PRODUCT MONOGRAPH

PrORTHO-CEPT®

desogestrel and ethinyl estradiol tablets, USP

0.150 mg desogestrel and 0.030 mg ethinyl estradiol tablets

Oral Contraceptive

Janssen Inc.
Toronto, Ontario
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SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non Medicinal Ingredients
Oral	Tablets 0.150 mg desogestrel and 0.030 mg ethinyl estradiol	Lactose *For a complete listing see Dosage Forms, Composition and Packaging section.*

PHARMACOLOGICAL CLASSIFICATION

Synthetic steroidal combination oral contraceptive.

CLINICAL PHARMACOLOGY

The primary mechanism of action of ORTHO-CEPT® Tablets 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.

INDICATIONS AND CLINICAL USE

ORTHO-CEPT® Tablets are indicated for conception control.

CONTRAINDICATIONS

- History of or actual thrombophlebitis or thromboembolic disorders
- Known thrombophilic conditions
- History of or actual cerebrovascular disorders
- History of or actual myocardial infarction or coronary arterial disease
- History of or actual prodromi of a thrombosis (e.g., transient ischaemic attack, angina pectoris)
- Active liver disease or history of or actual benign or malignant liver tumours
- Known or suspected carcinoma of the breast
- 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
- When pregnancy is suspected or diagnosed
- Valvular heart disease with complications
- Cholestatic jaundice or history of jaundice of pregnancy
- Migraine with focal aura
- History of or actual pancreatitis if associated with severe hypertriglyceridemia
- Presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
  - persistent blood pressure values ≥160 mm Hg systolic or ≥100 mm Hg diastolic
  - hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia (e.g., due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - over age 35 and smoke
  - diabetes mellitus with vascular involvement
  - major surgery associated with an increased risk of postoperative thromboembolism
  - prolonged immobilization
  - Severe dyslipoproteinemia
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container.

WARNINGS

1. *Predisposing Factors for Coronary Artery Disease*

Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs, including ORTHO-CEPT®, should not be used by women who are over 35 years of age and smoke.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension (persistent blood pressure values ≥140 mm Hg systolic or ≥90 mm Hg diastolic), 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.

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2. Venous and Arterial Thrombosis and Thromboembolism

Venous thrombosis and thromboembolism

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

The use of any COC carries an increased risk of VTE compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a COC. The increased risk is less than the risk of VTE associated with pregnancy, which is estimated as 60 cases per 100,000 pregnancies. VTE is fatal in 1–2% of cases.[1]

Data from some case control and cohort studies report that third generation oral contraceptives containing desogestrel (such as ORTHO-CEPT® Tablets) are associated with a two-fold increase in the risk of venous thromboembolic disease as compared to second generation pills containing other progestins. However, it is not known to what degree methodological limitations inherent to these studies may have affected the observed difference in risk.

The incidence of venous thromboembolism in non-users of oral contraceptives is estimated to be 4 events per 100,000 woman-years, and increases to 10-15 events per 100,000 woman-years with the use of second-generation oral contraceptives. The findings of the studies mentioned above could translate into an additional 4-15 events per 100,000 woman-years (to a total of 14-30 events per 100,000 woman-years) with the use of third-generation oral contraceptives. It should be noted, however, that the incidence of venous thromboembolism in oral contraceptive users overall is rare.

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

If a hereditary or acquired predisposition for venous thromboembolism is suspected, the woman should be referred to a specialist for advice before deciding on any COC use.

Arterial thrombosis and thromboembolism

The use of COCs increases the risk of arterial thrombotic and thromboembolic events. Reported events include myocardial infarction and cerebrovascular events (ischemic and hemorrhagic stroke and transient ischemic attack).

The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors. Caution must be exercised when prescribing COCs for women with risk factors for arterial thrombotic and thromboembolic events.

3. 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** ***Thromboembolic Complications - Post-surgery***.

C. Visual Defects – Partial or Complete

D. Papilledema or Ophthalmic Vascular Lesions

E. Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache

F. Increase in epileptic seizures

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

The use of COCs is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes. Other examples of medical conditions which have been associated with adverse circulatory events e.g., systemic lupus erythematosus[2], hemolytic uremic syndrome[3-5], chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis)[6], sickle cell disease[7], valvular heart disease and atrial fibrillation[8,9].

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COCs has not been firmly established: porphyria[10], systemic lupus erythematosus[11], hemolytic uremic syndrome[12], Sydenham's chorea[13,14], herpes gestationis[15,16] and otosclerosis-related hearing loss[17].

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

PRECAUTIONS

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

The first follow-up visit should be 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 Workshop on Screening for Cancer of the Cervix. Their suggestion was that, for women who had two consecutive negative Pap smears, screening could be continued every three years up to the age of 69.

2. 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.

If pregnancy occurs during treatment with ORTHO-CEPT®, further intake should be stopped.

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. Published studies with other COCs have indicated that during lactation, 0.1% of the daily maternal dose of the progestin[18] and 0.02% of the daily maternal dose of ethinyl estradiol[19] could be transferred to the newborn via milk. Adverse effects on the child have been reported, including jaundice and breast enlargement[20]. The nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child.

Pediatrics

The safety and efficacy of desogestrel and ethinyl estradiol tablets has not been established in women under the age of 18 years.

Use of this product before menarche is not indicated.

Geriatrics

ORTHO-CEPT® is not indicated in postmenopausal women.

3. Gastrointestinal

Published epidemiological studies indicate a possible association of COC use and the development of Crohn's disease and ulcerative colitis, although this has not been firmly established[21-25].

4. Hepatic/Biliary/Pancreatic

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

Jaundice

Patients who have had jaundice, including a history of cholestatic jaundice during pregnancy, should be given oral contraceptives with great care and under close observation. Oral contraceptive-related cholestasis has been described in women with a history of pregnancy-related cholestasis. Women with a history of cholestasis may have the condition recur with subsequent hormonal contraceptive use.

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

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

Hepatic Nodules

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

Gallbladder Disease

Gallbladder disease including cholecystitis and cholelithiasis has been reported with oral contraceptive use. Patients taking oral contraceptives have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

5. Cardiovascular

Hypertension

Patients with essential hypertension whose blood pressure (BP) is well-controlled may be given oral contraceptives but only under close supervision. If a significant persistent 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 and an alternate method of contraception should be prescribed (see **CONTRAINDICATIONS**).

6. Neurologic

Migraine and Headache

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

7. Endocrine and Metabolism

Diabetes

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

Lipid and Other Metabolic Effects

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

8. Ophthalmologic

Ocular Disease

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

9. Carcinogenesis and Mutagenesis

Breast Cancer

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age 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 an 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.

Cervical Cancer

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

Hepatocellular Carcinoma

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

10. **Genitourinary**

Vaginal Bleeding

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

Fibroids

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

11. **Immune**

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema[26-28].

12. **Psychiatric**

Emotional Disorders

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.

13. ***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
Free T_3 resin-uptake	Decreased

D. Adrenocortical Function Tests

Plasma Cortisol	Increased

E. Lipoproteins	Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions.
F. Gonadotropins	LH and FSH levels are suppressed by the use of oral contraceptives. Wait two weeks after discontinuing the use of oral contraceptives before measurements are made.

G. Miscellaneous Tests

Serum Folate	Occasionally decreased
Glucose Tolerance Test	Oral glucose tolerance remained unchanged or was slightly decreased.
Insulin Response	Mild to moderate increase
c-Peptide Response	Mild to moderate increase

14. Tissue Specimens

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

15. Skin

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

16. Sexual Function/Reproduction

Return to Fertility

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

Amenorrhea

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

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

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

Reduced Efficacy
The efficacy of COCs may be reduced in the event of missed tablets, gastro-intestinal disturbances or concomitant medication (see **DRUG INTERACTIONS**).

17. Thromboembolic Complications - Post-surgery
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.

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

Drug Interactions
The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent (Tables 1 and 2). Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low-dose formulations.

It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before oral contraceptives are prescribed.

Physicians are advised to consult the labelling of concurrently used drugs to obtain further information about interactions with hormonal contraceptives or the potential for enzyme alterations and the possible need to adjust dosages.

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

Table 1: Drugs that May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Anticonvulsants	Carbamazepine Eslicarbazepine acetate Ethosuximide Felbamate Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone Rufinamide Topiramate	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.
	Rifabutin Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Cholesterol Lowering Agents	Cholestyramine	May result in hastened elimination and impaired effectiveness.	
	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces OC efficacy.	Use another method.
HIV Protease Inhibitors	Nelfinavir Ritonavir Ritonavir-boosted protease inhibitors	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.

Other Drugs	Phenylbutazone Antihistamines Analgesics Antimigraine preparations Vitamin E Modafinil	Reduced OC efficacy has been reported. Remains to be confirmed.	
	Bosentan	Induction of hepatic microsomal enzymes.	Consider switching to a non-hormonal contraceptive method or adding a barrier method to oral contraceptive therapy.
	Colesevelam	Given together with a combined oral hormonal contraceptive, has been shown to significantly decrease the AUC of ethinyl estradiol.	Take contraceptive 4 hours before colesevelam.
	(fos)aprepitant	Induction of hepatic microsomal enzymes.	Use another method.

Antibiotics: There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical pharmacokinetic studies have not shown consistent effects of antibiotics on plasma concentrations of synthetic steroids.

Table 2: 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.
	Lamotrigine	Significantly decreased lamotrigine levels (due to induction of lamotrigine glucuronidation) may lead to breakthrough seizures.	Adjust dose of drug if necessary.
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.
	Salicylic acid	Plasma levels may be decreased (due to induction of glucuronidation).	Use with caution.
Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because OCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity.

Table 2 (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.
Corticosteroids	Prednisone Prednisolone	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.
Morphine		Decreased morphine levels (due to induction of glucuronidation).	Use 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.
Proton Pump Inhibitor	Omeprazole	May lead to an increase in omeprazole plasma levels (due to CYP inhibition).	Use with caution.
Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam Temazepam	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.
Other	Selegiline	May lead to an increase in selegiline plasma levels (due to CYP inhibition).	Avoid concomitant use.
	Tizanidine	May lead to an increase in tizanidine plasma levels (due to CYP inhibition).	Use with caution.
	Voriconazole	May lead to an increase in voriconazole plasma levels (due to CYP inhibition).	Use with caution.

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

Increase in Plasma Hormone Levels Associated With Co-Administered Drugs:

Some drugs and grapefruit juice may increase the plasma levels of ethinyl estradiol if co-administered. Examples include:

- acetaminophen
- ascorbic acid
- CYP3A4 inhibitors (including itraconazole, ketoconazole, voriconazole, fluconazole and grapefruit juice)
- some HIV protease inhibitors (e.g., atazanavir and indinavir)
- HMG-CoA reductase inhibitors (including atorvastatin and rosuvastatin)
- some non-nucleoside reverse transcriptase inhibitors (e.g., etravirine)

Drug-Herb Interactions

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

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.

Oral contraceptives **DO NOT PROTECT** against sexually transmitted infections (STIs) including HIV/AIDS. For protection against STIs, it is advisable to use latex or polyurethane condoms **IN COMBINATION WITH** oral contraceptives.

ADVERSE REACTIONS

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

Thrombophlebitis and venous thrombosis with or without embolism
Arterial thromboembolism
Pulmonary embolism
Mesenteric thrombosis
Neuro-ocular lesions (e.g., retinal thrombosis)
Myocardial infarction
Cerebral thrombosis
Cerebral hemorrhage
Hypertension
Benign hepatic tumours
Gallbladder disease

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:

Gastrointestinal symptoms (such as abdominal cramps and bloating)
Breakthrough bleeding
Spotting
Change in menstrual flow
Dysmenorrhea
Amenorrhea during and after treatment
Temporary infertility after discontinuance of treatment
Edema
Chloasma or melasma which may persist
Breast changes: tenderness, enlargement, and secretion
Change in weight (increase or decrease)
Endocervical hyperplasias
Possible diminution in lactation when given immediately postpartum
Cholestatic jaundice
Migraine
Increase in size of uterine leiomyomata
Rash (allergic)
Depression
Reduced tolerance to carbohydrates
Vaginal candidiasis
Premenstrual-like syndrome
Intolerance to contact lenses
Change in corneal curvature (steepening)
Cataracts
Optic neuritis
Retinal thrombosis
Changes in libido

Chorea
Changes in appetite
Cystitis-like syndrome
Rhinitis
Headache
Nervousness
Dizziness
Hirsutism
Loss of scalp hair
Erythema multiforme
Erythema nodosum
Hemorrhagic eruption
Vaginitis
Porphyria
Impaired renal function
Raynaud's phenomenon
Auditory disturbances
Hemolytic uremic syndrome
Pancreatitis
Change in cervical erosion and secretion
Acne
Colitis
Budd-Chiari Syndrome
Diarrhea
Hypersensitivity
Vaginal discharge

TREATMENT OF OVERDOSE OR ACCIDENTAL INGESTION

In case of overdose or accidental ingestion by children, the physician should observe the patient closely, although generally no treatment is required. Gastric lavage may be utilized if considered necessary. Overdosage may cause nausea and vomiting and withdrawal bleeding may occur in females. There are no antidotes and treatment should be symptomatic.

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

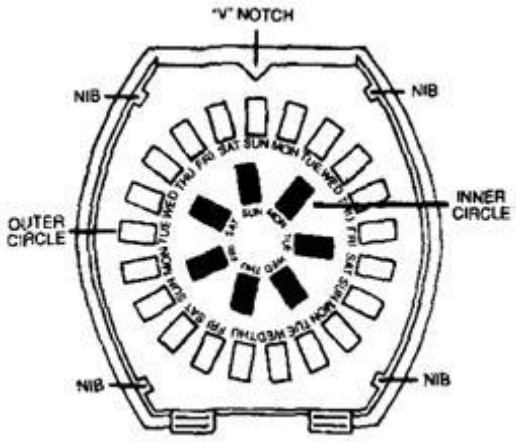
DOSAGE AND ADMINISTRATION

INFORMATION TO PATIENTS ON HOW TO TAKE THE BIRTH CONTROL PILL

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**:
   - 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.



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

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

5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH 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.

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

7. **IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE**:
   - when you start a pack late, or
   - when you miss pills at the beginning or at the very end of the pack.

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

- **AN EXTRA, FULL PACK OF PILLS**.

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

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

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

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

Decide with your doctor or clinic what is the best day for you to start taking your first pack of pills.

A. 28-DAY COMBINATION

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

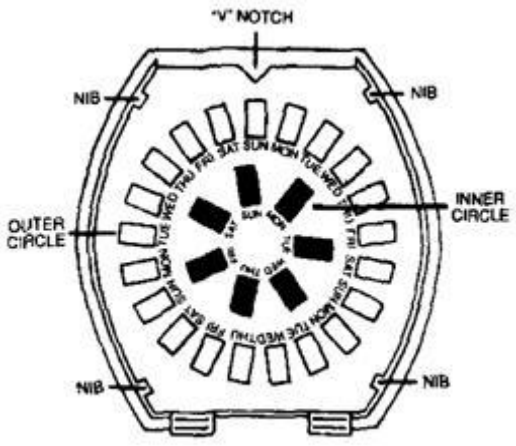
1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** The pills may be started up to Day 6 of your cycle. Your starting day will be chosen in discussion with your doctor. You will <u>always</u> begin taking your pill on this day of the week. Your doctor may advise you to start 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. 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 VERIDATE® TABLET DISPENSER

FOLLOW THESE INSTRUCTIONS CAREFULLY:

For 28-Day Regimen



ALWAYS COMPLETE THE ORANGE TABLETS BEFORE TAKING THE GREEN TABLETS

1. Open the compact. Place the blister card into the compact, with the tablets facing up, so that the V notch in the blister card matches up with the V shaped post at the top of the compact. Press down firmly on each edge of the blister card and make sure that the edge of the blister card is firmly seated under each of the nibs inside the compact (see diagram).

   There are 21 light orange "active" pills (with hormones) and 7 green "reminder" pills (no hormones).

2. If you are to start pill-taking on Sunday, take your first light orange pill on the first Sunday after your menstrual period begins. If your period begins on Sunday, take your first pill that day. Remove the first pill at the top of the dispenser (Sunday) by pressing the pill through the hole in the bottom of the dispenser.

3. If you are to start pill-taking on "Day 1", choose a light orange pill that corresponds with the day of the week on which you are taking the first pill. Remove that light orange pill by pressing the pill through the hole in the bottom of the dispenser.

4. Continue taking one light orange pill daily, clockwise, until no pills remain in the **outer circle**.

5. The next day take the green pill from the **inner circle** that corresponds with the day of the week it happens to be. Take a green pill each day until all seven pills are taken. During this time your period should begin.

6. After you have taken all the green pills, begin a new blister card (see Step 1 above in "Instructions for using your VERIDATE® Tablet Dispenser") and take the first light orange "active" pill on the next day, even if your period is not yet over.

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

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 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.**

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

Always be sure you have on hand:

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

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

SPECIAL NOTES ON ADMINISTRATION

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

Switching from another combination hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch): The woman should start ORTHO-CEPT® preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or inactive tablet of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using ORTHO-CEPT® preferably on the day of removal, but at the latest when the next application would have been due.

Switching from a progestogen-only-method (mini-pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS): The woman may switch from the mini-pill to ORTHO-CEPT® on any day of her cycle. Patients using a progestogen injection should start ORTHO-CEPT® on the day the next injection is due. Patients using an implant or an IUS should start ORTHO-CEPT® on the day it is removed. In all cases, the woman should be advised to use an additional barrier method for the first 7 days of ORTHO-CEPT® use.

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

Following delivery or second-trimester abortion: Women should be advised to start ORTHO-CEPT® on Day 21 to 28 after delivery or second trimester abortion, after consulting with their physician. When starting later, the woman should be advised to use an additional barrier method for the first seven days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of use or the woman should be advised to wait for her first menstrual period prior to starting ORTHO-CEPT®.

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

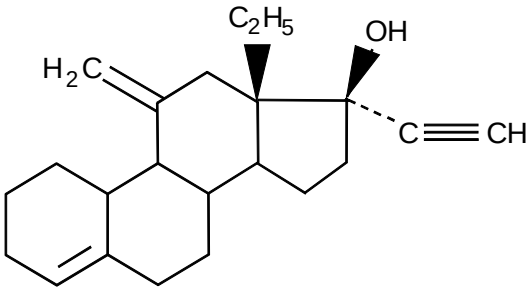
PHARMACEUTICAL INFORMATION

(i) DRUG SUBSTANCE

Desogestrel:

Chemical Name: 13-Ethyl-11-methylene,18,19-dinor-17α-pregn-4-en-20-yn-17-ol

Structural Formula:



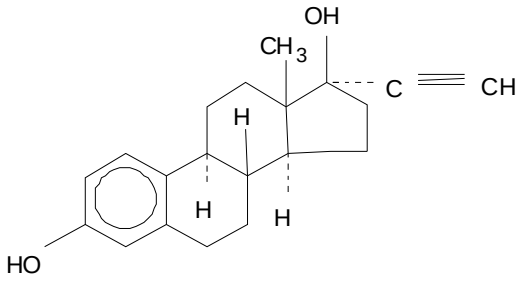
Molecular Weight: 310.48 Molecular Formula: $C_{22}H_{30}O$

Description:
Desogestrel is a white crystalline powder with a melting point of 110°C-112°C. Solubility at 20°C: n-Hexane: 40 mg/mL; Ethanol (96%): >200 mg/mL; Ethyl acetate: >150 mg/mL; Water: practically insoluble.

Ethinyl Estradiol:

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

Structural Formula:



Molecular Weight: 296.41 Molecular Formula: $C_{20}H_{24}0_2$

Description:
Ethinyl Estradiol is a white to creamy white, odorless, crystalline powder with a melting range of 183°C-184°C. It is insoluble in water, soluble in alcohol, in chloroform, in ether, in vegetable oils, and in solutions of fixed alkali hydroxides.

(ii) COMPOSITION
Each ORTHO-CEPT® Tablet (orange, unscored with D 150 engraved on each side) contains 0.15 mg desogestrel and 0.03 mg ethinyl estradiol. The orange tablet also contains vitamin E, starch, povidone, stearic acid, colloidal silicon dioxide, lactose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, iron oxide (red and yellow) and talc. Each green tablet, engraved with ORTHO P on each side, contains the following inactive ingredients: lactose, starch, magnesium stearate, indigotin blue or FD&C Blue No. 1, iron oxide (red and yellow), hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide and talc.

STORAGE RECOMMENDATIONS

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

AVAILABILITY

ORTHO-CEPT® Tablets are available in a blister card pack with a VERIDATE® tablet dispenser (unfilled). The blister card contains 28 tablets as follows:

- 21 LIGHT ORANGE tablets each containing 0.150 mg desogestrel and 0.030 mg ethinyl estradiol
- 7 GREEN tablets with inert ingredients

PHARMACOLOGY

Animal and *In Vitro* Pharmacology

Animal pharmacology and *in vitro* receptor binding studies indicate that 3-k-desogestrel, the biologically active metabolite, is a highly selective progestational agent (see table below) with no estrogenic effects, and only residual androgenicity.

COMPARISON OF RELATIVE BINDING AFFINITY OF DESOGESTREL, 3-k-DESOGESTREL AND PROGESTERONE FOR THE PROGESTERONE RECEPTOR IN UTERINE CYTOSOL.*

	RABBIT MYOMETRIUM	HUMAN MYOMETRIUM
Desogestrel	5	2
3-k-desogestrel	111	113
progesterone	32	18

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

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

The "selectivity index" (progestogen/androgen receptor binding affinity ratio) for 3-k-desogestrel in intact MCF-7 cells is higher than any other progestogen.

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

Human Pharmacology

After oral administration of desogestrel, typical antigonadotropic and progestational effects are observed; these include suppression of the hypothalamic-pituitary-gonadal axis; secretory transformation of an estrogen primed endometrium; impaired sperm penetration and "spinnbarkeit" of the cervical mucus. Endometrial morphology in chronic users of ORTHO-CEPT® Tablets show a homogeneous picture with findings typical of the luteal phase of the menstrual cycle.

Pharmacokinetics

Desogestrel (DSG) is rapidly and almost completely absorbed and converted into 3-keto-desogestrel, (3-K-DSG), its biologically active metabolite. After a single dose of ORTHO-CEPT® Tablets, maximum concentrations of 3-K-DSG of approximately 6 pmol/mL are reached at 1.6 hours. The area under the curve ($AUC_{0-\infty}$) is approximately 59 pmol/mL•hr after a single dose. At steady state, attained from at least day 19 onwards, maximum concentrations of approximately 18 pmol/mL are reached at 1.4 hours. The minimum plasma levels of 3-K-DSG at steady state are approximately 4 pmol/mL. The AUC_{0-24} at steady state is approximately 161 pmol/mL•hr. The relative bioavailability of 3-K-DSG is approximately 84%. The elimination half-life for 3-K-DSG is approximately 38 hours at steady state.

Major phase I metabolites are 3α-OH-desogestrel, 3β-OH-desogestrel, and 3α-OH-5α-OH-desogestrel. These degradation products are in part further converted by conjugation (phase II metabolism) into polar metabolites, mainly sulfates and glucuronides. Approximately 48% of 3-K-DSG is recovered unchanged in urine within 24 hours.

Ethinyl estradiol (EE) is rapidly and almost completely absorbed. After a single dose of ORTHO-CEPT® Tablets, maximum concentrations of EE of approximately 0.3 pmol/mL are reached at 1.6 hours. The $AUC_{0-\infty}$ is about 4.9 pmol/mL•hr after a single dose. At steady state, attained from at least day 19 onwards, maximum ethinyl estradiol concentrations of approximately 0.5 pmol/mL are reached at about 1.4 hours. The minimum serum levels of ethinyl estradiol at steady state are about 0.08 pmol/mL. The AUC_{0-24}, at steady state is approximately 4.6 pmol/mL•hr. The relative bioavailability is approximately 83% and the elimination half-life about 26 hours at steady state.

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

TOXICOLOGY

Acute Toxicity Studies

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

None of the test animals died during the oral or intraperitoneal studies. The orally dosed mice and rats had temporary signs of reduced activity, some motor incoordination, diminished food consumption, and other nonspecific signs related to the large dose of the test material. Likewise, mice and rats dosed intraperitoneally showed similar signs. Some evidence of serositis (localized peritoneal irritation) was associated with the test substances.

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

Multidose Toxicity Studies

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

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

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

Multidose Toxicity Studies

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

*DSG = desogestrel EE = ethinyl estradiol

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

Organ weight changes were consistent with those noted with other combination oral contraceptives. The liver weight was increased at 26 and 52 weeks in primarily intermediate-dose and high-dose animals; testes, epididymides, prostate, seminal vesicles, ovaries, uterus, adrenals, and the pituitary gland were also affected by treatment.

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

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

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

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

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

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

In rats, the absence of ethinyl estradiol in the test compound resulted in expected progestational changes at 26 and 52 weeks, such as secretory changes in the uterine endometrium, mucification of the vaginal epithelium, mild glandular hyperplasia of the mammary glands, and reduced pituitary weights. In the 52-week portion of the study, a small number of benign or malignant neoplasms were observed, but none of these were causally related to the test compound.

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

The 52-week segment of the dog study with desogestrel alone resulted in changes similar to those seen at 26 weeks; however, occasional small mammary nodules (5 mm or less) were present in 1 control (C), 1 low-dose (LD), 1 ID, and 4 high-dose animals. They disappeared in the 1 C and 2 high-dose animals. The remaining nodules were found to be non-neoplastic and proved to be either smaller superficial lymph nodes or dilated ducts. The uterine stimulation was increased at 52 weeks but did not result in the death of any animal.
Four multidose toxicity studies of up to 2 years in duration were conducted in rats, dogs, and monkeys. Desogestrel + ethinyl estradiol was studied in rats, monkeys, and dogs, and desogestrel alone was studied in rats.

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

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

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

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

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

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

Three-year studies were conducted in both Beagle dogs and Rhesus monkeys with desogestrel + ethinyl estradiol with a 1- and 2-year interim sacrifice in monkeys and a 2-year interim sacrifice in dogs. No tumorigenic response was noted. Mammary glands of dogs had lobulo-alveolar development with limited secretory change, an expected hormonal effect. Other tissue changes as described under the 2-year interim report, limited to the primary and secondary sex organs, were associated with the hormonal activities of the combination OC.

The monkey study conducted for 3 years, with a 1- and 2-year interim sacrifice, revealed no evidence of a tumorigenic effect. The changes observed, as described at the 2-year interim studies, were typical of the hormonal activities of the combination OC and included effects on the menstrual cycle, cervical mucus and endometrial morphology.

Reproductive Toxicity Studies

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

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

Desogestrel alone was studied in both Sprague Dawley and CFY rats. An additional study in Sprague Dawley rats was conducted after microphthalmia was increased in CFY offspring of the desogestrel-treated dams. No increase in microphthalmia was seen in the second Sprague Dawley study. The defect was thus thought to be strain-related. In all 3 studies the contraceptive effect of desogestrel was reversible. Treatment at contraceptive and subcontraceptive dose levels did not cause any serious aftereffects on the dams or their offspring.

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

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

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

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

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

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

Mutagenicity Studies

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

CLINICAL TRIALS

Extensive clinical experience, in excess of 125,000 cycles in published reports alone, has documented the efficacy of ORTHO-CEPT® (Desogestrel and Ethinyl Estradiol) Tablets.

NUMBER OF STUDIES, NUMBER OF SUBJECTS EXPOSED, ESTIMATED MINIMUM EXPOSURE AND NUMBER OF PREGNANCIES BY STUDY SIZE [10/137; 121/128]

STUDY SIZE	NUMBER OF STUDIES	TOTAL ENROLLED	CALCULATED MINIMUM EXPOSURE (#CYCLES)[a]	TOTAL NUMBER OF PREGNANCIES
>500	6	53,773	106,399	5
201-500	8	2,514	11,380	2
101-200	4	437	689	0
51-100	9	704	2,174	1
26-50	27	970	1,762	0
1-25	80	1,058	2,804	0
Total	134	59,456	125,208	8

[a] For the purpose of estimation of extent of exposure, it is assumed that dropouts were evenly distributed over the interval of observation (if 60 subjects discontinued over 6 months, it is assumed that 10 discontinued each month). Several studies provided inadequate information on the number of subjects at subsequent visits. Therefore, the actual number of cycles is likely to be substantially larger.

In addition, several well-controlled studies were designed to determine the efficacy and safety of ORTHO-CEPT® Tablets. One of these involved 1,195 patients who completed a total of 11,426 cycles.

(a) Pearl Index

The observed Pearl Index among ORTHO-CEPT® Tablets users compares favorably to what has been reported for other low-dose oral contraceptives. Nine patients participating in this study became pregnant. User failure accounted for all of these in-treatment pregnancies. Consequently, the Pearl Index for method failure is 0.00.

N	CYCLES	PEARL INDEX	
		METHOD	TOTAL
1,195	11,656	0.00	0.92

(b) Life Table estimates

The annual cumulative life-table pregnancy rate is estimated as 1.0/100 women-years.

CYCLE	PATIENTS	NO. OF PREGNANCIES	CUMULATIVE PREG. RATE/100 WOMEN
3	1037	4	0.39
6	904	4	0.82
9	734	0	0.82
12	525	1	1.00
15	307	0	1.00
18	139	0	1.00
23	9	0	1.00

(c) Cycle control

During the course of the study, 18 subjects (1.5%) discontinued due to menstrual problems. Absence of withdrawal bleeding (AWB) occurred in 1.7% of the cycles, while intermenstrual bleeding (IM) occurred in 8.0% of the total cycles. Both AWB and IM occurred more frequently during the first cycles of usage when compared to subsequent cycles. Spotting was more common than breakthrough bleeding (5.6% versus 2.5% of the cycles).

INCIDENCE BY CYCLE OF INTERMENSTRUAL BLEEDING AND ABSENCE OF WITHDRAWAL BLEEDING

	STARTERS			SWITCHERS		
Cycle	N	IM (%)	AWB (%)	N	IM (%)	AWB (%)
1	467	19.3	3.4	578	12.3	3.1
2	446	8.1	1.4	561	10.7	1.8
3	420	9.3	2.6	532	10.3	2.3
6	350	8.6	0.6	479	6.9	1.2
12	164	6.7	3.7	276	6.5	0.4

- intermenstrual bleeding (IM) was defined as any bleeding and/or spotting that started during the pill-taking interval that was not early or continued withdrawal bleeding
- absence of withdrawal bleeding (AWB) was defined as no bleeding and/or spotting episode that began during or continued into the pill-free interval

INCIDENCE BY CYCLE OF BREAKTHROUGH BLEEDING (BTB) AND SPOTTING (BTS)

	STARTERS			SWITCHERS		
Cycle	N	BTB (%)	BTS (%)	N	BTB (%)	BTS (%)
1	467	1.5	17.8	578	1.4	11.1
2	446	2.2	5.8	561	3.4	7.5
3	420	4.0	5.5	532	3.2	7.5
6	350	3.4	5.4	479	2.5	4.6
12	164	2.4	4.3	276	2.2	4.7

- breakthrough bleeding (BTB) was defined as any bleeding episode that occurred during the pill-taking interval that was not early or continued withdrawal bleeding
- breakthrough spotting (BTS) was defined as any spotting episode that occurred during the pill-taking interval that was not early or continued withdrawal bleeding

The results indicate that cycle control with ORTHO-CEPT® Tablets is generally excellent, resulting in very few dropouts due to irregular bleeding or to absence of withdrawal bleeding. These results are very similar to those obtained with other oral contraceptives.

(d) Tolerance

Eighty-six percent of the 1,195 subjects reported one or more adverse experiences. The majority of these (64%) were considered (by the investigators) to be unrelated to ORTHO-CEPT® Tablets usage. Of the total population, approximately 12% of the subjects discontinued due to an adverse experience.

OVERALL ASSESSMENT OF CLINICAL ADVERSE EXPERIENCES (AES)
ALL-PATIENTS-TREATED-GROUP

CLINICAL AE CATEGORIES	STARTERS N	(%)[a]	SWITCHERS N	(%)	TOTAL N	(%)
Total Patients Entered	549	(100.0)	645	(100.0)	1,194[b]	(100.0)
Patients with a Clinical AE	458	(83.4)	569	(88.2)	1,027	(86.0)
Patients with a Serious Clinical AE	20	(3.6)	18	(2.7)	38	(3.1)
Patients with Clinical AEs Contributing to Discontinuation[c]	76	(13.8)	70	(10.9)	146	(12.2)
Patients with a Reasonably Possibly, Probably or Definitely Drug-Related Clinical AE	197	(35.8)	236	(36.5)	433	(36.2)

[a]Percentages are of total patients entered.
[b]Starter/Switcher status could not be determined in one subject.
[c]A total of 145 patients actually had a clinical AE as the primary reason for discontinuation.

With the exception of menses-related adverse experiences, no significant changes in the incidence of adverse experiences over time were seen. No drug-related adverse effects were observed during general physical or pelvic examination. The breast examination showed a reduction in nodularity. No changes in body mass index or blood pressure were observed. Baseline distribution of abnormalities in cervical cytology were comparable to those at last visit. No patient developed a

clinically significant abnormal value for routine laboratory analyses that led to either early discontinuation or hospitalization.

Detailed ophthalmologic examinations, including slit-lamp, were performed in a subset of 28 healthy women at baseline and after 12 cycles. No patients were found to have a decrease in visual acuity. Complete ophthalmological examination failed to identify possible ORTHO-CEPT® Tablets-related changes.

PREVALENCE OF MOST FREQUENT[a] SIDE EFFECTS OVER CYCLES INCIDENCE DURING STUDY WITH N=1,195 TOTAL (PERCENT)

--Body System-- Adverse Experience	Cycle Number						
	1	2	3	6	12	18	21
	Number of Patients Per Cycle						
	1,095	1,064	1,001	863	465	115	30
--Body as a Whole--							
Abdominal Pain	115 (10.5)	71 (6.7)	58 (5.8)	42 (4.9)	20 (4.3)	4 (3.5)	1 (3.3)
Asthenia	27 (2.5)	18 (1.7)	11 (1.1)	11 (1.3)	2 (0.4)	1 (0.9)	1 (3.3)
Malaise	26 (2.4)	13 (1.2)	10 (1.0)	6 (0.7)	4 (0.9)	2 (1.7)	0 (0.0)
-- Digestive --							
Diarrhea	40 (3.6)	29 (2.7)	23 (2.3)	26 (3.0)	3 (0.6)	2 (1.7)	0 (0.0)
Dyspepsia	13 (1.2)	12 (1.1)	9 (0.9)	10 (1.2)	5 (1.1)	0 (0.0)	0 (0.0)
Nausea	99 (9.0)	66 (6.2)	55 (5.5)	26 (3.0)	8 (1.7)	3 (2.6)	0 (0.0)
Vomiting	25 (2.3)	22 (2.1)	21 (2.1)	16 (1.8)	4 (0.9)	0 (0.0)	1 (3.3)
-- Musculoskeletal --							
Back Pain	78 (7.1)	47 (4.4)	30 (3.0)	27 (3.1)	14 (3.0)	3 (2.6)	1 (3.3)
-- Nervous System / Psychiatric --							
Depression	25 (2.3)	20 (1.9)	18 (1.8)	10 (1.2)	4 (0.9)	1 (0.9)	0 (0.0)
Dizziness	18 (1.6)	16 (1.5)	8 (0.8)	18 (2.1)	3 (0.6)	1 (0.9)	0 (0.0)
Headache	389 (35.5)	286 (26.9)	220 (22.0)	191 (22.1)	87 (18.7)	19 (16.5)	5 (16.7)
Migraine	21 (1.9)	23 (2.2)	13 (1.3)	11 (1.3)	3 (0.6)	0 (0.0)	0 (0.0)
-- Respiratory --							
Allergic Rhinitis	9 (0.8)	11 (1.0)	13 (1.3)	9 (1.0)	12 (2.6)	1 (0.9)	0 (0.0)
Cough	26 (2.4)	17 (1.6)	17 (1.7)	16 (1.8)	5 (1.1)	2 (1.7)	0 (0.0)
Influenza	25 (2.3)	27 (2.5)	11 (1.1)	11 (1.3)	4 (0.9)	1 (0.9)	0 (0.0)
Pharyngitis	65 (5.9)	45 (4.2)	42 (4.2)	27 (3.1)	11 (2.4)	5 (4.4)	0 (0.0)
Upper Respiratory Infection	93 (8.5)	86 (8.1)	63 (6.3)	52 (6.0)	20 (4.3)	7 (6.1)	1 (3.3)
-- Urogenital --							
Breast Pain	75 (6.8)	55 (5.2)	51 (5.1)	15 (1.7)	4 (0.9)	1 (0.9)	0 (0.0)
Dysmenorrhea	323 (29.5)	155 (14.6)	121 (12.1)	88 (10.2)	49 (10.5)	8 (7.0)	5 (16.7)
Vaginal Candidiasis	11 (1.0)	12 (1.1)	7 (0.7)	14 (1.6)	9 (1.9)	3 (2.6)	0 (0.0)
Cystitis	9 (0.8)	11 (1.0)	7 (0.7)	5 (0.6)	4 (0.9)	1 (0.9)	0 (0.0)

[a] Adverse experiences reported by >5% of patients.

(e) Lipid Metabolism

A causal relationship between ischemic heart disease and unfavorable plasma lipid/lipoprotein profiles, specifically, a high LDL/HDL ratio, is now widely accepted on the basis of epidemiologic, biochemical, and other evidence. It has also been demonstrated that androgens influence the lipid/lipoprotein ratio unfavourably, while estrogens have a beneficial effect, largely by increasing HDL_2 and, to a lesser extent, by reducing LDL levels. Major adverse or counteractive effects on the beneficial action of estrogen are therefore of fundamental importance in any long-term medication.

ORTHO-CEPT® Tablets increased HDL-C levels, decreased LDL-C, but left HDL_2 and Apo B unchanged. Thus there was no significant effect on the HDL_2/LDL-C ratio. Like other oral contraceptives, ORTHO-CEPT® Tablets can be associated with an increase in triglyceride plasma levels.

NUMBER OF STUDIES DEMONSTRATING A PARTICULAR EFFECT ON LIPOPROTEIN METABOLISM AFTER 2 TO 4 MONTHS OF USE

		ORTHO-CEPT® Tablets
Total Cholesterol	No Change	12
	Increase	0
Triglycerides	No Change	4
	Increase	5
LDL-C	No Change	5
	Increase	0
HDL-C	Decrease	0
	No Change	5
	Increase	7

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CONSUMER INFORMATION
PrORTHO-CEPT®

desogestrel and ethinyl estradiol Tablets, USP

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ORTHO-CEPT®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
- prevention of pregnancy

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

Birth control pills work in two ways:

1. They inhibit the monthly release of an egg by the ovaries.
2. They change the mucus produced by the cervix. 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 per cent effective in preventing pregnancy when

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

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

The chance of becoming pregnant increases with incorrect use.

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

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

Reported Pregnancies per 100 Women per Year:

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

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

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

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

You should not use ORTHO-CEPT® 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 or thrombophlebitis (inflammation of the veins)
- a stroke, heart attack, or coronary artery disease (angina pectoris) or a condition that may be a first sign of a stroke (such as a transient ischemic attack or small reversible stroke)
- disease of the heart valves with complications
- persistent high blood pressure
- over age 35 and smoke
- you are scheduled for major surgery
- prolonged bed rest
- loss of vision due to blood vessel disease of the eye
- known or suspected cancer of the breast or sex organs
- liver tumour associated with the use of the pill or other estrogen-containing products
- jaundice (yellowing of skin and eyes) or liver disease if still present
- diabetes with complications of the kidneys, eyes, nerves, or blood vessels
- migraines with visual and/or sensory disturbances
- known abnormalities of blood clotting system that increase your risk for developing blood clots
- you are pregnant or if pregnancy is suspected
- pancreatitis (inflammation of the pancreas) associated with high levels of fatty substance (triglycerides) in your blood
- very high blood cholesterol or triglyceride levels and/or

- allergic reaction to ethinyl estradiol, desogestrel or to any of the other ingredients in ORTHO-CEPT® (see **What the nonmedicinal ingredients are).**

What the medicinal ingredients are:
Desogestrel and ethinyl estradiol

What the nonmedicinal ingredients are:
FD&C Blue No. 1 or indigotin blue, colloidal silicon dioxide, hydroxypropyl methylcellulose, iron oxide (red and yellow), lactose, magnesium stearate, stearic acid, povidone, polyethylene glycol, starch, talc, titanium dioxide and vitamin E

What dosage forms it comes in:
ORTHO-CEPT® (desogestrel and ethinyl estradiol) Tablets are available in a 28-day regimen.

28-day VERIDATE® Package contains: 21 ORANGE tablets containing 0.15 mg desogestrel and 0.03 mg ethinyl estradiol, 7 GREEN tablets with inactive ingredients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious side effects on the heart and blood vessels. This risk increases with age and becomes significant in hormonal contraceptive users older than 35 years of age and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including ORTHO-CEPT®, should not be used by women who are over 35 years of age and smoke.

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

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

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

BEFORE you use ORTHO-CEPT® talk to your doctor or pharmacist if the following apply to you:
- breast disease (e.g., breast lumps) or a family history of breast cancer
- 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
- wear contact lenses
- pregnant or breast-feeding
- systemic lupus erythematosus
- inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- hemolytic uremic syndrome
- sickle cell disease
- problems with the valves in your heart and/or have an irregular heart rhythm
- hereditary angioedema or have had episodes of swelling in body parts such as hands, feet, face, or airway passages
- gallbladder or pancreatic disease
- plans for forthcoming surgery
- history of jaundice (i.e. yellowing of skin and eyes) or other liver disease.

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

If you see a different doctor, inform him or her that you are using ORTHO-CEPT®.

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

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

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

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

THE RISKS OF USING ORTHO-CEPT®

1. 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. The risk of developing clots is high during the first year a woman uses a hormonal contraceptive. Clots may occur in many areas of the body.

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

- sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung.
- pain and/or swelling in the calf. These symptoms could indicate a possible blood clot in the leg.
- crushing chest pain or heaviness. These symptoms could

indicate a possible heart attack.
- sudden severe or worsening headache or vomiting, dizziness or fainting, disturbances of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke.
- sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.

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

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.**

2. Breast cancer

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

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

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

3. Cervical cancer

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

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

4. Gallbladder disease

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

5. Liver tumours

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.

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

6. Use during pregnancy

Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing. There is no evidence, however, that the pill can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

7. Use after pregnancy, miscarriage or an abortion

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

8. Pregnancy after stopping ORTHO-CEPT®

You will have a menstrual period when you stop taking ORTHO-CEPT®. 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.

9. Use while breast-feeding

The hormones in birth control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. Adverse effects on the child have been reported, including yellowing of the skin (jaundice) and breast enlargement. You should use another method of contraception and only consider starting the birth control pill once you have weaned your child completely.

INTERACTIONS WITH THIS MEDICATION

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

Drugs that may interact with ORTHO-CEPT® include:
- drugs used for epilepsy (e.g., primidone, phenytoin, carbamazepine, lamotrigine, oxcarbazepine, topiramate, rufinamide)
- drugs used for tuberculosis (e.g., rifampin and rifabutin)
- antibiotics (e.g., penicillins, tetracyclines) for infectious diseases
- (fos)aprepitant (drug used for nausea)
- selegiline (drug used for Parkinson's disease)
- tizanidine (drug used for multiple sclerosis [MS])
- antiretroviral drugs used for HIV/AIDS (e.g., atazanavir, indinavir, nelfinavir, ritonavir, ritonavir-boosted protease inhibitors, etravirine, nevirapine)
- salicylic acid
- bosentan (drug used for pulmonary hypertension which is high blood pressure in the blood vessels between the heart and the lungs)
- theophylline (drug used for asthma)
- stimulants (e.g., modafinil)
- lipid-lowering drugs (e.g., atorvastatin, rosuvastatin)

- colesevelam
- cyclosporine
- antifungals (e.g., griseofulvin, voriconazole, itraconazole, fluconazole, ketoconazole)
- the herbal remedy St. John's wort (primarily used for the treatment of depressive moods)
- antihypertensive drugs (for high blood pressure)
- antidiabetic drugs and insulin (for diabetes)
- prednisone, prednisolone
- sedatives and hypnotics (e.g., benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)
- pain medication (e.g., meperidine)
- antidepressants (e.g., clomipramine)
- acetaminophen
- grapefruit juice
- some nutritional supplements (e.g., vitamin B_{12}, vitamin C, folic acid)
- antacids (use 2 hours before or after taking ORTHO-CEPT®)

The pill may also interfere with the working of other drugs.

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

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

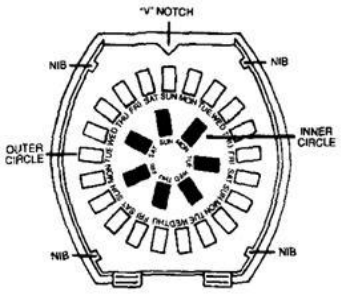
PROPER USE OF THIS MEDICATION

HOW TO TAKE ORTHO-CEPT®:

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:
   - 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.



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

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

5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH 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.

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

7. **IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:**
   - when you start a pack late, or
   - when you miss pills at the beginning or at the very end of the pack.

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

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

10. **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.

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

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

<u>WHEN TO START THE *FIRST* PACK OF PILLS</u>

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 ORTHO-CEPT® TABLETS ARE IN A 28-DAY PILL PACKAGE. With this type of birth control pill, you take 21 pills that contain hormones and seven pills that contain no hormones.

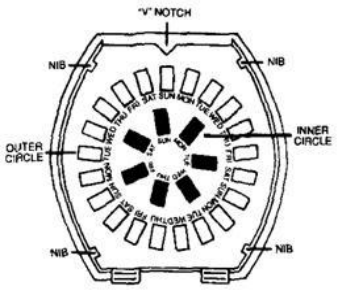
1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** The pills may be started up to Day 6 of your cycle. Your starting day will be chosen in discussion with your doctor. You will always begin taking your pill on this day of the week. Your doctor may advise you to start taking 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. 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 VERIDATE® TABLET DISPENSER. FOLLOW THESE INSTRUCTIONS CAREFULLY:

1. Open the compact. Place the blister card into the compact, with the tablets facing up, so that the V notch in the blister card matches up with the V shaped post at the top of the compact. Press down firmly on each edge of the blister card and make sure that the edge of the blister card is firmly seated under each of the nibs inside the compact (see diagram).

   There are 21 light orange "active" pills (with hormones) and 7 green "reminder" pills (no hormones).



2. If you are to start pill-taking on Sunday, take your first light orange pill on the first Sunday after your menstrual period begins. If your period begins on Sunday, take your first pill that day. Remove the first pill at the top of the dispenser (Sunday) by pressing the pill through the hole in the bottom of the dispenser.

3. If you are to start pill-taking on "Day 1", choose a light orange pill that corresponds with the day of the week on which you are taking the first pill. Remove that light orange pill by pressing the pill through the hole in the bottom of the dispenser.

4. Continue taking one light orange pill daily, clockwise, until no pills remain in the **outer circle**.

5. The next day take the green pill from the **inner circle** that corresponds with the day of the week it happens to be. Take a green pill each day until all seven pills are taken. During this time your period should begin.

6. After you have taken all the green pills, begin a new blister card (see Step 1 above in "Instructions for using your VERIDATE® Tablet Dispenser") and take the first light orange "active" pill on the next day, even if your period is not yet over.

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

Overdose:
Symptoms of overdose may include nausea, vomiting or vaginal bleeding. Available information from cases of accidental ingestion of oral contraceptives by children indicates no serious effects. Contact your doctor, your hospital or your local Poison Control Centre in case of accidental overdose.

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	**OTHER THAN SUNDAY START**
MISS ONE PILL	**MISS ONE PILL**
Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.
MISS TWO PILLS IN A ROW	**MISS TWO PILLS IN A ROW**
First Two Weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a 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	**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

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.**	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.**

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

Always be sure you have on hand:
- a back-up method of birth control (such as latex or polyurethane condoms and spermicidal foam or gel) in case you miss pills, and
- an extra, full pack of pills.

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

NON-CONTRACEPTIVE BENEFITS OF BIRTH CONTROL PILLS

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

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

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

The following additional symptoms have been reported in women taking hormonal contraceptives in general:
- difficulty wearing contact lenses
- vaginal irritation or infections
- urinary tract infections or inflammation
- upper respiratory tract infections (colds, bronchitis, runny or stuffy nose, sore throat, etc.)
- severe headaches
- insomnia
- amenorrhea (lack of a period or breakthrough bleeding)
- flu-like symptoms
- allergy, fatigue, fever
- diarrhea, flatulence

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

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

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Un-common	Abdominal pain, nausea or vomiting or lump in the abdomen		✓	
	Breast lump		✓	
	Crushing chest pain or heaviness			✓

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	
Pain or swelling in the leg			✓
Persistent sad mood			✓
Sharp pain in the chest, coughing blood, or sudden shortness of breath			✓
Sudden partial or complete loss of vision or double vision			✓
Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm or leg			✓
Unexpected vaginal bleeding		✓	
Unusual swelling of the extremities		✓	
Yellowing of the skin or eyes (jaundice)			✓

HOW TO STORE IT

Store in original packaging, between 15°C - 30°C. Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

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

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found at: http://www.janssen.ca or by contacting the sponsor, Janssen Inc. at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by
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