesia, migraine, cerebrovascular accident, dysgeusia, paraesthesia, aphasia, parosmia, disturbance in attention

Pregnancy, Puerperium and Perinatal Conditions: abortion spontaneous, pregnancy

Psychiatric Disorders: depression, mood swings, panic attack, mood altered, confusional state, anxiety, depressed mood

Renal and Urinary Disorders: dysuria, pollakiuria, haematuria

Reproductive System and Breast Disorders: **menstruation irregular, metrorrhagia, menstruation delayed, breast tenderness, dysmenorrhea**, menorrhagia, vaginal discharge, menstrual disorder, coital bleeding, hypomenorrhoea, polymenorrhoea, amenorrhoea, oligomenorrhoea

Respiratory, Thoracic and Mediastinal Disorders: dyspnoea, pulmonary embolism, dry throat

Skin and Subcutaneous Tissue Disorders: **acne**, alopecia, rash, urticarial, skin discolouration, dry skin, pruritus, hypertrichosis, erythema nodosum, skin warm, erythema, pruritus generalised, swelling face

Surgical and Medical Procedures: off label use

Vascular Disorders: hot flush

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 drug-drug interaction studies were conducted with GENERESS.

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.

Table 2 – Drugs which may decrease the efficacy of oral contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
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.
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

Several of the anti-HIV/HCV protease inhibitors (e.g., ritonavir, telaprevir, boceprevir) and nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine) have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase or decrease) in the mean AUC of the estrogen or progestin have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected. Healthcare providers should refer to the label of the individual anti-HIV/HCV protease inhibitor for further drug-drug interaction information.

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.
	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.

Table 3 – Modification of other drug action by oral contraceptives

Class of Compound	Drug	Modification of other drug action	Suggested Management
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: e.g., 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.

Drug-Food Interactions

GENERESS may be administered with or without food. A single-dose administration of GENERESS chewable tablets with food decreased the maximum concentration of norethindrone by 47% and increased the extent of absorption by 10-14% and decreased the maximum concentration of ethinyl estradiol by 39% but not 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 GENERESS 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, GENERESS must be taken exactly as directed. CHEW AND SWALLOW ONE TABLET WITHOUT WATER AT THE SAME TIME EVERY DAY. Tablets must be taken in the order directed on the blister pack. Tablets should not be skipped or taken at intervals exceeding 24 hours. GENERESS tablets may be administered without regard to meals.

Missed Dose

The possibility of follicular growth, ovulation, and risk of pregnancy increases with each successive day that scheduled light green (active) tablets are missed. If the patient misses one or more brown tablets, she is still protected against pregnancy provided she begins taking the active (light green) tablets again on the proper day. Delayed restarting of active tablets 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 light green 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.

Sunday Start	Day 1 Start
Miss 1 light green Pill	**Miss 1 light green Pill**
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.	
Miss 2 light green pills in a row in Week 1 or Week 2	**Miss 2 light green pills in a row in Week 1 or Week 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.	
Miss 2 light green pills in a row in Week 3 or Week4	**Miss 2 light green pills in a row in Week 3 or Week 4**
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.	
Miss 3 or more light green pills in a row at any time	**Miss 3 or more pills light green 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.	

If the patient forgets any of the four brown hormone-free tablets in Week 4, she should be advised to safely dispose of the tablets she missed, and then to keep taking one tablet each day until the pack is empty. A back-up method of birth control is not required.

Advice in case of vomiting or diarrhea: In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken. If vomiting or diarrhea occurs within 3-4 hours after taking a light green tablet, this can be regarded as a missed tablet.

Administration

Instruct the patient to begin taking GENERESS on Day 1 of her menstrual cycle (that is, the first day of her menstrual bleeding). One light green tablet should be taken daily for 24 consecutive days followed by one brown tablet daily for 4 consecutive days. Instruct the patient to use a non-

hormonal contraceptive as back-up during the first 7 days if she starts taking GENERESS other than on the first day of her menstrual cycle.

For postpartum women who do not breastfeed or after a second trimester abortion, GENERESS may be started no earlier than 4 weeks postpartum. Recommend use of a non-hormonal back-up method for the first 7 days. When combined oral contraceptives (COCs) are used during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered. The possibility of ovulation and conception before starting COCs should also be considered.

If the patient is switching from a combination hormonal method such as:

- Another pill
- Vaginal ring
- Patch

- Instruct her to take the first light green pill on the day she would have started a new cycle of her previous birth control pack (Day 1).
- If she previously used a vaginal ring or transdermal patch, she should start using GENERESS on the day she would have restarted the ring or patch.
- Instruct the patient to use a non-hormonal back-up method such as a condom and spermicide for the first 7 days.

If the patient is switching from a progestin-only method such as:

- Progestin-only pill
- Implant
- Intrauterine system
- Injection

- Instruct her to take the first light green pill on the day she would have taken her next progestin-only pill or on the day of removal of her implant or intrauterine system or on the day when she would have had her next injection.
- Instruct the patient to use a non-hormonal back-up method such as a condom and spermicide for the first 7 days.

OVERDOSAGE

There have been no reports of serious ill effects from overdose of oral contraceptives including ingestion by children. Overdosage may cause nausea, and withdrawal bleeding may occur in females.

The 4 non-hormonal brown tablets contain ferrous fumarate. Too much ferrous fumarate can seriously harm a child. Be sure to safely store and dispose of both the non-hormonal and the active tablets.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

COCs lower the risk of becoming pregnant primarily by suppressing ovulation. Other possible mechanisms may include cervical mucus changes that inhibit sperm penetration and endometrial changes that reduce the likelihood of implantation.

Pharmacodynamics

No specific pharmacodynamic studies were conducted with GENERESS.

Pharmacokinetics

Absorption

Norethindrone and ethinyl estradiol are absorbed with maximum plasma concentrations occurring within 2 hours after GENERESS (0.8 mg norethindrone and 0.025 mg ethinyl estradiol) administration (see Table 4). Both are subject to first-pass metabolism after oral dosing, and have bioavailabilities of approximately 64% for norethindrone and 43% for ethinyl estradiol.

The plasma norethindrone and ethinyl estradiol pharmacokinetics following single- and multiple-dose administrations of GENERESS (0.8 mg norethindrone and 0.025 mg ethinyl estradiol) in 17 healthy female volunteers are provided in Table 4.

Following multiple-dose administration of GENERESS (0.8 mg norethindrone and 0.025 mg ethinyl estradiol), mean maximum concentrations of norethindrone and ethinyl estradiol were increased by 126% and 113%, respectively, as compared to single-dose administration. Mean norethindrone and ethinyl estradiol exposures (AUC values) were increased by 239% and 155% respectively, as compared to single-dose administration of GENERESS (0.8 mg norethindrone and 0.025 mg ethinyl estradiol).

Mean sex hormone binding globulin (SHBG) concentrations were increased by 170% from baseline (40.0 pg/mL; CV = 65%) to 108 pg/mL (CV = 45%) at steady-state.

Table 4 – Pharmacokinetic Parameter Values Following Single and Multiple Dose Administration of GENERESS (0.8 mg norethindrone and 0.025 mg ethinyl estradiol)

	Arithmetic mean parameters (%CV)				
Regimen	**Analyte**	**C_{max}**	**t_{max}**	**AUC_{0-24h}**	**$t_{1/2}$ ***
Day 1 (Single Dose) N = 17	NE	9,840 (36)	1.4 (49)	41,680 (47)	
	EE	147 (25)	1.2 (27)	903 (18)	
Day 24 (Multiple Dose) N = 17	NE	22,200 (30)	1.6 (76)	141,200 (32)	10.8
	EE	168 (25)	1.2 (35)	1,400 (32)	17.1

* The harmonic mean for $t_{1/2}$ is presented, EE = ethinyl estradiol; NE = norethindrone
%CV = coefficient of variation; C_{max} = maximum plasma concentration (pg/mL); t_{max} = time of the maximum measured plasma concentration (h); AUC_{0-24h} = area under the plasma concentration versus time curve from time 0 to 24h (pg•h/mL); $t_{1/2}$ = apparent elimination half life (h)

Food Effect

GENERESS (0.8 mg norethindrone and 0.025 mg ethinyl estradiol) may be administered with or without food. A single-dose administration of GENERESS (0.8 mg norethindrone and 0.025 mg ethinyl estradiol) with food decreased the maximum concentration of norethindrone by 47% and increased the extent of absorption by 10-14%, and decreased the maximum concentration of ethinyl estradiol by 39% but not the extent of absorption.

Distribution

The 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, which may subsequently change the volume of distribution of norethindrone over time.

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 is metabolically converted to ethinyl estradiol, such that exposure to ethinyl estradiol following administration of 1 mg of norethindrone acetate is equivalent to oral administration of 2.8 mcg ethinyl estradiol; therefore 0.8 mg norethindrone would be equivalent to the oral administration of 2.6 mcg 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 CYP3A4. 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 0.8 mg norethindrone / 0.025 mg ethinyl estradiol tablets are approximately 11 hours and 17 hours, respectively.

Special Populations and Conditions

Hepatic Insufficiency: No studies have been conducted to evaluate the effect of hepatic disease on the disposition of GENERESS. However, steroid hormones may be poorly metabolized in patients with impaired liver function. Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal (see **WARNINGS AND PRECAUTIONS** - **Hepatic/Biliary/Pancreatic**).

Renal Insufficiency: The pharmacokinetics of GENERESS has not been studied in subjects with renal impairment.

STORAGE AND STABILITY

Store at 20-25ºC (68-77ºF).

Keep out of reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

GENERESS is available in blister packs.

Each blister pack (28 tablets) contains in the following order:

- 24 light green, round tablets (active) imprinted with “WC” on one side and “483” on the other and each containing 0.8 mg norethindrone and 0.025 mg ethinyl estradiol.

Each light green tablet contains lactose monohydrate, povidone, vitamin E, mannitol, microcrystalline cellulose, FD&C yellow no. 6 aluminum lake, FD&C blue no. 1 aluminum lake, D&C yellow no. 10, spearmint flavour, sodium starch glycolate, sucralose and magnesium stearate as excipients.

- 4 brown, round tablets (non-hormonal) imprinted with “WC” on one side and “624” on the other and each containing 75 mg ferrous fumarate (equivalent to 25 mg of elemental iron).

Each brown (non-hormonal) tablet contains ferrous fumarate, mannitol , povidone , microcrystalline cellulose, sodium starch glycolate, magnesium stearate, sucralose, spearmint flavour.

No therapeutic benefits from the ferrous fumarate in the non-hormonal chewable tablets have been established.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

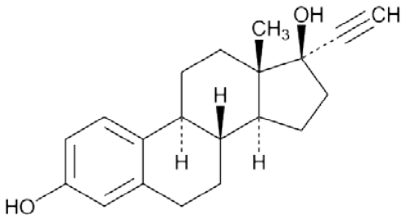
Drug Substance

Proper name: **ethinyl estradiol**

Chemical name: 19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)-

Molecular formula and molecular mass: $C_{20}H_{24}O_2$, and 296.40

Structural formula:



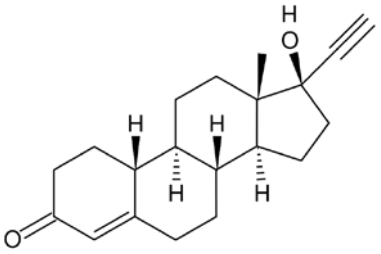
Physicochemical properties: a white to creamy white, odourless, crystalline powder. It is practically insoluble in water; soluble in alcohol, chloroform, ether, vegetable oils, and solutions of fixed alkali hydroxides. Ethinyl estradiol is synthesized from plant sterols, which may include soy. Soy is not present in the final drug product.

Proper name: **norethindrone**

Chemical name: 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one

Molecular formula and molecular mass: $C_{20}H_{26}O_2$, and 298.42

Structural formula:



Physicochemical properties: a white to creamy white, odourless, crystalline powder with a melting point of 202° and 208°C. It is stable in air, practically insoluble in water; soluble in chloroform, and in dioxane, sparingly soluble in alcohol, and slightly soluble in ether.

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 1 year.

Table 5 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

Study demographics and trial design

In a Phase 3 one-year (thirteen 28-day cycles) multicenter, open-label clinical trial, 1677 women 18 to 46 years of age were studied to assess the safety and efficacy of GENERESS. The ethnic origin of the 1,570 treated subjects who were evaluable for efficacy was: Caucasian (72.0%), African-American (13.0%), Hispanic (11.2%) and Asian (1.8%). The weight range was 33.6 to 110.5 kilograms (kg) with a mean weight of 67.6 kg. Women with a BMI >35 kg/m^2 were excluded from the study. Of treated women, 16.2% were lost to follow-up, 8.9% discontinued by withdrawing their consent and 8.5% discontinued due to an adverse event.

Table 6: Phase 3 Open-Label Efficacy and Safety Study PR-00207: Demographic and Baseline Characteristics (MITT Population)

Parameter	N=1570
Age (years)	
Mean (± SD)	28.8 (7.1)
Range	18, 46
Age cohorts, n (%)	
18-35 years	1251 (79.7)
>35 years	319 (20.3)
Ethnic origin, n (%)	
Asian	28 (1.8)
Black	204 (13.0)
Caucasian	1131 (72.0)
Hispanic	176 (11.2)
Native American	7 (0.4)
Other	24 (1.5)
User Status, n (%)	
Switcher	819 (52.2)
New User	751 (47.8)
Current smoker, n (%)	
Unknown	1 (0.1)
Yes	249 (15.9)
No	1320 (84.1)
Height (inches)	
Mean (± SD)	64.6 (2.7)
Range	48, 73
Weight (kg)	
Mean (± SD)	67.6 (13.2)
Range	33.6, 110.5

SD = Standard Deviation

Study results

The primary efficacy analysis was based on the Pearl Index (PI) in the group of women 35 years of age or less, including all at-risk cycles during which no other method of birth control had been used. In women aged 18 to 35 years in the MITT population (n=1251, all evaluable), 19 pregnancies occurred in 12297 at-risk cycles while using GENERESS. The PI was 2.01. The cumulative pregnancy rate was 2.00%.

The PI was also computed for all subjects regardless of age, including all at-risk cycles during which no other method of birth control had been used. In the overall MITT population (n=1570), all of the women had one or more cycles evaluable for pregnancy. Of these 1570 subjects, 20 women became pregnant during 15752 at-risk cycles while using GENERESS. The PI was 1.65. The cumulative pregnancy rate was 1.62%.

In the subgroup of women aged 36 to 46 years in the MITT population (n=319, all evaluable), one pregnancy occurred in 3455 at-risk cycles of treatment. The PI was 0.38. As only one subject became pregnant, no cumulative pregnancy rate was determined

Table 7: Phase 3 Open-Label Efficacy and Safety Study PR-00207: Summary of Pregnancy Outcomes – Pearl Index (MITT Population, N=1570)

	All Subjects	Subjects in the 18-35 Years Age Group	Subjects in the 36-46 Years Age Group
Number of Subjects	1570	1251	319
Number of Pregnancies	20	19	1
Number of Women Cycles of	15752	12297	3455
Pearl Index	1.65	2.01	0.38
95% Confidence Intervals[b]	1.008, 2.548	1.210, 3.135	0.010, 2.095

Note: Day 1 was the date of the first dose.
a: Only cycles for which no alternative method of contraception was used were included.
b: Confidence intervals were calculated using exact confidence intervals for binomial estimation of p, where p=(Number of pregnancies/Number of cycles).

A secondary objective of the study was to analyse the incidence of intracyclic bleeding (IB) and spotting. In this study bleeding was defined as any day in which a subject reported bleeding of any intensity except light bleeding that did not require sanitary protection. Such bleeding was defined as spotting.

Overall, in this study, 72.2% of subjects experienced an IB/spotting episode at some time during Cycles 2-13. The incidence decreased over the course of the study, from 31.3% in Cycle 2 to 22.5% in Cycle 13. Similar patterns were observed with bleeding-only and spotting-only episodes.

Table 8: Summary of incidence of intracyclic bleeding and spotting (MITT population, N=1570)

	n/N (%)		
Cycle(s)	**IB/Spotting[a]**	**Spotting Only[b]**	**Bleeding Only[c]**
Cycles 2-13	1028/1424 (72.2)	377/1424 (26.5)	918/1424 (64.5)

Table 8: Summary of incidence of intracyclic bleeding and spotting (MITT population, N=1570)

	n/N (%)		
Cycle(s)	**IB/Spotting[a]**	**Spotting Only[b]**	**Bleeding Only[c]**
Cycle 1	542/1462 (37.1)	153/1462 (10.5)	416/1462 (28.5)
Cycle 2	436/1393 (31.3)	94/1393 (6.7)	360/1393 (25.8)
Cycle 3	391/1322 (29.6)	76/1322 (5.7)	332/1322 (25.1)
Cycle 4	305/1243 (24.5)	57/1243 (4.6)	257/1243 (20.7)
Cycle 5	319/1206 (26.5)	56/1206 (4.6)	270/1206 (22.4)
Cycle 6	270/1162 (23.2)	48/1162 (4.1)	229/1162 (19.7)
Cycle 7	266/1134 (23.5)	40/1134 (3.5)	228/1134 (20.1)
Cycle 8	232/1097 (21.1)	32/1097 (2.9)	202/1097 (18.4)
Cycle 9	255/1062 (24.0)	43/1062 (4.0)	214/1062 (20.2)
Cycle 10	218/1031 (21.1)	36/1031 (3.5)	185/1031 (17.9)
Cycle 11	242/1021 (23.7)	29/1021 (2.8)	214/1021 (21.0)
Cycle 12	220/986 (22.3)	41/986 (4.2)	184/986 (18.7)
Cycle 13	217/964 (22.5)	36/964 (3.7)	186/964 (19.3)

Note: Only cycles evaluable for bleeding are included in the analysis.
a: IB/Spotting = patients had cycles with both bleeding and spotting.
b: Spotting only = patients had cycles with one or more days of spotting.
c: Bleeding only = patients had cycles with one or more days of bleeding.

The mean number of days per cycle of IB/spotting decreased over the course of the study from 1.31 days during Cycle 2 to 0.89 days during Cycle 13. Similarly, the mean number of spotting-only days per cycle decreased from 0.27 days in Cycle 2 to 0.13 days in Cycle 13 and the mean number of bleeding-only days per cycle decreased from 1.04 days in Cycle 2 to 0.76 days in Cycle 13.

For those women with unscheduled bleeding/spotting, the mean duration of unscheduled bleeding/spotting episodes ranged from 3.6 – 4.0 days in cycles 2-13. A total of 15 subjects out of 1,677 (0.9%) discontinued the study prematurely due to metrorrhagia or irregular menstruation.

The incidence of withdrawal bleeding decreased over the course of the study, from 74.5% of subjects during Cycle 2 to 56.6% during Cycle 13. An analysis of the median duration of withdrawal bleeding is summarized for the MITT population in Table 9 below.

Table 9: Median duration of withdrawal bleeding, Mean (SD) (MITT population, N=1570)

Cycle(s)	Median Duration, Days Mean (SD)
Cycle 2 through Cycle 13	3.72 (1.25)
Cycle 1	4.19 (1.78)
Cycle 2	4.02 (1.59)
Cycle 3	3.95 (1.62)
Cycle 4	4.00 (1.50)
Cycle 5	3.86 (1.46)
Cycle 6	3.76 (1.49)
Cycle 7	3.75 (1.47)
Cycle 8	3.71 (1.35)
Cycle 9	3.75 (1.37)
Cycle 10	3.61 (1.31)
Cycle 11	3.65 (1.38)
Cycle 12	3.67 (1.47)
Cycle 13	3.10 (1.56)

Note: Only cycles evaluable for bleeding are included in the analysis. For intervals including more than 1 cycle, the median parameter is taken by subject over cycle prior to taking the mean over all subjects. Only subjects with at least 1 withdrawal bleeding episode in the interval are included in the analyses of median duration.

The mean median duration of withdrawal bleeding was 3.72 days when assessed over Cycles 2 through 13. Examination of the by-cycle analysis revealed that the mean duration of withdrawal bleeding decreased from Cycle 2 (4.02 days) to a low value of 3.10 days during Cycle 13. The mean maximum intensity score for IB/spotting episodes remained fairly stable throughout the study between 1 and 2, i.e., between light and normal bleeding intensity.

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 17β-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

Single-dose Toxicity

Estrogen and progestin compounds possess low to moderate acute toxicity in experimental animals. The acute LD_{50} of EE and NE in rodents range from 0.5 g/kg to greater than 5 g/kg. Death in rodents given single large doses of EE or NE was attributed to liver and kidney failure.

Repeated-dose Toxicity

Dogs

The combination of NE acetate and EE (50:1) 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 semi-annually thereafter. Urinary steroid outputs were done once during the control period and annually thereafter.

One control dog and nine 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 each the 0.051 and 0.51 mg/kg/day dosage levels, and two 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 palpable in the mammary tissue of five control dogs, five dogs at the 0.051 mg/kg/day dosage level, six dogs at the 0.51 mg/kg/day level and six 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 the appeared to be 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. Vaginal discharge 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 parameters. 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 increased 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 the 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 in both control and treated groups, but the incidence at the high-dose was somewhat greater. No malignant mammary neoplasms were observed in any of the dogs in this study.

Monkeys

A combination of 50 parts of NE acetate to one part EE 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 mucus and inflammatory cells in the cervical canal, and dilatation of acini and ducts in mammary glands of monkeys from the high-dose group. These changes were considered to be related to the pharmacologic effect of the drug combination. No drug-related neoplasms were observed in the study.

Genotoxicity

NE and NE acetate were found to be non-mutagenic in *in vitro* bacterial reverse mutation assays in *Salmonella typhimurium*. In an *in vitro* chromosomal aberration assay, NE was not clastogenic in human RKO (colorectal cancer) cells; however, a weak positive response was seen in Chinese hamster ovary cells. Chromosomal aberration assays of NE and NE acetate have also been conducted in human lymphocytes and significant increases in chromosomal aberrations were observed with both NE and NE acetate.

EE was non-mutagenic at high concentrations in bacterial and mammalian cell test systems. EE at high concentrations produced chromosomal damage characterized by increased sister chromatid exchanges, chromosomal aberrations (breaks, stickiness), aneuploidy and mitotic arrest in some *in vitro* mammalian cell systems. In human lymphocytes, EE promoted chromosomal aberrations and sister chromatid exchanges in the presence of metabolic activation with NADP.

The frequency of micronuclei formation in bone marrow of female Swiss albino mice dosed with EE and NE in combination (1:80) at up to 8 mg/kg/day for 15 days was not significantly increased. There was, however, a significant increase in the incidence of breaks, gaps, translocations, centric fusions, stickiness, and pulverizations at doses of 0.8-8 mg/kg/day. Chromosomal aberrations increased in a dose-related manner and were noted at 24 hours after treatment, after which they decreased with increasing time.

Carcinogenicity

The ability of certain estrogenic and progestrogenic agents to induce tumours in rodents has long been known. High doses of these agents alone or in combination to susceptible strains of rodents have been shown to increase the incidence of specific tumours in the pituitary gland, mammary gland, uterus, and liver.

Mice receiving 7 or 70 µg of a mixture of EE and NE (1:50) in oil by oral gavage for 84-89 weeks had a higher occurrence of pituitary tumours, mammary tumours, and hepatomas than control animals. EE administered in combination with NE also increased incidences of malignant tumours of the uterine fundus in female mice.

Albino rats were fed a diet containing the combination of EE and NE (1:50) at doses between 0.3 to 4 mg/kg/day for 2 years and observations included dose-related growth retardation, transient alopecia, mastopathy, liver hyperplasia and gonadal atrophy. There were no significant differences between the control and treated animals in the total number of tumours. However, a difference in specific tumour types was noted between the control and drug-treated animals; there were higher incidences of hepatocellular adenomas, uterine polyps, pituitary adenomas, and mammary gland tumours in the drug-treated rats.

Reproductive and Developmental Toxicity

Studies in rats and nonhuman primates have indicated that NE and EE can be embryolethal and embryotoxic, but not teratogenic. As with other oral contraceptives, GENERESS should be contraindicated during pregnancy.

Pregnant rats orally administered NE and EE in combination at doses of 250 mg + 0.5 mg and 125 mg + 0.25 mg per kg weight during the period of organogenesis demonstrated embryolethality. Marked enlargement of the uterus and profound nipple development was observed in female fetuses, and male fetuses showed visibly feminized external genitalia, nipple development and arrest of testicular descent. Growth retardation and skeletal malformations were also observed in rat fetuses. The no-observed-effect level (NOEL) was the lowest dose, 62.5 mg NE + 0.12 mg EE. This dose represents a NE/EE safety margin of 12X/6X over the therapeutic human dose of GENERESS based on AUC systemic exposure comparisons.

Pregnant Rhesus monkeys given EE and NE in combination (1:50) at doses of 10 and 25 mg/day during the period organogenesis experienced a higher rate of fetal mortality than controls. Surviving offspring were without teratogenic or abnormal histopathologic findings. The fetal NOEL for EE/NE was 5 mg/day or approximately 1 mg/kg/day. This dose is approximately 2X/0.2X the NE/EE human systemic exposure from GENERESS. Virilisation of female fetuses was occasionally seen in other nonhuman primates (rhesus, cynomolgus and baboons) treated with high doses of ethinyl estradiol/norethindrone combination."

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PART III: CONSUMER INFORMATION

PRGENERESS ™
norethindrone and ethinyl estradiol chewable tablets
ferrous fumarate chewable tablets

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

GENERESS is a chewable birth control pill. It contains two female sex hormones, an estrogen called ethinyl estradiol and a progestin called norethindrone.

GENERESS has been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Your chance of getting pregnant depends on how well you follow the directions for taking your birth control pills. The more carefully you follow the directions, the less chance you have of getting pregnant.

GENERESS lowers the risk of becoming pregnant primarily by suppressing ovulation.

Effectiveness of GENERESS

Based on the results of one clinical study, about 2 out of 100 women may get pregnant during the first year they use GENERESS. 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 GENERESS protects against pregnancy in such women. If you are overweight (obese) discuss with your healthcare provider whether GENERESS is the best choice for you.

Other ways to prevent pregnancy:

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 1 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

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.

When it should not be used:

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

You should not use GENERESS 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 or to any of the other ingredients in GENERESS (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 and ethinyl estradiol

What the non-medicinal ingredients are:

Active tablet: lactose monohydrate, povidone, vitamin E, mannitol, microcrystalline cellulose, FD&C yellow no. 6 aluminum lake, FD&C blue no. 1 aluminum lake, D&C yellow no. 10, spearmint flavour, sodium starch glycolate, sucralose and magnesium stearate

Hormone-free tablet: ferrous fumarate, mannitol, povidone, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, sucralose, spearmint flavour

No therapeutic benefits from the ferrous fumarate in the hormone-free chewable tablets have been established.

What dosage forms it comes in:

GENERESS is available in blister packs.

Each blister pack (28 tablets) contains in the following order:

- 24 light green, round tablets (active) imprinted with “WC” on one side and “483” on the other and each containing 0.8 mg norethindrone and 0.025 mg ethinyl estradiol.
- 4 brown, round tablets (hormone-free) imprinted with “WC” on one side and “624” on the other and each containing 75 mg ferrous fumarate. No therapeutic benefits from the ferrous fumarate in the hormone-free chewable tablets have been established.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Do not use GENERESS if you smoke cigarettes and are over 35 years old. Smoking increases your risk of serious cardiovascular side effects (heart and blood vessel problems) from birth control pills, including death from heart attack, blood clots or stroke. This risk increases with age and the number of cigarettes you smoke.**
- **Oral contraceptives DO NOT PROTECT against sexually transmitted infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex condoms in combination with oral contraceptives.**

BEFORE you use **GENERESS** 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 GENERESS.

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

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

THE RISKS OF USING GENERESS

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 discolouration 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 GENERESS after childbirth, miscarriage or therapeutic abortion.

8. Pregnancy after stopping GENERESS
You will have a menstrual period when you stop using GENERESS. 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 GENERESS. 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 GENERESS 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 B12
- cyclosporine
- antacids (use 2 hours before or after taking GENERESS)
- bosentan

GENERESS may also interfere with the working of other drugs.

Consider using another birth control method when you take medicines that may make birth control pills less effective.

Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy. This may increase the risk of seizures, so your healthcare

provider may need to adjust the dose of lamotrigine.

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

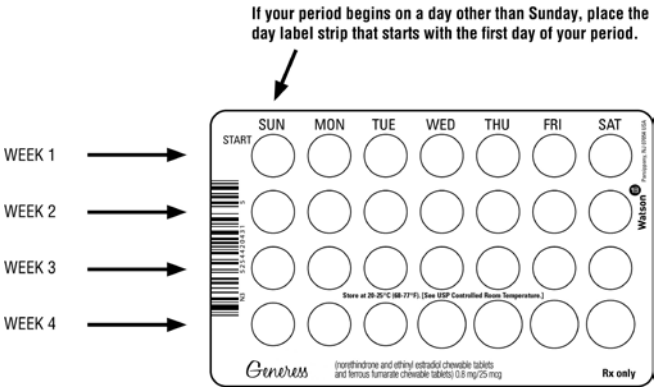
PROPER USE OF THIS MEDICATION

Usual dose: One pill at approximately the same time every day.

CHEW THE TABLET, AND SWALLOW WITHOUT WATER.

Before you start taking GENERESS

- Decide what time of day to take your pill. It is important to take it at the same time every day and in the order as directed on the blister pack.



Look at your GENERESS blister pack. The blister pack has four rows of 7 pills each, for a total of 28 pills. Find:

- where on the pack to start taking your pills

- in what order to take the pills

Each GENERESS blister pack has 28 pills.

- 24 light green pills with hormones for Weeks 1, 2 and 3 and the first part of Week 4 that are to be chewed and swallowed with or without food at the same time of day
- 4 brown pills without hormones for the remainder of Week 4 that are to be chewed and swallowed preferably with food at the same time of day

Be sure to have ready at all times another kind of birth control (such as a condom and spermicide) to use as a back-up in case you miss pills.

When to Start GENERESS

If you start taking GENERESS and you did not use a hormonal birth control method before:

DAY-1 START:

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). Pick a time of day that will be easy to remember.

Place this day label strip on the tablet dispenser over the area that has the days of the week (starting with Sunday) printed on the plastic.

Chew and swallow, without water, the first light green pill of the first pack during the first 24 hours of your period.

You will not need to use a back-up method of birth control because you are starting the pill at the beginning of your period. However, if you start on a day other than the first day of your period or if you are starting after having been pregnant and have not yet had a period, use a back-up method of birth control such as a condom and spermicide until you have taken a light green pill for *7 days* in a row.

Chew and swallow, without water, the brown pill with food. After taking the last brown pill (day 28) of the blister pack, start taking the first light green pill from a new blister pack the very next day whether or not you are having your period.

If you start taking GENERESS and you are switching from a combination hormonal method such as:

- another pill
- vaginal ring
- patch

Take the first light green pill on the first day you would have started your previous birth control pack.

If you previously used a vaginal ring or transdermal patch, finish the 21 days of use and wait *7 days* after removal of the ring or transdermal patch before starting GENERESS.

Use a non-hormonal back-up method such as a condom and spermicide for the first *7 days* you take GENERESS.

If you start taking GENERESS and you are switching from a progestin-only method such as a:

- progestin-only pill
- implant
- intrauterine system
- injection

Take the first light green pill on the day you would

have taken your next progestin-only pill or on the day of removal of your implant or intrauterine system or on the day when you would have had your next injection.

Use a non-hormonal back-up method such as a condom and spermicide for the first *7 days* you take GENERESS.

Overdose:

No serious problems have been reported from a birth control pill overdose, even when accidentally taken by children.

The 4 **hormone-free** brown tablets contain ferrous fumarate. Too much ferrous fumarate can seriously harm children. Be sure to safely store and dispose of both the non-hormonal and the active tablets.

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

Missed Dose:

If you forgot to start a new blister pack, **you may already be pregnant.** Use back-up contraception (such as a condom and spermicide) anytime you have sex. Call your healthcare provider if you are unsure whether you are pregnant.

Your birth control pills may not be as effective if you miss any light green pills, and particularly if you miss the first few or the last few light green pills in a pack.

If you MISS ONE light green pill

Take it as soon as you remember. Take the next pill at your regular time. This means you may take two pills in 1 day.

- You do not need to use a back-up birth control method if you have sex.

If you MISS TWO light green pills in a row in WEEK 1 or WEEK 2 of your pack

- Take two pills on the day you remember and two pills the next day.
- Then take one pill a day until you finish the pack.
- You could become pregnant if you have sex during the *7 days* after you restart your pills. You MUST use a non-hormonal birth control method (such as a condom and spermicide) as a back-up for those *7 days*.

If you MISS TWO light green pills in a row in WEEK 3 or WEEK 4 of your pack

- THROW OUT the rest of the pill pack and start a new pack that same day.
- You could become pregnant if you have sex during the *7 days* after you restart your pills. You MUST use a non-hormonal birth control method (such as a condom and spermicide) as a backup for those *7 days* after you restart your pills.

If you MISS THREE OR MORE light green pills in a row at any time

- THROW OUT the rest of the pill pack and start a new pack that same day.
- You could become pregnant if you have sex on the days when you missed pills or during the first *7 days* after restarting your pills. You MUST use a non-hormonal birth control method (such as a condom and spermicide) as a back-up the next time you have sex and for the first *7 days* after you restart your pills.

You may already be pregnant or COULD BECOME PREGNANT if you had sex on the days after the pills were missed. The more pills missed and the closer they are to the end of the cycle, the higher the risk of a pregnancy. You should call your doctor or healthcare provider if you are unsure whether you are already pregnant.

If you forget any of the four brown "hormone-free" pills in WEEK 4

- THROW AWAY the pills you missed.
- Keep taking one pill each day until the pack is finished.
- You do not need to use a back-up method of birth control.

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

- Call your healthcare provider.
- Use a back-up contraception (such as a condom and spermicide) anytime you have sex and keep taking 1 pill each day.

If you have vomiting or diarrhea, your birth control pills may not work as well. Use another birth control method, like a condom and spermicide, until you check with your healthcare provider.

Noncontraceptive benefits of birth control pills

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like pregnancy, birth control pills increase the risk of serious blood clots, especially in women who have other risk factors, such as smoking, obesity, or age greater than 35. It is possible to die from a problem caused by a blood clot, such as a heart attack or a stroke. Some examples of serious blood clots are blood clots in the:

- Legs (thrombophlebitis)
- Lungs (pulmonary embolus)
- Eyes (loss of eyesight)
- Heart (heart attack)
- Brain (stroke)

A few women who take birth control pills may get:

- High blood pressure
- Gallbladder problems
- Rare cancerous or noncancerous liver tumours

All of these events are uncommon in healthy women.

Call your healthcare provider right away if you have:

- Persistent leg pain
- Sudden shortness of breath
- Sudden blindness, partial or complete
- Severe pain in your chest
- Sudden, severe headache unlike your usual headaches
- Weakness or numbness in an arm or leg, or trouble speaking
- Yellowing of the skin or eyeballs

What are the common side effects of birth control pills?

The most common side effects of birth control pills are:

- Spotting or bleeding between menstrual periods
- Nausea
- Breast tenderness
- Headache

These side effects are usually mild and usually disappear with time.

Less common side effects are:

- Acne
- Less sexual desire
- Bloating or fluid retention
- Blotchy darkening of the skin, especially on the face
- High blood sugar, especially in women who already have diabetes
- High fat levels in the blood
- Depression, especially if you have had depression in the past. Call your healthcare provider immediately if you have any thoughts of harming yourself.
- Problems tolerating contact lenses
- Weight changes

What if I miss my scheduled period when taking GENERESS?

Women who use GENERESS may not have a period at the end of every 28-day pack of pills.

If you miss more than two periods in a row or miss one period when you have not taken your birth control pills according to directions, call your healthcare provider. Also notify your healthcare provider if you have symptoms of pregnancy such as morning sickness or unusual breast tenderness. It is important that your healthcare provider checks you to find out if you are pregnant. Stop taking GENERESS if you are pregnant.

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

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Sharp pain in the chest, coughing blood, or sudden shortness of breath			✓
	Pain or swelling in the leg			✓
	Crushing chest pain or heaviness			✓
	Sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg			✓
	Sudden partial or complete loss of vision			✓
	Abdominal pain nausea, or vomiting or lump in the abdomen		✓	
	Persistent sad mood			✓
	Yellowing of the skin or eyes (jaundice)			✓
	Unusual swelling of the extremities		✓	
	Breast lumps		✓	
	Unexpected (Abnormal) vaginal bleeding		✓	

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

HOW TO STORE IT

Store at 20-25ºC (68-77ºF).
Keep out of reach of children.

The 4 **hormone-free** brown tablets contain ferrous fumarate. Too much ferrous fumarate can seriously harm a child. Be sure to safely store and dispose of both the non-hormonal and the active tablets.

REPORTING SUSPECTED SIDE EFFECTS

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

$ Report online at www.healthcanada.gc.ca/medeffect

$ Call toll-free at 1-866-234-2345

$ Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or

- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, 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 www.healthcanada.gc.ca/medeffect.

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 Allergan Inc. at 1-800-668-6424.

This leaflet was prepared by:
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CANADA

Last revised: January 31, 2020