PRODUCT MONOGRAPH

[Pr]PREVIFEM

0.250 mg norgestimate and 0.035 mg ethinyl estradiol

Tablets

Novopharm Standard

Oral Contraceptive

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[Pr]PREVIFEM

norgestimate and ethinyl estradiol

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	tablets / 0.250 mg norgestimate and 0.035 mg ethinyl estradiol	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

PREVIFEM Tablets (norgestimate and ethinyl estradiol) are indicated for:

- conception control.

Pediatrics:
No data is available.

CONTRAINDICATIONS

- When pregnancy is suspected or diagnosed.
- Patients who are hypersensitive to PREVIFEM (norgestimate and ethinyl estradiol) or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- History of or actual thrombophlebitis or thromboembolic disorders.
- History of or actual cerebrovascular disorders.
- History of or actual myocardial infarction or coronary arterial disease.
- Active liver disease or history of or actual benign or malignant liver tumours.
- Known or suspected carcinoma of the breast.
- Known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal vaginal bleeding.
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

Oral contraceptives **do not protect** against sexually transmitted diseases (STD's) including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **in combination with** oral contraceptives.

General

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

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

1. Predisposing Factors for Coronary Artery Disease

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

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

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

2. Discontinue Medication at the Earliest Manifestation of the Following:

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 oral contraceptives when surgery is contemplated , see PRECAUTIONS.

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

Carcinogenesis and Mutagenesis

Breasts

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

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

Cardiovascular

Hypertension

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

Genitourinary

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

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

Hepatic
Patients who have had jaundice, including a history of cholestatic jaundice during pregnancy, should be given oral contraceptives with great care and under close observation.

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

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

Hepatic nodules (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 with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

Neurologic
The onset or exacerbation of migraine or the development of headache of a new pattern that is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause.

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

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

Psychiatric
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 alternative 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.

Sexual Function/Reproduction

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

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

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

Special Populations

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

Nursing Women: In breast-feeding women, the use of 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.

Pediatrics: Norgestimate and ethinyl estradiol have not specifically been studied in this population.

Monitoring and Laboratory Tests

Physical Examination and Follow-up
Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities, and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active.

The first follow-up visit should be three months after oral contraceptives are prescribed.

Thereafter, examinations should be performed at least once a year, or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on the Periodic Health examination.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Thrombophlebitis
Pulmonary embolism
Mesenteric thrombosis
Neuro-ocular lesions (e.g. retinal thrombosis)
Myocardial infarction
Cerebral thrombosis
Cerebral hemorrhage
Hypertension
Benign hepatic tumours
Gallbladder disease
Congenital anomalies

Clinical Trial Adverse Drug Reactions

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

The 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 per cent or less patients during the first cycle. Other reactions, as a general rule are seen less frequently or only occasionally, as follows:

Cardiovascular System:	Edema
	Slight rise of blood pressure
Genital Tract:	Breakthrough bleeding
	Spotting
	Change in menstrual flow
	Dysmenorrhea
	Amenorrhea during and after treatment
	Vaginal candidiasis
	Premenstrual-like syndrome
	Temporary infertility after discontinuance of treatment
	Vaginitis
	Endocervical hyperplasias
Neoplasms:	Malignant hepatic tumors

	Cervical cancer
	Increase in size of uterine leiomyomata
	Breast cancer
Breast:	Pain, tenderness, enlargement, and secretion
	Possible diminution in lactation when given immediately postpartum.
Skin and Subcutaneous	Chloasma or melasma which may persist
Tissue:	Rash (allergic)
	Hirsutism
	Loss of scalp hair
	Erythema multiforme
	Erythema nodosum
	Raynaud's phenomenon
	Hemorrhagic eruption
	Porphyria
	Acne
	Seborrhea
	Pemphigoid (herpes gestationis)
	Urticaria
	Angioedema
CNS:	Migraine
	Depression
	Headache
	Nervousness
	Dizziness
	Changes in libido
	Chorea
Metabolic:	Reduced tolerance to carbohydrates
	Change in weight (increase or decrease)
	Changes in appetite
Gastro-intestinal tract:	Gastrointestinal symptoms (such as abdominal cramps and bloating)
	Colitis
	Pancreatitis
Hepatobiliary:	Cholestatic jaundice,
	Budd-Chiari syndrome
Eyes:	Intolerance to contact lenses
	Change in corneal curvature (steepening)
	Cataracts
	Optic neuritis
	Retinal thrombosis
Urinary:	Impaired renal function
	Hemolytic uremic syndrome
	Cystitis-like syndrome
Others:	Rhinitis
	Auditory disturbances

DRUG INTERACTIONS

Overview

The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent (Tables I and II). 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, including herbal preparations/remedies, before oral contraceptives are prescribed.

Drug-Drug Interactions

Some drugs, such as cholestyramine, may impair the enterohepatic circulation of estrogens, and may result in hastened elimination and impaired effectiveness.

Some data has indicated a decrease in the serum levels of the estrogenic component of oral contraceptives in conjunction with topiramate. Therefore, the efficacy of low-dose oral contraceptives may be reduced with concomitant use. Patients should be encouraged to report any change in bleeding patterns.

Some protease inhibitors and some anti-retroviral agents have been found to either increase (e.g. indinavir) or decrease (e.g. ritonavir) circulating levels of combination hormonal contraceptives.

> Refer to *Oral Contraceptives 1994* (Chapter 8), Health Canada, for other possible drug interactions with OCs.

TABLE I
Drugs that May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	Carbamazepine Ethosuximide Phenobarbital Phenytoin Primidone	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose OCs (50 μg ethinyl estradiol), another drug or another method.
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.
	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 OCs, increasing the risk of cholestatic jaundice.	
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 OC efficacy.	Use another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or use another drug. For long course, use another method or higher dose OCs.
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Other Drugs	Phenylbutazone Antihistamines Analgesics Antimigraine Preparations Vitamin E	Reduced OC efficacy has been reported. Remains to be confirmed.	

TABLE II
Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha–II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	OCs increase clotting factors, decrease efficacy. However, OCs may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Fluid retention may increase risk of seizures.	Use another method.
Antidiabetic Drugs	Oral Hypoglycemics and Insulin	OCs may impair glucose tolerance and increase blood glucose.	Use low dose estrogen and progestin OC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low dose estrogen OC or use another method.
	Beta Blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of OCs.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminiocaproic Acid		Theoretically, a hypercoagulable state may occur because OCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity.

TABLE II (cont'd)
Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Caffeine		The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol Lowering Agents	Clofibrate	Their action may be antagonized by OCs. OCs may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly 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		OCs have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All Phenothiazines, Reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose OCs . If galactorrhea or hyperprolactinemia occurs, use other method.
Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic Antidepressants	Clomipramine (possibly others)	Increased side effects; i.e. depression.	Use with caution.
Vitamin B_{12}		OCs have been reported to reduce serum levels of Vitamin $B_{12.}$	May need to increase dietary intake, or supplement.

Drug-Food Interactions

The actions of caffeine may be enhanced by concomitant use of oral contraceptives. Oral contraceptives may impair the hepatic metabolism of caffeine, therefore use with caution.

The use of alcohol with oral contraceptives may possibly result in increased levels of ethanol or acetaldehyde, therefore use with caution

Drug-Herb Interactions

The metabolism of oral contraceptives may be influenced by various drugs and herbal preparations including St. John's wort. Of potential clinical importance are drugs and herbal supplements that are known to affect the induction of enzymes that are responsible for the degradation of contraceptive steroid hormones (e.g. St. John's wort). Decreased effectiveness of the estrogenic component of oral contraceptives may result in spotting, breakthrough bleeding and possible pill failure. It is possible that induction of these enzymes may lead to reductions in the circulating levels of the progestational component of PREVIFEM Tablets. In actual practice, reduced efficacy has been associated with concomitant use of St. John's wort.

Drug-Laboratory Interactions

Laboratory Tests

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

A.	*Liver Function Tests*	
	Bromsulphthalein Retention Test (BSP)	Moderate Increase
	AST (SGOT) and GGT	Minor Increase
	Alkaline Phosphatase	Variable Increase
	Serum Bilirubin	Increased, particularly in conditions predisposing to or associated with hyperbilirubinemia
B.	*Coagulation Tests*	
	Factors II, VII, IX, X, XII and XIII	Increased
	Factor VIII	Mild increase
	Platelet aggregation and adhesiveness	Mild increase in response to common aggregating agents
	Fibrinogen	Increased
	Plasminogen	Mild increase
	Antithrombin III	Mild decrease
	Prothrombin Time	Increased
C.	*Thyroid Function Tests*	
	Protein-bound Iodine (PBI)	Increased
	Total Serum Thyroxine (T_4)	Increased
	Thyroid Stimulating Hormone (TSH)	Unchanged
D	*Adrenocortical Function Tests*	
	Plasma Cortisol	Increased
E.	*Miscellaneous Tests*	
	Serum Folate	Occasionally decreased

Glucose Tolerance Test	Variable increase with return to normal after 6-12 months
Insulin Response	Mild to moderate increase
c-Peptide Response	Mild to moderate increase

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

NON-CONTRACEPTIVE BENEFITS OF ORAL CONTRACEPTIVES

Several health advantages other than contraception have been reported.

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

2. Oral contraceptives reduce the likelihood of developing benign breast disease and, as a result, decrease the incidence of breast biopsies.

3. Oral contraceptives reduce the likelihood of development of functional ovarian cysts.

4. Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.

5. The use of oral contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome, and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders.

6 Oral contraceptives decrease the incidence of acute pelvic inflammatory disease and, thereby, reduce as well the incidence of ectopic pregnancy.

7 Oral contraceptives have potential beneficial effects on endometriosis.

DOSAGE AND ADMINISTRATION

Recommended Dose

Tablets must be taken in the order directed on the package every day at about the same time. The patient may begin using Previfem (norgestimate and ethinyl estradiol) on Day 1 of her menstrual cycle (i.e., the 1st day of menstrual flow), on Day 5, or on the 1st Sunday after her period begins. If the patient's period begins on Sunday, she should start that same day. If Previfem tablets are taken later than Day 1 when first starting medication, an additional (barrier) method of birth control is recommended for the first 7 days of use.

PREVIFEM 21 (21 Day Regimen)

One blue tablet is to be taken daily for 21 days, Tablets are then discontinued for 7 consecutive days. Withdrawal bleeding usually occurs within 2 or 3 days following discontinuation.

The patient begins each subsequent course of PREVIFEM 21 tablets on the same day of the week that she began her first course. She begins taking her next course on the 8th day after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.

PREVIFEM 28 (28 Day Regimen)

One blue tablet is to be taken daily for 21 days followed by 1 green tablet daily for 7 consecutive days. Withdrawal bleeding usually occurs within 2 or 3 days following the last blue tablet (i.e., while the patient is taking the green tablets).

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

Missed Dose

The following chart outlines the actions you should take if you miss 1 or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack.

SUNDAY START **MISS ONE PILL**	**OTHER THAN SUNDAY START** **MISS ONE PILL**
Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.
MISS TWO PILLS IN A ROW	**MISS TWO PILLS IN A ROW**
First Two Weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL, YOUR DOCTOR OR CLINIC.**	**First Two Weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL, YOUR DOCTOR OR CLINIC**.
MISS THREE OR MORE PILLS IN A ROW	**MISS THREE OR MORE PILLS IN A ROW**
Any Time in the Cycle 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC**.	**Any Time in the Cycle** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the 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**.

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NOTE: 28-DAY PACK: If you forget any of the 7 "reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking 1 pill each day until the pack is empty. You do not need to use a back-up method.

Always be sure you have on hand:

- A back up method of birth control (such as latex condoms and spermicidal foam or gel) in case you miss pills, and
- An extra, full pack of pills.

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

Special Notes on Administration

Switching from another combined oral contraceptive: The patient should start Previfem on the day she would normally start her next pack of combined oral contraceptive.

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

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

Following delivery or second trimester abortion: Patients should be advised to start Previfem on day 21 to 28 after delivery or second trimester abortion, after consulting with their physician. When starting later, the patient should be advised to use an additional (barrier) method for the first seven days of Previfem use. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of use, or the woman should be advised to wait for her next menstrual period prior to starting Previfem. When the tablets are administered in the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered.

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

Although the occurrence of pregnancy is unlikely if Previfem is taken according to directions, if withdrawal bleeding does not occur, the possibility of pregnancy must be considered. If the patient has not adhered to the prescribed dosing schedule (missed one or more active tablets or started taking them on a day later than she should have), the probability of pregnancy should be considered at the time of the first missed period and appropriate diagnostic measures taken before the medication is resumed. If the patient has adhered to the prescribed regimen and missed two consecutive periods, pregnancy should be rule out before continuing the contraceptive regimen.

Advice in case of vomiting: If vomiting occurs within three to four hours after a tablet is taken, absorption may not be complete. In such an event, the advice concerning management of missed doses is applicable. (See Missed Dose).

OVERDOSAGE

In case of overdose or accidental ingestion by children, the physician should observe the patient closely although generally no treatment is required[2]. Gastric lavage may be utilized if considered necessary.

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PREVIFEM (norgestimate and ethinyl estradiol) is a synthetic steroidal combination oral contraceptive.

The primary mechanism of action of PREVIFEM tablets (norgestimate and ethinyl estradiol) is an inhibition of ovulation. Additionally, other effects caused by the treatment (for example, alteration of the endometrium and the thickening of the cervical mucus), appear to interfere with implantation and conception.

Pharmacokinetics

Investigations of norgestimate alone and of norgestimate plus ethinyl estradiol tablets were carried out to study the pharmacokinetics of the drug in oral dosage forms.

Orally administered norgestimate plus ethinyl estradiol (0.250 mg and 0.035 mg respectively) has been shown to be absorbed rapidly, with maximum blood levels being reached in 0.5 to 1.0 hours for the norgestimate and in 1.0 to 2.0 hours for the ethinyl estradiol (C_{max}, the plasma concentration ± S.D = 278 ± 140 pg/mL for norgestimate and 119 ± 50 pg/mL for ethinyl estradiol; AUC, the area under the plasma level vs time curve, ± S.D = 1,064 ± 425 hr•pg/mL for norgestimate and 984 hr•pg/mL for ethinyl estradiol). It has also been shown that norgestimate, like ethinyl estradiol, is highly bound to plasma proteins (99% as determined *in vitro* for norgestimate); this is consistent with literature reports on other progestational agents.[2] The elimination of norgestimate ($t_{1/2}$ = 4.4 - 7.2 hours) has been shown to be unaffected by ethinyl estradiol. A major norgestimate serum metabolite, 17-deacetyl norgestimate (serum $t_{1/2}$ = 12 - 30 hours) appears rapidly in serum with concentrations greatly exceeding that of norgestimate. This metabolite is pharmacologically active with a pharmacologic profile similar to that of norgestimate. Norgestimate is extensively metabolized and eliminated by renal and fecal pathways (similar to other contraceptive steroids). Following administration of ^{14}C-norgestimate, 47% (45 - 49%) and 37% (16 - 49%) of administered radioactivity was eliminated in urine and feces, respectively.[3,4]

Absorption: Orally administered norgestimate plus ethinyl estradiol in tablets have been shown to be absorbed rapidly

Distribution: It has been shown that norgestimate, like ethinyl estradiol, is highly bound to plasma proteins (99% as determined *in vitro* for norgestimate); this is consistent with literature reports on other progestational agents.

Metabolism: Norgestimate is extensively metabolized by first-pass mechanisms in the gastrointestinal tract and/or liver. Norgestimate's primary active metabolite is norelgestromin. Subsequent hepatic metabolism of norelgestromin occurs and metabolites include norgestrel, which is also active and various hydroxylated and conjugated metabolites. Ethinyl Estradiol (EE) has been reported to be subject to presystemic conjugation in both small bowel mucosa and the liver. Metabolism occurs primarily by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronide and sulphate. CYP3A4 in the liver are responsible for the 2-hydroxylation which is the major oxidative reaction. The 2 hydroxy metabolite is further transformed by methylation and glucuronidation prior to urinary and fecal excretion.

Excretion: The elimination of norgestimate has been shown to be unaffected by ethinyl estradiol. While some biliary excretion and enterohepatic circulation is seen with norgestimate (similar to that seen with other contraceptive steroids), elimination is primarily rena1.

Special Populations and Conditions

Pediatrics: Pharmacokinetic differences in pediatrics in comparison to adults have not been studied. This medication should not be used before menarche.

Gender: PREVIFEM (norgestimate and ethinyl estradiol) is only intended for women.

Race: Pharmacokinetic differences based on race have not been studied.

Hepatic Insufficiency: No studies with norgestimate and ethinyl estradiol have been conducted in women with hepatic insufficiency.

Renal Insufficiency: No studies with norgestimate and ethinyl estradiol have been conducted in women with renal insufficiency.

Genetic Polymorphism: Pharmacokinetic differences based on genetic polymorphism have not been studied.

STORAGE AND STABILITY

Store between 15°C – 30°C. Leave contents in protective packaging until time of use.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PREVIFEM (norgestimate and ethinyl estradiol) tablets are available in a 21-day regimen (PREVIFEM 21) and a 28-day regimen (PREVIFEM 28).

PREVIFEM 21
21-Day Package contains:

- 21 BLUE tablets each containing 0.250 mg norgestimate and 0.035 mg ethinyl estradiol.

PREVIFEM 28
28-Day Package contains:

- 21 BLUE tablets each containing 0.250 mg norgestimate and 0.035 mg ethinyl estradiol.
- 7 GREEN tablets with inert ingredients.

Each blue PREVIFEM Tablet contains the following nonmedicinal ingredients: lactose monohydrate, FD & C Blue # 1 HT, pregelatinized starch, magnesium stearate, hydroxypropyl methylcellulose and polyethylene glycol.

Each green tablet contains inert ingredients, namely, pigment blend green PB-1766 (FD & C Blue #2 & Iron Oxide Yellow), lactose monohydrate, pregelatinized starch, magnesium stearate, hydroxypropyl methylcellulose and polyethylene glycol.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

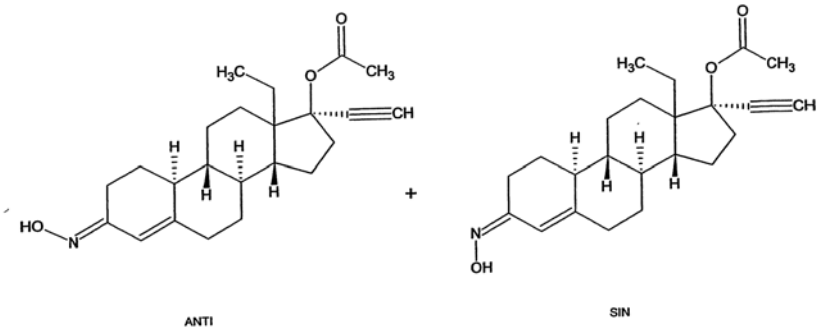
Drug Substance

Common name: Norgestimate

Chemical name: 18,19-dinor- 17-pregn-4-en-2O-yn-3-one,17-(acetyloxy)- 13-ethyl-, oxime, (17α)-(+)-

Molecular formula and molecular mass: $C_{23}H_{31}NO_3$ 369.51

Structural formula:



ANTI SIN

Physicochemical Properties:
Norgestimate is a white crystalline powder. Melting Point: 213ºC to 218ºC.

Norgestimate is freely soluble in chloroform; soluble in alcohol; sparingly soluble in ethylacetate and methanol; insoluble in water.

PHARMACEUTICAL INFORMATION

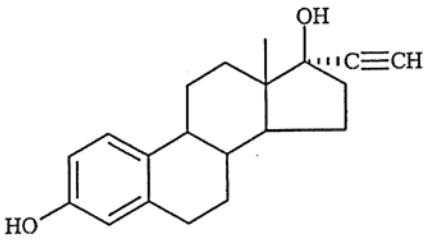
Drug Substance

Common Name: Ethinyl Estradiol

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

Molecular Formula and Molecular Mass: $C_{20}H_{24}O_2$ 296.41

Structural Formula:



Physicochemical Properties:
White to practically white crystals or powder. Melting Point: 180ºC to 186ºC.

Solubility
Dioxane: 1 in 4;
Diethyl ether: 1 in 4;
Acetone: 1 in 5;
Ethanol: 1 in 6;
Chlorform: 1 in 20;
Water: practically insoluble.

CLINICAL TRIALS

This is a randomized, single-dose, double-blind, two-period, crossover study to evaluate the comparative bioavailability between norgestimate/ethinyl estradiol 0.25/0.035mg tablets (Novopharm Limited, Canada) and [Pr]CYCLEN norgestimate/ethinyl estradiol 0.25/0.035mg tablets (Janssen-Ortho, Inc., Canada) after a single-dose in 24 healthy female adult subjects under fasting conditions.

Norgestimate / Ethinyl Estradiol
17-Desacetyl Norgestimate Data
(2 x 0.250/0.035 mg Tablets)
From measured data
uncorrected for potency
Geometric Mean
Arithmetic Mean (CV %)

Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_{0-72} (pg · hr/mL)	23701.04 24581.502 (28.3%)	25507.52 26111.671 (23.1%)	92.9	86.6 – 99.7
AUC_I (pg · hr/mL)	28564.37 29776.622 (30.4%)	30795.00 31712.350 (26.2%)	92.8	86.3 – 99.7
C_{max} (pg/mL)	2757.84 2869.583 (28.8%)	2794.80 2947.500 (34.0%)	98.7	89.0 - 109
T_{max} § (hrs)	1.785 (23.6%)	1.543 (25.4%)		
$T_{½}$ § (hrs)	31.812 (30.6%)	32.158 (35.0%)		

* Previfem (norgestimate and ethinyl estradiol) Tablets 0.25/0.035 mg (Novopharm Lot No. 751E007)

† [Pr]CYCLEN (norgestimate and ethinyl estradiol) Tablets0.25/0.035 mg (Janssen-Ortho Inc, Canada, Lot No. 04JS84K); Purchased in Canada.

§ Expressed as the arithmetic mean (CV%).

Norgestimate / Ethinyl Estradiol
Ethinyl Estradiol
(2 x 0.250/0.035 mg Tablets)
From measured data
uncorrected for potency
Geometric Mean
Arithmetic Mean (CV %)

Parameter	**Test***	**Reference†**	**% Ratio of Geometric Means**	**Confidence Interval (90%)**
AUC_T (pg · hr/mL)	1666.46 1746.085 (31.6%)	1713.26 1795.450 (32.3%)	97.3	92.7 - 102
AUC_I (pg · hr/mL)	1785.12 1969.595 (31.7%)	1818.94 1899.332 (31.0%)	98.1	93.5 - 103
C_{max} (pg/mL)	162.96 171.913 (33.1%)	173.85 189.092 (48.4%)	93.7	87.4 - 100
T_{max} § (hrs)	1.493 (39.1%)	1.661 (49.1%)		
$T_{½}$ § (hrs)	18.324 (23.8%)	17.181 (24.4%)		

* Previfem (norgestimate and ethinyl estradiol) Tablets 0.25/0.035 mg (Novopharm Lot No. 751E007)

† PrCYCLEN (norgestimate and ethinyl estradiol) Tablets0.25/0.035 mg (Janssen-Ortho Inc, Canada, Lot No. 04JS84K); Purchased in Canada.

§ Expressed as the arithmetic mean (CV%).

CLINICAL EVALUATION OF NORGESTIMATE / ETHINYL ESTRADIOL TABLETS

The contraceptive efficacy and side effect pattern of norgestimate and ethinyl estradiol tablets have been evaluated in three major controlled and open Phase III studies conducted in the United States. These Phase III studies of norgestimate and ethinyl estradiol tablets involved 1,647 women who completed a total of 22,237 cycles of use; of these 927 (56.3%) completed 12 cycles and 424 (25.7%) completed 24 cycles of therapy.

In the two comparative Phase III studies combined, norgestimate and ethinyl estradiol tablets were taken by 736 subjects of whom 382 (51.9%) completed 12 cycles and 198 (26.9%) completed 24 cycles of therapy.

Contraceptive Efficacy

In the three studies combined, only 16 unplanned pregnancies were reported by patients while on therapy, giving a Pearl Index of 0.86 and a Life Table Rate of 0.94. In 8 cases, tablets had not been taken according to the recommended regimen and these pregnancies were considered patient failures. The resulting corrected Pearl Index (theoretical efficacy) is 0.43.

Miscellaneous Effects

For the controlled and open studies combined, the adverse experiences which occurred in 5% or more of the subjects taking norgestimate and ethinyl estradiol tablets were, in decreasing order of frequency: headache (31.2%), upper respiratory infection (17.7%), flu (8.3%), mastodynia (5.6%), and female genitalia pain (5.4%).

For the two comparative studies combined, the adverse experiences which occurred in 5% or more of the subjects taking norgestimate and ethinyl estradiol tablets were: headache (29.5%), upper respiratory infection (15.1%), flu (7.3%), and mastodynia (6.4%).

In the three Phase III studies 17.9% of patients (294 of 1,647) discontinued norgestimate and ethinyl estradiol tablets for medical use-related reasons during the entire 24 cycles (cumulative gross probability of discontinuation of 0.2319, standard error = 0.0125).

Extensive studies of norgestimate plus ethinyl estradiol tablets establishing the safety and efficacy of the combination in Phase III trials have been carried out in the United States, Canada, Mexico and Europe.

Tolerance

A perspective on patient tolerance to effects reported during the course of administration of norgestimate and ethinyl estradiol tablets can be obtained from an examination of the incidence of "drop-out" from the studies for the undesirable effects reported above.

ADVERSE EXPERIENCES CAUSING DISCONTINUATION
IN 2% OR MORE OF SUBJECTS

Adverse Experience	Norgestimate and Ethinyl Estradiol Tablets Three Major Studies Combined	Norgestimate and Ethinyl Estradiol Tablets Two Comparative Studies
Breakthrough Bleeding or Spotting	6.8%	6.8%
Headache	4.1%	3.8%
Nausea and/or Vomiting	3.8%	4.3%
Mood Alterations	3.2%	3.8%
Menstrual Disturbances other than amenorrhea or breakthrough bleeding/ spotting	2.9%	3.5%
All other	5.6%	5.8%

Laboratory Tests

Changes observed in thyroid analytes were clinically insignificant and consistent with those expected for low-dose oral contraceptive use.

While the changes observed in lipid tests were small and remained within reference ranges of the United States population of reproductive-aged women, norgestimate and ethinyl estradiol tablets appeared to have minimal adverse impact on cholesterol, triglycerides, and LDL while being associated with a salutary positive impact on HDL.

The mean changes in fasting glucose are small and clinically insignificant for all studies, regimens, and cycles, although there are several statistically significant changes. The results of glucose tolerance testing for all the studies and regimens are clinically neutral and show minimal changes.

Norgestimate and ethinyl estradiol tablets also exhibited minimal androgenicity. Sex hormone binding globulin levels were increased and testosterone was not readily displaced from its binding sites by norgestimate.

DETAILED PHARMACOLOGY

Pharmacodynamics

Oral Contraception

Norgestimate, alone and in combination with ethinyl estradiol, is an effective antiovulatory agent. It is moderately potent in the standard *in vivo* progestational assay which measures endometrial

proliferation in rabbits, and it effectively blocks ovulation in rats, hamsters and rabbits. In rats, this blockade correlates well with suppression of the proestrus LH surge and the antiovulatory activity of norgestimate is overcome by LHRH. The blockade appears, like that of other progestational agents, to be the result of inhibition of the hypothalamic/pituitary axis. Norgestimate is an active progestin when administered either orally or parenterally and binds to progestational receptors *in vitro*. Like other progestins, norgestimate inhibits the action of estrogen but is not estrogenic itself. Studies measuring the stimulation of ventral prostate growth in rats, the ability to bind to human SHBG *in vitro*, and the effects on serum SHBG levels in rabbits demonstrate that in contrast to levonorgestrel, norgestimate is not androgenic. It also does not inhibit the action of androgen in rats. No adverse effects on the reproductive, thyroid or adrenal endocrine systems were seen in rats given norgestimate orally for 7 days at doses up to 100 times the clinical dose. *In vitro* studies indicate that norgestimate does not directly alter ovarian aromatase activity. Norgestimate does not exhibit central nervous system or autonomic nervous system activities in rats and does not interfere with autonomic-mediated responses of the cardiovascular system in dogs. *In vitro* studies indicate that norgestimate does not possess antimicrobial activity against diverse pathogenic microorganisms. Ethinyl estradiol is a potent estrogen which stimulates the uterus and the vagina. Its preclinical pharmacology is well established.

In humans, the primary mechanism of action of the combination is an inhibition of ovulation. Additionally, other effects caused by the treatment, i.e. alteration of the endometrium and the thickening of the cervical mucus appear to interfere with implantation and conception. Studies evaluating the effect of the combination on cervical mucus characteristics, hormonal levels and also on the endometrial tissue yielded results that were consistent with the known mechanism of action (i.e. suppression of ovulation) of the combination.

Norgestimate plus ethinyl estradiol elevated HDL levels across all studies. Norgestimate plus ethinyl estradiol exhibited minimal androgenicity. Sex hormone binding globulin levels were increased and testosterone was not readily displaced from its binding sites by norgestimate.

TOXICOLOGY

Toxicology studies have evaluated norgestimate alone as well as in combination with ethinyl estradiol in the mouse, rat, rabbit, dog and monkey. Ethinyl estradiol has also been evaluated both alone and in combination with synthetic steroidal progestogens in the rat, rabbit, dog and monkey. Compound-related gross and microscopic lesions have been minimal and show the typical pathological changes that are known to occur with the administration of progestogen and estrogen.

Acute Toxicity Studies

Mice

In HaM/1CR CD-1 mice oral norgestimate alone and oral norgestimate + ethinyl estradiol (5:l) each had an LD_{50} greater than 5 g/kg body weight. Norgestimate alone at 5 g/kg caused no overt signs of toxicity while the combination caused transient changes in behaviour and one death (one female out of 10 females and 10 males) at 5 g/kg. Oral ethinyl estradiol alone at 5 g/kg caused a

transient period of depression and slightly laboured breathing (in males only) with no mortality. The drug was given as a single dose, suspended in carboxymethylcellulose or carboxymethylcellulose and sesame oil.

Rats

In hooded Long-Evans rats no deaths or toxic signs were seen at 5 g/kg or 6.2 g/kg orally of norgestimate alone. Norgestimate in combination with ethinyl estradiol (5:l) orally at 5 g/kg caused no deaths or overt signs of toxicity other than a slight decrease in body weight compared to controls. At autopsy prostate, seminal vesicles and testes were smaller in animals receiving 5 g/kg of the combination than in controls. Ethinyl estradiol alone had an oral LD_{50} of 5.3 g/kg for males and 3.2 g/kg for females. Drug was administered suspended in carboxymethylcellulose.

Dogs

Oral norgestimate at 5 g/kg caused no deaths or signs of toxicity in female beagles. Also, no deaths or signs of toxicity were seen in female beagles given ethinyl estradiol 5.0 g/kg orally. Drugs were given suspended in carboxymethylcellulose.

Norgestimate (14.3 mg/kg) plus ethinyl estradiol (2.0 mg/kg) in ethanol given by i.v. infusion caused no deaths and the only toxic signs were those of acute ethanol intoxication and were also seen in controls.

Subacute Toxicity Studies

Rats

In female hooded Long-Evans rats oral norgestimate at 10.0, 2.5, 1.0, 0.5 and 0 mg/kg/day for 90 days caused no deaths; and all animals appeared normal on the 90th day. Daily observation showed no symptoms of drug-induced effect or toxicity. Hematological examination results were within normal range and urinalysis results gave no indication of toxicity throughout the test period. Biochemical evaluation showed blood components to be within normal range at termination. A dose-related decrease in cholesterol levels was seen. Gross pathological and histopathological examination did not reveal any toxic effects at any dose level.

Norgestimate plus ethinyl estradiol (10:1), given orally at 11.0, 2.75, 1.10, 0.55 mg/kg/day for 90 days, and caused no deaths or symptoms indicating drug-induced toxicity. Lab testing and necropsy results were all in the normal range although treated animals appeared to have an increased incidence of nephrocalcinosis and unilateral hydronephrosis.

Dogs

Female beagles were given oral doses of norgestimate up to 5.0 mg/kg/day. No deaths were seen. Hematological test results were normal as were clinical chemistry values except for a slight depression of cholesterol in higher-dose animals early in the study. Urinalysis results were normal.

Some test groups showed a decrease in organ weight or organ/body weight ratio for uterus and ovaries when compared to controls and test animals showed suppression of luteinization and/or follicular maturation. Glandular cystic hyperplasia of gallbladder was seen in treated dogs. An extremely low degree of toxicity was exhibited.

Female beagles were given oral doses of norgestimate + ethinyl estradiol (5:1) up to 5.5 mg/kg/day for 90 days. No deaths occurred. Hematological test values were normal for control and low-dose (0.28 mg/kg) animals while WBC was elevated in the two higher-dose groups. Clinical chemistry results were normal except for 1 dog in the high-dose and 2 in middle-dose groups which had slightly depressed BUN values. Uterus weight increased and ovary weight decreased in test animals when compared to controls. Test animals showed suppression of luteinization and/or follicular maturation and gallbladder glandular hyperplasia.

Monkeys

Female Rhesus monkeys given norgestimate orally at doses of 5.0, 1.50, 0.25 and 0 mg/kg/day for 90 days showed no signs of toxicity in their behaviour, body weight, hematology results, urinalysis, or clinical chemistry values. Histological examination revealed no lesions attributable to the drug. The same was seen for oral norgestimate +ethinyl estradiol (10:1) for doses of 5.5, 1.65, 0.275 and 0 mg/kg/day for 90 days except in high-dose animals. These animals showed hypertrophy of cervical mucus glands and an increase in size and number of mammary acini. Evidence of hyperplasia and epithelial sloughing of uterine endometrium was also noted. There was a dose-dependent stimulation of mucus secretion of the cervix.

Long-Term Toxicity Studies

Rats

Adult female Long-Evans rats were given norgestimate + ethinyl estradiol (5:1) at doses of 3.00, 0.60, 0.15 and 0 mg/kg/day orally for 24 months. There were 70 animals in each group receiving drug and 110 animals in the vehicle- only group.

One hundred and five animals did not survive the dosing schedule. The highest mortality rate was seen in controls. In drug-treated rats, the middle-dose group had the lowest mortality rate while the low-dose group had the highest.

Mean body weights of all treated groups decreased slightly as compared to controls, while the mean food consumption was not significantly different. In all test groups, there was a slight to moderate decrease in RBCs, hematocrit and hemoglobin compared to controls. Clinical chemistry showed a significant decrease in serum cholesterol in all drug-treated groups.

Hepatic changes were seen in all groups (including controls) at 2 years. The severity and incidence of these changes was higher in high- and mid-dose groups than in others. These changes were: Nodular or generalized hepatocyte hypertrophy and hyperplasia, hyperplasia foci of hepatocyte coagulation necrosis, sinusoidal telangiectasis, and formation of hematocysts. The reproductive organs showed little microscopic evidence of drug effect, although uterine endometrial hyperplasia was increased in treated animals. The incidence of benign mammary tumours was higher in treated animals than in controls. However, the incidence was statistically significant only in the highest- dose group. At 50 to 1000 times the human dose, this combination produced effects remarkably similar to those of other progestin-estrogen combinations.

In a second study, female Long-Evans rats were given norgestimate plus ethinyl estradiol at (5:1) at 0.150, 0.0375 and 0.01875 mg/kg/day (6.5 to 50 times the human dose), norgestimate alone

and ethinyl estradiol alone each at 0.025 mg/kg/day (50 times human dose) or d-norgestrel at 0.150, 0.075, and 0.0375 mg/kg/day (50 times human dose) for 104 weeks. There were 50 rats in each test group and 100 vehicle controls. Mortality was 55.9% overall with no difference between groups. Minor transient changes were seen for food consumption and body weight early in the study. Periodic hematological examination showed no deviations beyond normal range except for a slight decrease in hematocrit in the high-dose norgestimate + ethinyl estradiol groups. All clinical chemistry parameters measured demonstrated large variations associated with aging in all groups. The only statistically significant changes were a decrease in the cholesterol in ethinyl estradiol only and norgestimate + ethinyl estradiol high-dose groups, and an elevation of triglycerides in all combination groups. There was no significant difference between control and test rats for either benign or malignant tumours.

Dogs

Adult female beagles were given norgestimate + ethinyl estradiol orally at doses of 0.60 mg/kg/day (16 dogs) and 0.15, 0.06, and 0 (vehicle controls) mg/kg/day (20 dogs/group) for two years. This constitutes 20 to 200 times the human dose.

No deaths occurred. All animals were in good health at termination and no changes in behaviour were noted. In year 1, estrus was seen in all controls. In year 2, it was seen in 13 of 16 controls and was not seen in any test dog during the study. High-dose dogs had decreased RBCs and hematocrit throughout the study and an increased WBC count from 3 to 18 months of study. Decreased lymphocytes were seen in high- and mid-dose dogs and cholesterol was decreased in the low- and mid-dose dogs. Histologic changes were all estrogenic in nature with minimal evidence of progestational response.

In a seven-year study, 15 female beagles/group were given oral doses of 0.1425, 0.057, 0.0057 and 0 mg/kg/day norgestimate + ethinyl estradiol in the 21 days on followed by 7 days off cycle. There were 9 deaths during the study: 2 in the control, 2 in the high-dose, 4 in the mid-dose and 1 in the low-dose group. Daily observation revealed no unexpected adverse effects. Near the end of the study, slight to moderate alopecia and enlarged uteri were palpated in some dogs from the high- and the intermediate dose groups. Hysterectomies resulting from pyometra were greatest in high-dose and least in low-dose and control animals. Nodules palpated during mammary exams were greatest in number for the low-dose group followed by controls and lowest in the high-dose groups; none appeared drug-related. Heart rate, blood pressure and ECG intervals were all within normal range and no meaningful differences were seen in mean body weights between treated and control dogs.

Hematology findings in the last year included decreases in hematocrit, hemoglobin, and red blood cell mean values in the high-dose group. Throughout, a decline in hematocrit was observed in all groups, but was most evident in the high-dose group, and appears to be drug-related. White blood cell counts were generally normal. Mean percent of segmented neutrophil values were higher in the high-dose group at the 84-month interim, but over the course of the study, this was not generally the case. Mean sedimentation rates at 84 months were increased, primarily in the high-dose group. However, over the entire study, changes in sedimentation rates noted were related to isolated individual increases observed in all test groups.

Coagulation parameters showed sporadic, statistically significant differences, but in general,

values over the study were within normal limits. No trends were observed. Decreases in cholesterol and triglycerides and slight increases in potassium and albumin values occurred during the study in treated dogs.

Urinalysis results were generally normal although near the end of the study some dogs from control, high- and low- dose groups had trace to 4^+ protein.

Monkeys

Norgestimate + ethinyl estradiol was given orally to female Rhesus monkeys (20/group except for the high-dose group which had 16) at 0.60, 0.30, 0.06 and 0 mg/kg/day in a 21-day treatment followed by seven-day no-treatment cycle for 2 years. This dose represents 20 to 200 times the human dose. During the study 1 control, 1 high-dose and 4 mid-dose monkeys died.

No changes in behaviour were observed. A grey mammary discharge was seen more frequently in treated animals as compared to controls, and was seen mainly during withdrawal periods. Early in the study, treated monkeys had lower mean RBC, hematocrit and hemoglobin values, but were comparable to controls and within normal limits by month 12. All treated groups showed elevated triglycerides and decreased alkaline phosphatase values throughout the study. Decreased serum albumin and low total serum protein values were seen at various times during the study. Other clinical chemistry results were within normal limits, as were clotting study results, urinalysis and urinary steroid determinations. Pap smears produced no evidence of neoplasia.

At autopsy, no drug-related gross or microscopic pathologic lesions were observed in any monkeys, including those that died during the study. Isolated cases of focal hepatic sinusoidal dilation, congestion and/or small hemorrhages were seen at the capsular surfaces. It is believed that they are of little pathological importance due to an absence of any significant liver changes over the two-year dosing period and the high- (up to 200 times the human dose) dose levels of drug. Except for an increase in intralobular stromal tissue in a high-dose monkey, mammary nodules found were focal nodular hyperplasia and these occurred in both control and treated animals. The only organ weight changes seen were decreased ovarian and uterine weights in treated monkeys from the 0.30 and 0.60 mg/kg/day groups.

In a 10-year study, female Rhesus monkeys (16/group) were given oral norgestimate + ethinyl estradiol (5:1) at 150, 30, 3, and 0 mcg/kg/day in a 21 day on followed by 7 days off repeating cycle for the first 4 years. For the remaining 6 years, the monkeys received the medications in a 7:l ratio, (285, 57, 5.7, 0 mg/kg/day) in the same cycle. Six (3 control, 1 low- and 2 high-dose) monkeys died during the study.

While there were some early differences in weight gains all groups were similar from the second year on. Mammary nodules were noted in all groups during the study and most regressed or disappeared. At the end of the study, the number of animals with nodules was 0, 0, 1 and 1 in the low, mid, high, and control dose groups, respectively. Mammary secretions were noted in some mid- and high-dose monkeys throughout the study.

Hematocrit, erythrocytic parameter changes, mean corpuscular volume, mean leukocyte counts and coagulation parameters were generally similar for all groups.

Clinical chemistry showed a dose-related increase in SGPT. All groups also showed an increase with time. Generally lower alkaline phosphatase values for treated monkeys and intermittent slight decreases in serum protein for treated monkeys were seen. BUN for all groups was well within reference range and no difference between groups was noted for glucose. Reports from the literature indicate a dose-related increase in triglycerides and a decrease in cholesterol for the mid-dose group[5].

Thyroid function test results were typical of those expected for oral contraceptive use in humans. Urinalysis results showed no difference between groups and the results for urinary steroids were unremarkable.

Terminal organ weights for the liver and pituitary were increased while the ovary weights decreased.

The salient non-neoplastic histologic findings consisted predominantly of genito-urinary changes and multifocal myocardial fibrosis. Except for minor histopathologic differences in the ovaries, findings affecting the lower-dose animals were essentially comparable with those of the controls. The findings seen in the tissues of the genital tracts and related tissues in the mid- and high-dose animals included: ovarian atrophy associated with absence of active corpora lutea and occasional reduction in the number of maturing follicles, varying degrees of endometrial atrophy occasionally associated with stromal proliferation and/or decidualization of the endometrial stroma, increased mucus secretion of the cervix often associated with villous elongation and crypt dilation of the mucosa, atrophy and columnar cell metaplasia of the vaginal mucosa, occasional atrophy of the oviduct, lobular hyperplasia of some of the mammary glands and dose-related hypertrophy of the pars distalis of the pituitary gland. Multifocal myocardial fibrosis was noted in animals of each group, including controls, although in a slightly higher incidence in the treated groups. This finding was most prominent in 4 of 7 affected high-dose animals. The significance of this lesion is uncertain based on its presence in controls and the known spontaneous occurrence especially in aging animals.

Carcinogenicity

Neoplasms of tissues other than the genito-urinary tract were few and all were considered to be spontaneous. Neoplasms associated with the genito-urinary tract were as follows:

Neoplasm	Dose Group
One muco-epidermoid adenocarcinoma of cervix	high[a]
One leiomyoma of vagina	high[a]
One lobular carcinoma *in situ* of mammary gland	high[b]
One papilloma of mammary gland	high[b]
One adenoma of mammary gland	high
One urinary bladder papilloma	mid

a = Same Animal
b = Same Animal

The previously listed tumours of monkeys are single occurrences and are generally in different organs. Each of these tumour types have been reported in the literature as spontaneous occurrences. It is difficult to make a definitive etiologic association of the single cervical adenocarcinoma in one high-dose monkey. However, the absence of any antecedent changes (dysplasia, carcinoma *in situ*) in any of the other 47 treated monkeys, the known spontaneous occurrence (although rare in monkeys) suggest the tumour is probably spontaneous in origin.

REPRODUCTIVE STUDIES

A fertility and general reproductive performance study was conducted in female Long-Evans rats to assess the effects of norgestimate + ethinyl estradiol (5:1) at 0.120, 0.0833, 0.060, 0.050 and 0.030 mg/kg/day on conception rates, fetal development, parturition and lactation and the viability, growth and reproductive performance of the offspring.

Norgestimate + ethinyl estradiol results in a dose-related suppression of fertility, decreased implantation efficiency and litter size, and an increased fetal resorption in the F_0 females at all dose levels. Slight increases in the incidence of stillbirths were noted in all of the treated females. In addition, there was a decrease in neonatal survival at 0.060, 0.0833 and 0.120 mg/kg/day.

Similar dose-related findings were observed for the F_1 females but to a lesser degree than the F_0 generation. Trends toward decreased fertility, decreased implantation, F_2 litter size, and increased resorptions were noted in all dose groups. Dystocia and an increased number of stillbirths occurred at the 0.060 mg/kg level. At the 0.060 and 0.0833 mg/kg dose levels, survival of offspring was reduced.

TERATOLOGY AND FETAL TOXICITY

Rats

Female Long-Evans rats were treated orally with norgestimate + ethinyl estradiol (5:1) at 0 (vehicle), 0.012, 0.060, and 0.300 mg/kg/day dose levels on days 6-15 of gestation. An increase in "wavy ribs" was noted in rats receiving 0.060 (3/159 fetuses) and 0.300 mg/kg/day (9/128 fetuses) which was statistically significant only in the high-dose group compared to controls (1/152 fetuses). A reduction in the implantation efficiency and an increase in the number of resorptions were also noted in the high-dose group.

In addition, norgestimate + ethinyl estradiol (5:1) was administered orally to pregnant Long-Evans rats from day 15 of pregnancy through day 21 of lactation at dose levels of 0 (vehicle), 0.03, 0.18, 0.30, and 0.60 mg/kg/day. These levels represent approximately 10, 60, 100, and 200 times the proposed human dose levels. In the F_0 generation, no significant adverse effects were seen on maternal growth, behaviour and reproductive performance. However, there was some evidence of lactational insufficiency at the high-dose level.

In the F_1 generation, viability, growth and reproductive performance were unaffected in the 0.03 mg/kg/day group. At 0.18, 0.30 and 0.60 mg/kg/day, there was a dose-related reduction in female

fertility. The remaining drug effects were limited to the high-dose level which showed significantly decreased offspring viability from birth to weaning and depressed pup weight during the mid-lactation period.

There was no significant drug effect on F_2 generation development at any dose level.

Rabbits

Female New Zealand white rabbits were given oral doses of 0.5% sodium carboxymethylcellulose suspensions of norgestimate + ethinyl estradiol (5:1) at concentrations of 0 (vehicle), 0.012, 0.060 or 0.300 mg/kg/day from day 7 through day 19 of gestation. The only drug-related effect was the high rate of fetal resorptions, 100% and 65.5%, observed in the high- and intermediate- dose groups, respectively. No drug-related teratogenic changes were observed in any of the fetuses examined.

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PART III: CONSUMER INFORMATION

PrPREVIFEM
norgestimate and ethinyl estradiol

This leaflet is part III of a three-part "Product Monograph" published when PREVIFEM was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PREVIFEM. 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:
PREVIFEM is a birth control pill which contains two female sex hormones (norgestimate and ethinyl estradiol) and has been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills, except in smokers older than age 35.

How Birth Control Pills Work
The birth control pills work in two ways:
1. They inhibit the monthly release of an egg by the ovaries.

2. They change the mucus produced by the cervix. This slows the movement of the sperm through the mucus and through the uterus (womb).

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

- the pill is **TAKEN AS DIRECTED**, and
- the amount of estrogen is 20 micrograms or more.

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

The mini-pill (progestin only) is slightly less effective than combination birth control pills.

Other ways to prevent pregnancy
Other methods of birth control are available to you. They are usually less effective than birth control pills. Used properly, however, other methods of birth control are effective enough for many women.

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

Reported Pregnancies Per 100 Women Per Year

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

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

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

Non-Contraceptive Benefits Of Birth Control Pills
Several health advantages have been linked to the use of birth control pills.

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

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

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

- unusual vaginal bleeding that has not yet been diagnosed;
- blood clots in the legs, lungs, eyes, or elsewhere;
- a stroke, heart attack, or chest pain (angina pectoris);
- known or suspected cancer of the breast or sex organs;
- liver tumour associated with the use of the pill or other estrogen-containing products: and/or
- jaundice or liver disease if still present

The pill should not be taken if you are pregnant or if pregnancy is suspected.

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:
norgestimate and ethinyl estradiol

What the nonmedicinal ingredients are:
FD & C Blue #1 HT, FD & C Blue #2, hydroxypropyl methylcellulose, iron oxide yellow, lactose monohydrate, magnesium stearate, pregelatinized starch and polyethylene glycol.

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

PREVIFEM 21
21-Day Package contains:
- 21 BLUE tablets each containing 0.250 mg norgestimate and 0.035 mg ethinyl estradiol.

PREVIFEM 28
28-day Package contains:
- 21 BLUE tablets each containing 0.250 mg norgestimate and 0.035 mg ethinyl estradiol.
- 7 GREEN tablets with inert ingredients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users over 35 years of age. Women should not smoke.
- Oral contraceptives **do not protect** against sexually transmitted diseases (STD's) including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **in combination with** oral contraceptives.

BEFORE you use PREVIFEM talk to your doctor or pharmacist if you have:
•breast conditions
•a strong family history of breast cancer
•breast disorders including pain, discharge from the nipples, thickenings, or lumps. In some circumstances, benefit may be derived from taking the pill; in other cases, adverse effects may follow.
•diabetes
•high blood pressure
•abnormal levels of fats in the bloodstream (high cholesterol or triglycerides)
•cigarette smoking
•migraine headaches
•heart or kidney disease
•epilepsy
•depression
•fibroid tumours of the uterus
•gallbladder or pancreatic disease
•plans for forthcoming surgery
•history of jaundice or other liver disease.

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

Inform your doctor if you are taking or if you start to take other medications. This applies to both prescription and non-prescription drugs, including herbal or "natural" preparations or remedies. These medications may change the effectiveness and/or cycle control of your birth control pills. You may need to use a back-up (barrier) method of birth control.

If You Decide To Take Birth Control Pills
If you and your doctor decide that, for you, the benefits of birth control pills outweigh the risks, you should be aware of the following:

1. Take the pills only on the advice of your doctor and carefully follow all directions given to you. You must take the pills exactly as prescribed. Otherwise, you may become pregnant.

2. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.

3. 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 in the calf. This symptom could indicate a possible blood clot in the leg;
•crushing chest pain or heaviness. This symptom 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;
•severe pain or lump in the abdomen. These symptoms could indicate a possible tumor of the liver;
•severe depression;
•yellowing of the skin (jaundice);
•unusual swelling of the extremities; and/or
•breast lumps. **ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTIONS ON REGULAR SELF-EXAMINATION OF YOUR BREASTS**.

4. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing.

5. You will have a menstrual period when you stop taking birth control pills. You should delay pregnancy until another menstrual period occurs within four to six weeks. Contact

your doctor for recommendations on alternative methods of contraception during this time.

6. The hormones in birth control pills are known to appear in breast milk. 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. There is no evidence that birth control pills are harmful to the nursing infant.

7. Should you require **MAJOR** surgery, inform your surgeon that you are using birth control pills.

8. **If you see a different doctor, inform him or her that you are taking birth control pills.** Tell the doctor that your birth control pills are **PREVIFEM Tablets**.

Birth control pills **DO NOT PROTECT** against sexually transmitted diseases (STDs) including HIV/AIDS. For protection against STDs it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

The Risks Of Birth Control Pills
Circulatory disorders **(including blood clots in legs, lungs, heart, eyes or brain)**
Blood clots are the most common serious side effects of birth control pills. Clots can occur in many areas of the body.
•In the brain, a clot can result in a stroke.
•In a blood vessel of the heart, a clot can result in a heart attack.
•In the legs and pelvis, a clot can break off and travel to the lung resulting in a pulmonary embolus.
•In a blood vessel leading to an arm or leg, a clot can result in damage to or loss of a limb.
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.

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

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

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

Women with the following conditions should be examined yearly by their doctors no matter what method of contraception they use:

•a strong history of breast cancer in the family;
•breast nodules or thickenings; and/or
•discharge from the nipple.

Dangers to developing child if birth control pills are used during pregnancy.
Birth control pills should not be taken by pregnant women. There is no evidence, however, that the pill can damage a developing child.

There is also no evidence that the use of birth control pills immediately before a pregnancy will adversely affect a baby's development. When a woman stops taking birth control pills to become pregnant, however, her doctor may recommend a different method of contraception until she has a period on her own. In this way, the pregnancy can be more accurately dated.

Gallbladder disease and liver tumours
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.

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

INTERACTIONS WITH THIS MEDICATION

Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Drugs that may interact with PREVIFEM include:
-drugs used for the treatment of epilepsy (e.g., primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate); tuberculosis (e.g., rifampicin)
-antibiotics (e.g., penicillins, tetracyclines) for infectious diseases
-antifungals (griseofulvin)
-the herbal remedy St. John’s Wort (primarily used for the treatment of depressive moods)
-cholesterol-lowering drugs (e.g. clofibrate)
-antihypertensive drugs (for high blood pressure)
-antidiabetic drugs and insulin (for diabetes)
-prednisone
-sedatives (e.g. meperidine) and hypnotics (e.g. benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
-antidepressants (e.g. clomipramine)
-some nutritional supplements (e.g. Vit. B12, folic acid)
-antacids (use 2 hours before of after taking PREVIFEM)

Some drugs (e.g., cyclosporine) may inhibit the metabolism of

PREVIFEM. The pill may also interfere with the working of other drugs (See bolded text under WARNINGS AND PRECAUTIONS).

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

PROPER USE OF THIS MEDICATION

Usual dose:

HOW TO TAKE PREVIFEM

1. Read these directions before you start taking your pills, and any time you are not sure what to do.

2. LOOK AT YOUR PILL PACK to see if it has 21 or 28 pills:

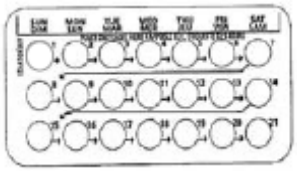
• 21-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week

or

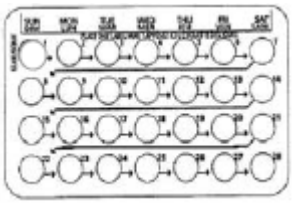
• 28-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

ALSO CHECK: the pill pack for instructions on 1) where to start and 2) direction to take pills.

21-Day Package



28-Day Package



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

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

5. IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES, such as antibiotics, your pills may not work as well. Use a back-up (barrier) method, such as latex condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

6. Periodic Examination

A complete medical and family history is necessary before birth control pills are prescribed. A physical examination should include measuring blood pressure, and examining the breasts, abdomen, pelvic organs, and limbs.

A second visit to your doctor should take place three months or sooner after starting birth control pills. During this visit, any side effects should be evaluated and your blood pressure checked again. Afterward, an annual examination similar to the first visit is recommended. A Pap smear is usually taken before starting birth control pills and then at intervals recommended by your doctor.

7. MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL. If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

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

9. THERE IS NO NEED TO STOP TAKING BIRTH CONTROL PILLS FOR A REST PERIOD.

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

WHEN TO START THE *FIRST* PACK OF PILLS
BE SURE TO READ THESE INSTRUCTIONS:

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

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

DIRECTIONS FOR 21-DAY AND 28-DAY PILL PACKS

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE**. The pills may be started up to Day 6 of your cycle. Your starting day will be chosen in discussion with your doctor. You will always begin taking your pill on this day of the week. Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

2. **IF YOU ARE USING A:**

21-DAY Pill Pack

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

Take one pill at approximately the same time every day for 21 days. **THEN DO NOT TAKE A PILL FOR SEVEN DAYS**. Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period.)

28-DAY Pill Pack

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

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

INSTRUCTIONS FOR USING YOUR PACKAGE FOR BOTH 21-DAY AND 28-DAY PACKS.
FOLLOW THESE INSTRUCTIONS CAREFULLY:

For Day 1 start: Start with Day 1 of your menstrual period (the first day of menstruation is Day 1). For example, if your first day of menstruation is Tuesday, take the pill on Tuesday. Peel label strip from the front of the day labels with TUE beginning first and press firmly on blister pack.

OR

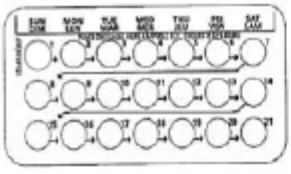
For Day 5 start: Start with the day that is 5 days after your period begins. (Count 5 days including the first day of menstruation.) For example, if your first day of menstruation is Saturday, then take the pill on Wednesday. Peel label strip from the front of the day labels with WED beginning first and press firmly on blister pack.

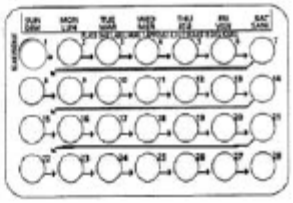
OR

For Sunday start: The Package is printed for a Sunday start. (The first Sunday after your period begins, or, if your period starts on Sunday, start that same day.) Discard day labels.

To begin taking your pills, start with the pill on the top left corner of the blister pack. This pill should correspond to the day of the week that you are taking your first pill. To remove the pill, push through the back of the package.

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





WHAT TO DO DURING THE MONTH

1. **TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY**.

- Try to associate taking your pill with some regular activity such as eating a meal or going to bed.
- Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
- Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK**

- **21 PILLS**

WAIT SEVEN DAYS to start the next pack. You will have your period during that week.

- **28 PILLS**

Start the next pack **ON THE NEXT DAY**. Take one pill every day. Do not wait any days between packs.

Overdose:
In case of overdose please contact your doctor. Overdosage may cause nausea and withdrawal bleeding may occur in females. PREVIFEM 28: If you have taken the last 7 tablets from row 4 of the blister this is harmless because they do not contain active ingredients.

In the event of overdosage, contact your doctor, hospital emergency department or regional Poison Control Centre.

Missed Dose:
MISSING PILLS ALSO CAN CAUSE SOME SPOTTING OR LIGHT BLEEDING, even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take two pills to make up for missed pills.

IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:

- when you start a pack late, or
- when you miss pills at the beginning or at the very end of the pack.

ALWAYS BE SURE YOU HAVE READY:

- **ANOTHER KIND OF BIRTH CONTROL** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
- **AN EXTRA, FULL PACK OF PILLS**.

IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW, talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

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

WHAT TO DO IF YOU MISS PILLS

The following chart outlines the actions you should take if you miss one or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack.

SUNDAY START **MISS ONE PILL**	**OTHER THAN SUNDAY START** **MISS ONE PILL**
Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.
MISS TWO PILLS IN A ROW	**MISS TWO PILLS IN A ROW**
First Two Weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**	**First Two Weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a 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 THREE OR MORE PILLS IN A ROW	**MISS THREE OR MORE PILLS IN A ROW**
Any Time in the Cycle 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills 4. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**	**Any Time in the Cycle** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (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.**

NOTE: 28-DAY PACK - If you forget any of the seven "reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING , OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL. If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

Most side effects of the pill are not serious. The most common such effects are:

- nausea
- vomiting
- bleeding between menstrual periods
- weight gain
- breast tenderness
- difficulty wearing contact lenses
- acne
- vaginal irritation or infections
- urinary tract infections or inflammations (cystitis)
- upper respiratory tract infections (colds, bronchitis, etc.)
- migraine, severe headaches
- depression
- amenorrhea (lack of a period or breakthrough bleeding)
- back pain
- abdominal pain

These side effects, especially nausea and vomiting may subside within the first three months of use. If symptoms persist or worsen, please consult your doctor.

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

As the use of birth control pills may be associated with the occurrence of blood clots in the lungs or in the legs, be alert for the following symptoms and signs of these and other 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 in the calf. This symptom could indicate a possible blood clot in the leg;
- crushing chest pain or heaviness. This symptom 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;
- severe pain or lump in the abdomen. These symptoms could indicate a possible tumour of the liver;
- severe depression;
- yellowing of the skin (jaundice);
- high blood pressure; although blood pressure usually returns to normal when the pill is stopped;
- unusual swelling of the extremities; and/or
- breast lumps. **ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTION ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.**

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/blood clot in the lung.			√
	Pain in the calf. /blood clot in the leg			√
	Crushing chest pain or heaviness./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/stroke			√
	Sudden partial or complete loss of vision/blood clot in the eye			√
	Severe pain or lump in the abdomen/liver tumour.			√
	Severe depression.			√
	Yellowing of the skin/ jaundice			√
	Unusual swelling of the extremities.		√	
	Breast lumps/breast cancer.		√	

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

HOW TO STORE IT

Store between 15°C - 30°C. Leave contents in protective packaging until time of use. Keep out of reach of children.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and
Effectiveness Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting,
Novopharm Limited:
at: 1-800-268-4127 ext. 5005 (English);
1-877-777-9117 (French)
or druginfo@novopharm.com

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