

PRODUCT MONOGRAPH

PrORTHO[®] 1/35

norethindrone and ethinyl estradiol Tablets, USP

1.0 mg norethindrone and 0.035 mg ethinyl estradiol Tablets

Oral Contraceptive

Janssen Inc.
19 Green Belt Drive
Toronto, Ontario
M3C 1L9
www.janssen.com/canada

Date of Revision:

March 14, 2017

Submission Control No.: 201117

© 2017 Janssen Inc.

All trademarks used under license.

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS	4
ADVERSE REACTIONS	13
DRUG INTERACTIONS	15
DOSAGE AND ADMINISTRATION	21
OVERDOSAGE	28
ACTION AND CLINICAL PHARMACOLOGY	29
STORAGE AND STABILITY	29
DOSAGE FORMS, COMPOSITION AND PACKAGING	29
PART II: SCIENTIFIC INFORMATION	30
PHARMACEUTICAL INFORMATION	30
CLINICAL TRIALS	31
DETAILED PHARMACOLOGY	35
TOXICOLOGY	36
REFERENCES	44
PART III: CONSUMER INFORMATION	49

PRODUCT MONOGRAPH

PrORTHO[®] 1/35

norethindrone and ethinyl estradiol Tablets, USP
1.0 mg norethindrone and 0.035 mg ethinyl estradiol Tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non Medicinal Ingredients
Oral	Tablet 1.0 mg norethindrone and 0.035 mg ethinyl estradiol	Lactose <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

ORTHO[®] 1/35 Tablets are indicated for conception control.

CONTRAINDICATIONS

- History of or actual thrombophlebitis or thromboembolic disorders.
- Known thrombophilic conditions.
- History of or actual cerebrovascular disorders including transient ischemic attack.
- History of or actual myocardial infarction or coronary arterial disease including angina pectoris.
- Active liver disease or history of or actual benign or malignant liver tumours.
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal vaginal bleeding.
- Steroid-dependent jaundice, cholestatic jaundice or history of jaundice in pregnancy.
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
- When pregnancy is suspected or diagnosed.
- Current or history of migraine with focal aura.
- Valvular heart disease with complications.
- History of or actual pancreatitis if associated with severe hypertriglyceridemia.
- Presence of severe or multiple risk factor(s) for arterial or venous thrombosis:

- severe hypertension (persistent values of ≥ 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),
- severe dyslipoproteinemia,
- over age 35 and smoke,
- diabetes mellitus with vascular involvement,
- major surgery associated with an increased risk of postoperative thromboembolism,
- prolonged immobilization.
- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Use with Hepatitis C virus (HCV) combination drug regimen paritaprevir, ritonavir, ombitasvir, with or without dasabuvir (see **WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious cardiovascular events associated with combination oral contraceptive use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including ORTHO[®] 1/35, should not be used by women who are over 35 years of age and smoke (see **Cardiovascular** section below).

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

General

Discontinue Medication at the Earliest Manifestation of 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 **WARNINGS AND PRECAUTIONS, Peri-operative Considerations**.

C. Visual Defects – Partial or Complete

D. Papilledema or Ophthalmic Vascular Lesions

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

F. Increase in Epileptic Seizures

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

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes. Other examples of medical conditions which have been associated with adverse circulatory events e.g., systemic lupus erythematosus⁽¹⁾, hemolytic uremic syndrome⁽²⁻⁴⁾, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis)⁽⁵⁾, sickle cell disease⁽⁶⁾, valvular heart disease and atrial fibrillation^(7,8).

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⁽⁹⁾, systemic lupus erythematosus⁽¹⁰⁾, hemolytic uremic syndrome⁽¹¹⁾, Sydenham's chorea^(12,13), herpes gestationis^(14,15) and otosclerosis-related hearing loss⁽¹⁶⁾.

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

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 papillomavirus (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 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. See ***Product Monograph Part II: TOXICOLOGY*** for discussion on animal data.

Cardiovascular

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Combination oral contraceptives (COC) increase this risk, particularly in women over 35 years of age, and with the number of cigarettes smoked. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use by women who smoke. For this reason, COCs, including ORTHO[®] 1/35 should not be used by women who are over 35 years of age and smoke.

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

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

Hypertension

Patients with essential hypertension whose blood pressure (BP) is well-controlled may be given oral contraceptives but only under close supervision. If a persistent and significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary and an alternative method of contraception should be prescribed (see **CONTRAINDICATIONS**).

An increase in BP has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use.

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 **CONTRAINDICATIONS**). Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Gastrointestinal

Published epidemiological studies suggest a possible association of COC use and the development of Crohn's disease and ulcerative colitis, although this has not been firmly established⁽¹⁷⁻²²⁾.

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.

Hematologic

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 combined oral contraceptive (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 or restarts (following a 4-week or greater pill-free interval) the same or a different 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⁽²³⁾.

If a hereditary or acquired predisposition for VTE 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.

Other Risk Factors for Venous or Arterial Thromboembolism or of a Cerebrovascular Accident

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

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency and antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

Postpartum Period

Since the immediate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than four weeks after delivery in women who elect not to breast-feed (see **DOSAGE AND ADMINISTRATION, Special Notes on Administration**).

Post-abortion/Post-miscarriage

After an induced or spontaneous abortion that occurs at or after 20 weeks gestation, hormonal contraceptives may be started either on Day 21 post-abortion or on the first day of the first spontaneous menstruation, whichever comes first (see **DOSAGE AND ADMINISTRATION, Special Notes on Administration**).

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.

Gallbladder Disease

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

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.

Hepatitis C

ORTHO[®] 1/35 must be discontinued prior to starting therapy with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS**). During clinical trials with ombitasvir, paritaprevir, ritonavir, with or without dasabuvir, ALT elevations 5 to >20 times the upper limit of normal (ULN) were significantly more frequent in healthy female subjects and HCV infected women using ethinyl estradiol-containing medications such as COCs. Physicians are advised to consult the labelling of concurrently-used HCV combination drug regimen ombitasvir, paritaprevir, ritonavir with and without dasabuvir to obtain further information about restarting ORTHO[®] 1/35.

Immune

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema⁽²⁴⁻²⁶⁾.

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**).

Ophthalmologic

Ocular Lesions

There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained transient, partial or complete loss of vision; onset of proptosis or diplopia; papilledema; or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately.

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.

Peri-operative Considerations

Thromboembolic Complications - Post-surgery

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of hormonal contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions.

Hormonal contraceptives should be discontinued and an alternative method substituted at least four weeks prior to elective surgery of a type associated with an increase in risk of thromboembolism and during prolonged immobilization. Hormonal contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery or following prolonged immobilization.

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.

Renal

Fluid Retention

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

Sexual Function/Reproduction

Return to Fertility

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

Amenorrhea

In the event of amenorrhea, pregnancy should be ruled out.

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, vomiting, diarrhea or concomitant medication (see **DRUG INTERACTIONS**).

Skin

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

Special Populations

Pregnant Women

ORTHO[®] 1/35 is contraindicated during pregnancy. If pregnancy occurs during treatment with ORTHO[®] 1/35, further pill use should be stopped. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child.

Nursing Women

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 of related progestins have indicated that during lactation, small amounts of the daily maternal dose of the progestin⁽²⁷⁾ and 0.02% of the daily maternal dose of ethinyl estradiol⁽²⁸⁾ could be transferred to the newborn via milk. Adverse effects on the child have been reported, including jaundice and breast enlargement⁽²⁹⁾. 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 ORTHO[®] 1/35 have been established in women of reproductive age. Use of this product before menarche is not indicated.

Geriatrics

ORTHO[®] 1/35 is not indicated for use in post-menopausal women.

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 should be evaluated if a first-degree family member has suffered from thromboembolic disease or event (e.g., deep vein thrombosis, stroke, myocardial infarction) at a young age. Breasts, liver, extremities and pelvic organs should be examined and a Papanicolaou (PAP) smear should be taken if the patient has been sexually active.

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

Tissue Specimens

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Cardiovascular System:	Edema Slight rise of blood pressure
Genital Tract:	Breakthrough bleeding Spotting Change in menstrual flow Dysmenorrhea Amenorrhea during and after treatment Vaginal candidiasis Premenstrual-like syndrome Temporary infertility after discontinuance of treatment Vaginitis Endocervical hyperplasias Increase in cervical erosion and secretion Vaginal discharge
Neoplasms:	Malignant hepatic tumours Cervical cancer Increase in size of uterine leiomyomata Breast cancer
Breast:	Pain, tenderness, enlargement, and secretion Possible diminution in lactation when given immediately postpartum
Skin and Subcutaneous Tissue:	Chloasma or melasma which may persist Rash (allergic) Hirsutism

	Loss of scalp hair
	Erythema multiforme
	Erythema nodosum
	Raynaud's phenomenon
	Hemorrhagic eruption
	Porphyria
	Acne
	Seborrhea
	Pemphigoid (herpes gestationis)
	Urticaria
	Angioedema
CNS:	Migraine
	Mental depression
	Headache
	Nervousness
	Dizziness
	Changes in libido
	Chorea
Metabolic:	Reduced tolerance to carbohydrates
	Change in weight (increase or decrease)
	Changes in appetite
Gastro-intestinal Tract:	Gastrointestinal symptoms (such as abdominal cramps, diarrhea and bloating)
	Colitis
	Pancreatitis
	Abdominal pain
Hepatobiliary:	Cholestatic jaundice
	Budd-Chiari syndrome
Eyes:	Intolerance to contact lenses
	Change in corneal curvature (steepening)
	Cataracts
	Optic neuritis
Urinary:	Impaired renal function
	Hemolytic uremic syndrome
	Cystitis-like syndrome
Others:	Rhinitis
	Auditory disturbances
	Hypersensitivity
	Fluid retention

Post-Market Adverse Drug Reactions

Adverse drug reactions first identified during post-marketing experience with ORTHO[®] have been listed.

Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps): Breast cancer, Breast mass, Breast neoplasm, Cervix carcinoma, Cervical dysplasia, Hepatic neoplasm malignant, Hepatic adenoma

Immune System Disorders: Anaphylactic/Anaphylactoid reaction, Hypersensitivity

Metabolism and Nutrition: Dyslipidemia, Glucose tolerance impaired

Nervous System Disorders: Cerebrovascular accident

Eye Disorders: Retinal vascular thrombosis

Cardiac Disorders: Myocardial infarction

Vascular Disorders: Deep vein thrombosis

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary embolism

Gastrointestinal Disorders: Pancreatitis, Thrombosis mesenteric vessel

Hepatobiliary Disorders: Hepatitis, Cholelithiasis, Budd-Chiari Syndrome

Skin and Subcutaneous Tissue Disorders: Angioedema, Erythema nodosum, Urticaria, Pruritus, Photosensitivity reaction

Reproductive System and Breast Disorders: Galactorrhea, Breast enlargement, Suppressed lactation, Vulvovaginal dryness, Menstruation irregular

General Disorders and Administration Site Conditions: Asthenia, Malaise

DRUG INTERACTIONS

Overview

The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent (see 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, including herbal preparations/remedies, 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 other possible drug interactions with OCs⁽³⁰⁾.

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 oral contraceptive efficacy.	Use another method.
HIV Protease Inhibitors	Nelfinavir Ritonavir Ritonavir-boosted protease inhibitors	Induction of hepatic microsomal enzymes.	Use another drug or another method.
HCV Protease Inhibitors	Boceprevir Telaprevir	Uncertain, but may be due to an effect on GI transporters, leading to a decrease in the AUC of ethinyl estradiol	Exposure to ethinyl estradiol was decreased when co-administered with telaprevir or boceprevir. Additional methods of non-hormonal contraception should be used when hormonal contraceptives are co-administered with telaprevir or boceprevir.
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	A bile acid sequestrant, 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 Methyl dopa	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.
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 Inhibitors	Omeprazole	May lead to an increase in omeprazole plasma levels (due to CYP inhibition).	Use with caution.

Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
	Temazepam	Decreased temazepam plasma level (due to induction of glucuronidation)	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 Drugs	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)

Contraindicated co-administration

Ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (direct-acting antiviral medicinal products) have been shown to be associated with increases in ALT levels 5 to >20 times the upper limit of normal in healthy female subjects and HCV infected women using ethinyl estradiol-containing medications such as COCs (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic**).

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

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

Drug-Laboratory Test Interactions

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

<i>A. Liver Function Tests</i>	
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
<i>B. Coagulation Tests</i>	
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
<i>C. Thyroid Function Tests</i>	
Protein-bound Iodine (PBI)	Increased
Total Serum Thyroxine (T ₄)	Increased
Thyroid Stimulating Hormone (TSH)	Unchanged
T ₃ Resin-uptake	Decreased
Free T ₄ Concentration	Unchanged
<i>D. Adrenocortical Function Tests</i>	
Plasma Cortisol	Increased
<i>E. Miscellaneous Tests</i>	
Serum Folate	Occasionally decreased
Glucose Tolerance Test	May be decreased
Insulin Response	Mild to moderate increase
c-Peptide Response	Mild to moderate increase

Lipoproteins

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

Gonadotropins

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

NON-CONTRACEPTIVE BENEFITS OF ORAL CONTRACEPTIVES

Several health advantages other than contraception have been reported.

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

DOSAGE AND ADMINISTRATION

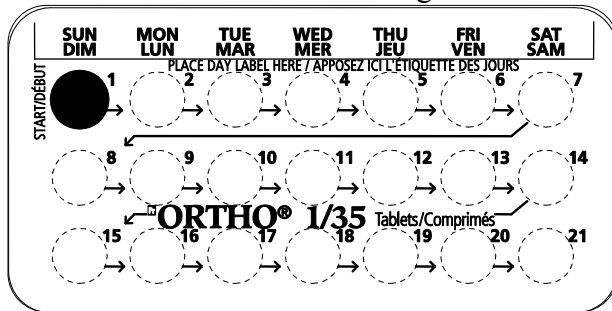
INFORMATION TO PATIENTS ON HOW TO TAKE THE BIRTH CONTROL PILL

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

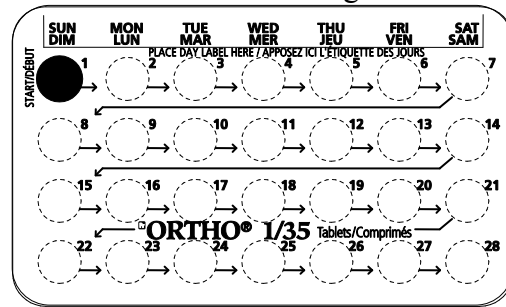
2. **LOOK AT YOUR PILL PACK** to see if it has 21 or 28 pills:
- **21-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week or
 - **28-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no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

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

21-Day
DISCREET Package



28-Day
DISCREET Package



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. Your pills may be either a 21-day or a 28-day type.

DIRECTIONS FOR 21-DAY AND 28-DAY PILL PACKS

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

2. **IF YOU ARE USING A:**
21-DAY Pill Pack:

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

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

28-DAY Pill Pack:

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

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

INSTRUCTIONS FOR USING YOUR DISCREET PACKAGE FOR BOTH 21-DAY AND 28-DAY PACKS

FOLLOW THESE INSTRUCTIONS CAREFULLY:

1. **For Day 1 start:** Label the DISCREET Package by selecting the day label that starts with Day 1 of your menstrual period (the first day of menstruation is Day 1). For example, if your first day of menstruation is Tuesday, attach the day label that begins with **TUE** in the space provided.

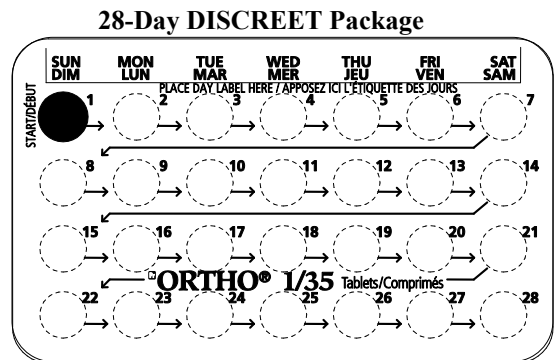
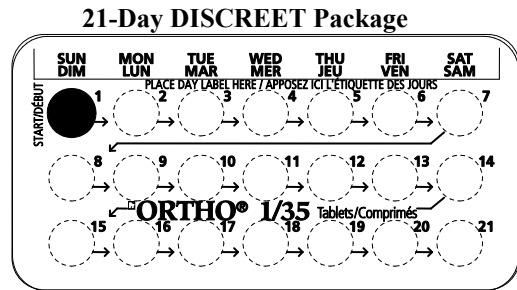
OR

For Day 5 start: Label the DISCREET Package by selecting the day label that starts with the day that is 5 days after your period begins. (Count 5 days including the first day of menstruation.) For example, if your first day of menstruation is Saturday, place the day label that starts with **WED** in the space provided.

OR

For Sunday start: No day label is required. The DISCREET Package is printed for a Sunday start. (The first Sunday after your period begins, or, if your period starts on Sunday, start that same day.)

2. Place the day label in the space where you see the words "Place day label here". Having the DISCREET Package labelled with the days of the week will help remind you to take your pill every day.
3. To begin taking your pills, start with the pill inside the red circle (where you see the word **START**). This pill should correspond to the day of the week that you are taking your first pill. To remove the pill, push through the back of the DISCREET Package.
4. On the following day, take the next pill in the same row, always proceeding from left to right (→). Each row will always begin on the same day of the week.



WHAT TO DO DURING THE MONTH

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

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

2. WHEN YOU FINISH A PACK

- **21 PILLS**

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

- **28 PILLS**

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

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
<p>First Two Weeks</p> <ol style="list-style-type: none"> 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. <p>Third Week</p> <ol style="list-style-type: none"> 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. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>	<p>First Two Weeks</p> <ol style="list-style-type: none"> 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. <p>Third Week</p> <ol style="list-style-type: none"> 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. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>
MISS THREE OR MORE PILLS IN A ROW	MISS THREE OR MORE PILLS IN A ROW
<p>Any Time in the Cycle</p> <ol style="list-style-type: none"> 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. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>	<p>Any Time in the Cycle</p> <ol style="list-style-type: none"> 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. <p>IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.</p>

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

Use after childbirth

The use of ORTHO[®] 1/35 for contraception should be started no earlier than 4 weeks postpartum in women who elect not to breast-feed. When the tablets are administered during the postpartum period, the increased risk of thromboembolic disease associated with the postpartum period must be considered (See **WARNINGS AND PRECAUTIONS, Hematologic**). The possibility of ovulation and conception prior to initiation of medication should be considered.

Use after abortion or miscarriage

After an abortion or miscarriage that occurs prior to 20 weeks gestation, ORTHO[®] 1/35 may be started immediately. An additional method of contraception is not needed. Be advised that ovulation may occur within 10 days of an abortion or miscarriage.

After an induced or spontaneous abortion that occurs at or after 20 weeks gestation, ORTHO[®] 1/35 may be started either on Day 21 post-abortion or on the first day of the first spontaneous menstruation, whichever comes first. The incidence of ovulation on Day 21 post-abortion (at 20 weeks gestation) is not known. A non-hormonal contraceptive must be used concurrently for the first 7 days of the first cycle.

OVERDOSAGE

In case of overdose or accidental ingestion by children, the physician should observe the patient closely, although generally no treatment is required.⁽²⁰⁾ 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The primary mechanism of action of ORTHO[®] 1/35 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.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

ORTHO[®] 1/35 Tablets are available in:

21-Day DISCREET Package that contains:

- 21 PEACH tablets each containing 1.0 mg norethindrone and 0.035 mg ethinyl estradiol

28-Day DISCREET Package that contains:

- 21 PEACH tablets each containing 1.0 mg norethindrone and 0.035 mg ethinyl estradiol
- 7 GREEN tablets with inert ingredients.

Composition

Each ORTHO[®] 1/35 tablet (peach, unscored with "C135" engraved on each side) contains 1.0 mg norethindrone plus 0.035 mg ethinyl estradiol.

Each peach tablet contains lactose, magnesium stearate, Red Ferric Oxide and Yellow Ferric Oxide, and starch as non-medicinal ingredients.

In the 28-day regimen the green tablets, engraved on each side with "C-C", contain inert ingredients, namely D&C Yellow #10 Lake, FD&C Blue #2 Lake, lactose, magnesium stearate, microcrystalline cellulose, and starch.

PART II: SCIENTIFIC INFORMATION

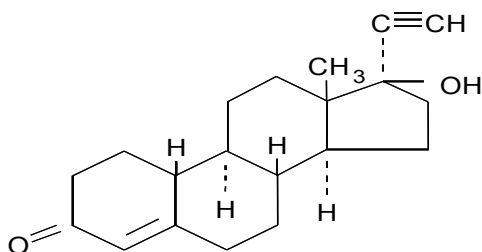
PHARMACEUTICAL INFORMATION

Drug Substance

Norethindrone:

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

Structural Formula:



Molecular Weight: 298.42

Molecular Formula: C₂₀H₂₆O₂

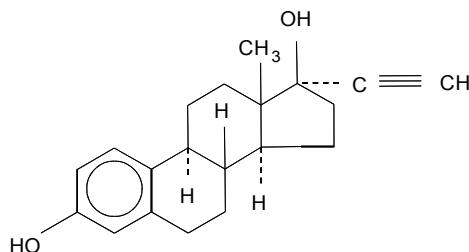
Description:

Norethindrone is a white to creamy-white, odourless, crystalline powder with a melting range of 202°C – 208°C. It is practically insoluble in water, soluble in chloroform and in dioxan, sparingly soluble in alcohol, and slightly soluble in ether.

Ethinyl Estradiol:

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

Structural Formula:



Molecular Weight: 296.41

Molecular Formula: C₂₀H₂₄O₂

Description:

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

CLINICAL TRIALS (21,31,37,38)

Extensive clinical experience with formulations containing norethindrone alone or in combination with mestranol, as well as 0.05 mg of ethinyl estradiol in combination with various progestogens other than norethindrone, has been documented in the literature.⁽³²⁻³⁴⁾ Such formulations have been extremely effective in controlling conception, the combined products being more successful than the progestogen alone products.

CLINICAL EVALUATION OF NORETHINDRONE (1.0 mg) AND ETHINYL ESTRADIOL (0.035 mg) FORMULATION

The contraceptive efficacy and side effect pattern of tablets containing 1.0 mg norethindrone and 0.035 mg ethinyl estradiol have been evaluated in an open study, conducted by a combined total of 17 investigators for the United States, Canada, Mexico, and Puerto Rico. This recently terminated study involved 940 patients who completed a total of 14,366 cycles of use with a pregnancy rate of 0.17 per hundred women-years.

Contraceptive Efficacy

In this study only two unplanned pregnancies were reported by patients while on therapy. In both cases tablets had not been taken according to the recommended regimen and these pregnancies were considered patient failures.

(a) PEARL INDEX⁽³⁵⁾

Pregnancy rate = 0.17/100 women-years.

(b) LIFE TABLE METHOD OF ANALYSIS⁽³⁶⁾

<u>Cycles of Use</u>	<u>Number of Patients</u>	<u>Cumulative Pregnancy Rate per 100 women</u>
6	697	0.00
12	449	0.00
18	314	0.27
24	247	0.27
30	144	0.27
36	107	1.20
42	58	1.20
48	10	1.20
51	1	1.20

(c) MENSTRUAL IRREGULARITIES

<u>Effect</u>	<u>Overall Cycle Incidence</u>		<u>Overall Patient Incidence</u>	
	<u>No. of Cycles</u>	<u>% of Cycles</u>	<u>No. of Patients</u>	<u>% of Patient Enrollment</u>
(a) Intermenstrual Spotting	697	4.9	357	38.0
(b) Intermenstrual Breakthrough Bleeding (BTB)	686	4.8	344	36.6
(c) Amenorrhea	111	0.8	83	8.8

(d) MISCELLANEOUS EFFECTS

<u>Effect</u>	<u>Overall Cycle Incidence</u>		<u>Overall Patient Incidence</u>	
	<u>No. of Cycles</u>	<u>% of Cycles</u>	<u>No. of Patients</u>	<u>% of Patient Enrollment</u>
(a) Nausea	256	1.8	146	15.5
(b) Vomiting	91	0.6	40	4.3
(c) Other Gastro-intestinal	1	0.01	1	0.1
(d) Total G.I. Disturbances	348	2.4	170	18.1
(e) Headache (including migraine)	175	1.2	75	7.9

Although somewhat higher in the first cycle, the incidence of menstrual and gastrointestinal disturbances decreased in subsequent therapy cycles. Unlike intermenstrual spotting and breakthrough bleeding, where the highest incidence occurred in the first cycle, the frequency of amenorrhea had no definitive pattern, except to say that the incidence was evenly distributed throughout all cycles of therapy. Other incidents reported on therapy were of a mild nature, low frequency or considered unrelated to therapy.

(e) INTERMENSTRUAL SPOTTING

<u>Cycles of Use</u>	<u>Number of Patients in Cycle</u>	<u>Number of Cycles with Incidence</u>	<u>% of Cycles</u>
1	940	116	12.3
2	865	95	11.0
3	811	68	8.4
4	759	32	4.2
5	729	46	6.3
6	697	40	5.7

(f) INTERMENSTRUAL BREAKTHROUGH BLEEDING (BTB)

Cycles of Use	Number of Patients in Cycle	Number of Cycles with Incidence	% of Cycles
1	940	118	12.6
2	865	76	8.8
3	811	57	7.0
4	759	49	6.5
5	729	34	4.7
6	697	34	4.9

(g) GASTROINTESTINAL DISTURBANCES (GID)

Cycles of Use	Number of Patients in Cycle	<u>Number of Cycles with Incidence</u>			Total GID	% of Cycles
		Nausea	Vomiting	Other		
1	940	90	15		105	11.2
2	865	50	12		62	7.2
3	811	33	6	1	40	4.9
4	759	17	2		19	2.5
5	729	12	4		16	2.2
6	697	8	1		9	1.3

Tolerance

(a) THERAPY DISCONTINUATION

A perspective on patient tolerance to effects reported during the course of administration of tablets containing 1.0 mg norethindrone and 0.035 mg ethinyl estradiol can be obtained from an examination of the incidence of "drop-out" from the study for the undesirable effects reported above.

<u>Effect</u>	<u>Patient Incidence of Effect</u>		<u>Patient Drop-out Incidence due to Effect</u>	
	<u>No. of Patients</u>	<u>% of Patient Enrollment</u>	<u>No. of Patients</u>	<u>% of Patient Enrollment</u>
(a) Intermenstrual Spotting	357	38.0	17	1.8
(b) Intermenstrual Breakthrough Bleeding (BTB)	344	36.6	48	5.1
(c) Amenorrhea	83	8.8	37	3.9
(d) Headache (including migraine)	75	7.9	20	2.1
(e) Total Gastro-intestinal Disturbances (GID)	170	18.1	17	1.8

(b) LABORATORY TESTS

Patients were selected at random from two investigational groups for ophthalmologic examinations and from two investigational groups for laboratory testing (CBC, urinalysis, SMA-12, PBI, and T₃ determinations). No abnormal results were reported for these tests.

(c) ENDOMETRIAL BIOPSY

A clinical study of endometrial biopsies in patients administered tablets containing 1.0 mg norethindrone and 0.035 mg ethinyl estradiol was conducted in Mexico by a single investigator. Endometrial biopsies were performed pretherapy and again after approximately six months on therapy. The biopsies of the twenty-three patients who completed the study did not show any changes of pathological significance. Five women experienced breakthrough bleeding and seven experienced spotting during therapy. Other clinical data were unremarkable. Two patients withdrew from the study, one for non-medical reasons and one for breakthrough bleeding. In the majority of women, changes consistent with the administration of an oral contraceptive, specifically a suppressed endometrium with small and inactive glands, were observed upon completion of the study at cycle 6.

DETAILED PHARMACOLOGY

Both norethindrone (NET) and ethinyl estradiol (EE) have been subjected to extensive biological examination over the past two decades.⁽²¹⁻²⁷⁾ Norethindrone, using the Clauberg assay with rabbits, has been variously estimated to possess an oral progestational activity at least 10 times that of injected progesterone.⁽²⁷⁾ Only slight estrogenic activity along with some androgenic activity (9% that of methyl testosterone) has been evident. Ethinyl estradiol has been

demonstrated to be slightly more active than 17 β -estradiol using the vaginal cornification test in rats.⁽²⁵⁾

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

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

TOXICOLOGY

Toxicology studies have evaluated norethindrone alone, as well as in combination with mestranol in the mouse, rat, rabbit, dog, and monkey.^(21,28-30) Ethinyl estradiol has also been evaluated both alone and in combination with synthetic steroidal progestogens in the mouse, rat, rabbit, dog, and monkey.^(21,28-30) Compound-related gross and microscopic lesions have been minimal and show the typical pathological changes known to occur with the administration of progestogen and estrogen.

Acute Toxicity Studies

The acute oral toxicity of norethindrone in combination with ethinyl estradiol (1.0/0.035) was assessed in male and female hooded Long-Evans derived rats and Swiss Webster mice. This combination at an oral dose level of 4 g/kg produced no deaths in either species. Animals were observed for 28 days post-administration.

In addition, the acute oral toxicity of ethinyl estradiol alone has been assessed in male and female Swiss Webster mice, male and female Long-Evans rats, and female Beagle dogs.

Mice:

An acute oral LD₅₀ study was performed with ethinyl estradiol in male and female mice. EE was suspended in 0.25% carboxymethylcellulose at a concentration of 166.67 mg/mL and used in a range-finding study at dosage levels of 5, 4, 3, 2, and 1 g/kg administered orally to one male and one female for each level. The dose volume was 0.03 mL/g of body weight. Observation of these mice for a period of 2 days revealed no mortality or other overt signs of toxicity. Subsequently, the highest dosage level of 5 g/kg, using the EE suspension of 166.67 mg/mL, was administered orally to ten male and ten female mice. The animals were observed immediately after dosing, at 1 and 4 hours, and daily thereafter for 14 days. An initial period of depression lasting approximately 2 hours was observed in male mice; no other overt signs of toxicity or mortality were noted in male or female mice during the 14-day observation period.

Necropsies performed at the end of the study revealed no gross pathological findings, with the exception of slightly enlarged uteri in the female mice.

Under the conditions of this study it was concluded that the oral LD₅₀ of ethinyl estradiol in mature HaM/1CR CD-1 male and female mice was greater than 5 g/kg.

Rats:

An acute oral LD₅₀ study was performed with ethinyl estradiol in Long-Evans derived male and female rats. Each animal was dosed by gavage with ethinyl estradiol suspended in 0.25% sodium carboxymethylcellulose. Doses of 3.2 g/kg, 4.0 g/kg, and 5.0 g/kg were administered. Each dose was given once to ten male and ten female rats. The animals were then observed immediately, at 1 and 4 hours after dosing, and daily for 14 days thereafter. All animals were examined macroscopically either upon death during the study, or at sacrifice after the 14-day observation period.

Depression, ataxia, and exophthalmos were the toxic signs exhibited, with severity and frequency of occurrence related to increase in dosage levels. Among the males, 10% of the mortality occurred at the 3.2 g/kg level, no deaths at the 4.0 g/kg level, and a 50% mortality at the 5.0 g/kg level. The females dosed at 3.2 g/kg exhibited 50% mortality and at 4.0 and 5.0 g/kg a 70% and 90% mortality, respectively.

There were no drug- or dose-related macroscopic changes seen at necropsy.

Under the conditions of this experiment the oral LD₅₀ value for ethinyl estradiol in Long-Evans derived young adult rats was 5.3 g/kg for males and 3.2 g/kg for females.

Dogs:

An acute oral toxicity study was conducted in female Beagle dogs with ethinyl estradiol alone to determine the maximum tolerated oral dose.

Animals were dosed by gavage with ethinyl estradiol suspended in 0.25% carboxymethylcellulose. Two dogs per dosage level were given 1.0, 2.5, or 5.0 g/kg and three dogs received the vehicle alone. The doses were divided into two or three portions and administered at two- to three-hour intervals. The dogs were observed immediately after dosing and 14 days thereafter. Body weights were recorded prior to dosing and at the end of the observation period. The animals were necropsied at the end of the study.

There were no deaths during the 14-day observation period of the animals dosed orally with ethinyl estradiol.

Under the conditions of this experiment, ethinyl estradiol administered orally to female Beagle dogs at dose levels of 1.0, 2.5, or 5.0 g/kg produced no significant adverse effects. The maximum tolerated oral dose of ethinyl estradiol in carboxymethylcellulose for the female Beagle dog was greater than 5.0 g/kg.

Chronic Toxicity Studies

Chronic toxicity studies of the combination of norethindrone - ethinyl estradiol have been conducted in male and female mice and rats.

Mice:

Young adult CFW mice (45 males and 45 females per dose group) were dosed with NET/EE (20/1) at 0.10 + 0.005, 0.60 + 0.030, and 2.00 + 0.100 mg/kg/day for 80 weeks. Administration of the drug was admixture in the diet, concentrations being adjusted throughout the test to conform with changing body weight and food intake.

Changes in physical condition, appearance, and behaviour were observed more frequently in the intermediate- and high-dose drug-treated groups. While food consumption changes were not dose-related, drug-treated groups experienced a dose-related decrease in body weight when compared to control animals.

Eighty-nine animals did not survive the dosing schedule (28 females, 61 males). In females, mortality was distributed equally among dose groups, whereas highest male mortality was observed in control and high-dose groups.

At autopsy, uterine and testicular organ weight analysis revealed a decrease of organ weights in all drug-treated groups. Ovarian and adrenal weights in females and prostatic weights in males were decreased in the intermediate- and high-dose levels. Pituitary and adrenal weights were increased in male animals in drug-treated groups.

Histopathological examination of processed tissues revealed spontaneous non-neoplastic and neoplastic lesions. No non-neoplastic lesions were found that could be related to the drug combination, except in some changes observed in the gonads and secondary sex organs. The distribution of neoplastic lesions was similar to that reported by the British Committee.⁽²⁹⁾ Males and females in the high-dose drug-treated group exhibited urinary bladder transitional cell carcinoma.

From the results the "no-effect dose" in mice treated for 80 weeks is greater than 0.100 mg NET + 0.005 mg EE/kg/day, but less than 0.60 mg NET + 0.030 mg EE/kg/day.

Rats:

Young adult Blue Spruce Farms, Long-Evans derived, hooded rats (45 females, 45 males per dose group) were dosed with NET/EE (20/1) at 0.10 + 0.005, 0.60 + 0.030, and 2.00 + 0.100 mg/kg/day for 116 weeks. Administration of the drug was by addition to the diet, concentrations being adjusted throughout the test to conform to changing body weight and food consumption.

No unusual changes in gross clinical observations were found, and the expected dose-dependent depression in food consumption and growth occurred.

One hundred and fifty-three animals failed to survive the dosing schedule (63 females, 90 males). In the females, the highest mortality was observed in the high-dose and control groups. The highest mortality in the males was in the control, low-dose, and high-dose levels.

At autopsy, individual organ weight analysis revealed weight decrease in the ovaries in the intermediate- and high-dose groups, a decrease in brain and kidney weights in the high-dose level, and an increase of uterine weights in the intermediate- and high-dose levels. In the males at the high-dose levels, kidney, testicular, and prostatic weights were decreased. The liver weights were increased in the males at the intermediate- and high-dose levels.

No non-neoplastic histopathological lesions were found that could be referable to drug treatment. Certain of the non-neoplastic lesions could be grouped as aging changes, while the other spontaneous lesions of this type were equally distributed among the dose groups.

Pheochromocytoma of the adrenals and transitional cell carcinoma of the renal pelvis were more frequently observed in male control animals than in treatment groups. Treated female rats had a lower incidence of malignant pituitary tumours than the female controls. The incidence of adenocarcinoma of the mammary glands was comparable in controls and treatment groups. A high incidence of hepatoma was observed in both treated male and female rats, indicating a dose-related response.

The "no effect dose" in rats treated with NET/EE (20/1) for 116 weeks is less than 0.60 mg NET + 0.030 mg EE/kg/day. Also, the tumour incidence pattern in this species does not vary from that previously reported in the literature for similar hormonal combinations.⁽²⁸⁾

Lifetime Toxicity Studies

Lifetime studies of norethindrone and ethinyl estradiol administered orally in combination to female Beagle dogs and female Rhesus monkeys continue.⁽²¹⁾

Dogs:

A combination of norethindrone plus ethinyl estradiol (20 parts norethindrone to 1 part ethinyl estradiol) has been administered orally for a period of sixty-nine months to sixteen mature female Beagle dogs at a dosage level equivalent to twenty-five times the human dosage level (0.525 mg/kg/day of the combination). The regimen has been cyclic, three weeks of compound administration followed by one week of no administration.

An additional sixteen dogs comprise a control group receiving vehicle (0.5% methocel) only.

The general appearance and behaviour of the animals has been normal, with most dogs gaining or maintaining body weight during the course of the study. Alopecia has been observed for some control and all treated dogs since initiation of the study. A red vaginal discharge has been observed sporadically both among control and treated dogs.

After sixty-nine months of study, mammary nodules have been noted in one control and four treated dogs.

Ophthalmological examinations have revealed eye changes in six control and two treated animals, which are not considered to be compound related.

A moderate to marked elevation in erythrocyte sedimentation rate (ESR) has been noted in a small number of dogs from both treated and control groups. Mean values of this parameter did not differ significantly between control and treated groups.

Decreases in mean erythrocyte and hemoglobin values have been noted which are statistically significant for the treated groups.

Mean fibrinogen values have been significantly greater in treated than in control dogs. Values have been above normal in a small number of dogs from both the control and treated groups. Platelet counts, prothrombin times, and partial thromboplastin time have been reported to be significantly greater in treated than in control animals, although all values have been within accepted normal ranges. There have been no other changes in hematologic or clinical chemistry parameters.

The surviving test population consists of twelve control and nine treated dogs.

The seven-year study continues.

Monkeys:

A combination of norethindrone plus ethinyl estradiol (20 parts norethindrone to 1 part ethinyl estradiol) has been administered orally for a period of sixty-nine months to sixteen mature female monkeys at a dosage level equivalent to fifty times the human dosage level (1.05 mg/kg/day of the combination). The regimen has been cyclic, three consecutive weeks of compound administration followed by one week of no administration. Two monkeys have been added to the study as replacements for monkeys that died or were sacrificed *in extremis*.

An additional sixteen monkeys comprise a control group receiving a food vehicle only on the same regimen as the treated monkeys.

Most monkeys have maintained or shown minimal changes in body weight over the duration of the study. However, treated monkeys have demonstrated significantly less weight gains than control monkeys when compared to mean baseline values.

Red vaginal discharge has occurred in all the treated monkeys during the compound withdrawal phase of each cycle since the sixty-sixth cycle. The occurrence has been sporadic in most control monkeys during both the vehicle and withdrawal phase of each cycle.

Alopecia has been observed with equal frequency in both control and treated monkeys. A white or gray mammary discharge has been observed more frequently in treated animals than in control animals.

No behavioural changes considered to be compound related have been observed in treated animals.

Indirect ophthalmological examinations have been unremarkable. However, the use of a fundus camera as a direct ophthalmoscope has revealed the presence of hypopigmented spots in the maculae of both control and treated monkeys. There are no clinically observable defects in the visual acuity of these monkeys. Although the etiology of these clinical findings still requires

definition, no significant interpretative differences in the findings have been reported in the period that direct ophthalmological examinations have been employed.

Marginal fluctuations in erythrocyte counts, hemoglobin concentration, hematocrit, and total leucocyte counts have occurred in both control and treated groups.

A statistically significant increase in erythrocyte sedimentation rate has been observed in the treated group compared to controls.

With the exception of SGPT, clinical chemistry determinations have remained within normal limits. While the mean SGPT activity for the treated group remains high and was progressive from the 48-month period through the sixty-three-month period, this value has decreased over the subsequent two reporting periods.

An increase in protein bound iodine (PBI) concentration has been observed since the thirty-month period in three control and nine treated monkeys.

Other clinicopathologic parameters have remained unremarkable.

The surviving population consists of nine control monkeys and ten treated monkeys.

The ten-year study continues.

Lifetime studies of norethindrone alone administered orally to Beagle dogs and Rhesus monkeys were initiated.⁽²¹⁾ The seven-year safety study in female dogs is complete; the ten-year safety study in female monkeys continues.

Dogs:

Norethindrone was administered orally for a period of eighty-four months (seven years) to mature female Beagle dogs daily at dosage levels of 0.007, 0.07, and 0.175 mg/kg/day (1, 10, and 25 times the human dosage); an additional group of dogs was administered 0.25% agar and served as a control group. Each group was assigned sixteen test animals.

There were no remarkable changes in general behaviour, body weight, ophthalmologic or hematologic parameters.

Clinicopathologic changes which were considered to be drug related were increased fibrinogen, serum glutamic pyruvic transaminase, and blood glucose.

The histopathologic changes which represented the exaggerated pharmacologic effects of the drugs were cystic changes in the uterus and gallbladder and inhibition of ovulation. The presence of endometrial-like glands in the lamina propria of the vagina was of uncertain etiology.

This seven-year drug safety study revealed no significant adverse changes attributable to long-term use of this compound.

Monkeys:

Norethindrone has been administered orally for a period of one hundred and eleven months to mature female Rhesus monkeys daily at dosage levels of 0.007, 0.07, and 0.35 mg/kg/day. An additional group of monkeys has been administered vehicle only and serves as a control group. Each group has been assigned sixteen test animals.

Daily observations of general health revealed no evidence of overt effects of drug treatment or significant changes in behaviour. The mean body weight of control and treated groups showed comparable weight gains.

Red vaginal discharge was noted more frequently and for a longer period in the control and low dosage groups than in the intermediate and high dosage groups.

Monthly mammary examination of all monkeys revealed, as of the one hundred and seventh month, an intermediate dosage monkey with a palpable structure, designated as a nodule, in the region of the mammary gland. This mammary gland nodule remains unchanged as of the one hundred and eleventh month and no other mammary gland nodules or signs of secretory activity have been found.

Comparable hemograms were noted among the four test groups except for the following differences: mean percent segmented neutrophils for the high and intermediate dosage groups were significantly less than the low dosage group ($p < 0.05$); the mean for the low dosage group was also greater than the control group mean ($p < 0.01$).

The opposite trend was seen for mean percent lymphocytes, with the high dosage ($p < 0.01$) and intermediate dosage ($p < 0.05$) group means greater than the low dosage group; the low dosage group mean was also lower than the control group ($p < 0.01$). Mean percent basophils was significantly greater ($p < 0.05$) in the intermediate dosage group than in the control. These trends were also apparent in the absolute differential values.

No significant differences were noted in coagulation parameters with the following exceptions. The mean activated partial thromboplastin time (APTT) for the intermediate dosage group was less than the control group mean ($p < 0.05$), and the mean fibrinogen for the high dosage group was greater than the control ($p < 0.01$), intermediate and low dosage group means ($p < 0.05$). The difference between mean APTT values for the intermediate and control groups was random and therefore is not considered to be drug related. However, the differences in mean fibrinogen values among the dosage groups appear to be dose related.

The high dosage group mean for total protein was significantly less ($p < 0.05$) than that for the low dosage group mean.

The high dosage group T_3 uptake mean was significantly less than the control ($p < 0.01$), intermediate and low dosage group means ($p < 0.05$). The mean T_3 (RIA) value for the high dosage group was significantly greater ($p < 0.05$) than the low dosage group mean. The high dosage group was observed to have a mean T_4 significantly higher ($p < 0.05$) than the control group.

One low-dose monkey continues to show evidence of hemoconcentration as indicated by high hematocrit, hemoglobin, and red blood cell count. The total white blood cell count was normal, but there was a higher percent segmented neutrophil count with a corresponding lower lymphocyte count as compared to other animals in the study. The platelet count and sedimentation rate were normal, but the prothrombin time and activated partial thromboplastin time were prolonged. There was insufficient plasma to analyze fibrinogen. Cholesterol, BUN, and T₃ RIA were high normal and SGPT was borderline. Alkaline phosphatase for this animal was high. Direct ophthalmoscopic examination of monkey eyes has indicated the presence of hypopigmented foci in the macular region of the retina in some monkeys from all test groups including controls. In examinations to date, the incidence of this phenomenon has appeared to be greater in the dosed groups than in the control group.

The ten-year study continues.

REPRODUCTION STUDIES

A perinatal and postnatal study was conducted using Long-Evans derived hooded rats to determine the effects of norethindrone on late fetal development, maternal labour, delivery, lactation, and growth and reproductive performance of the offspring. At the high-dose level (0.35 mg/kg), there was a growth retardation in the F₂ generation. At the lower dose level (0.07 mg/kg), there was retardation in skeletal development in those stillborn fetuses that were cleared and stained. No other significant effects attributed to the compound were observed.⁽²¹⁾

TERATOLOGY

A study was done to determine the teratogenic effect of norethindrone on the embryo and developing fetus of the hooded female rat (Long-Evans derived). The potential of the drug to produce fetal resorption and fetal malformation was specifically investigated. At a dose level of 0.7 mg/kg (which is approximately 100 x the human dose), no significant effect on the fetus was seen.⁽³⁾

A similar study was conducted on New Zealand white rabbits. As with the rat study, no significant effect on the fetus was observed at a dose level of 0.7 mg/kg⁽²¹⁾.

REFERENCES

1. Asherson RA, Cervera R, Font J. Multiorgan thrombotic disorders in systemic lupus erythematosus: a common link? *Lupus* 1992;1(4):199-203.
2. Kwaan HC, Soff GA. Management of thrombotic thrombocytopenic purpura and haemolytic uremic syndrome. *Semin Hematol* 1997;34(2):81-9.
3. Sibai BM, Kustermann L, Velasco J. Current understanding of severe preeclampsia, pregnancy-associated hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, hemolysis, elevated liver enzymes, and low platelet syndrome, and postpartum acute renal failure: different clinical syndromes or just different names? *Curr Opin Nephrol Hypertens* 1994;3(4):436-45.
4. Stewart CL, Tina LU. Hemolytic uremic syndrome. *Pediatr Rev* 1993;14(6):218-24.
5. Koenigs KP, McPhedran P, Spiro HM. Thrombosis in inflammatory bowel disease. *J Clin Gastroenterol* 1987;9(6):627-31.
6. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Sick Cell Disease. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 243-6.
7. Adams HP, Biller J. Ischemic cerebrovascular disease. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, editors. *Neurology in clinical practice*. Boston: Butterworth-Heinemann; 1996. p. 1014-9.
8. Carlone JP, Keen PD. Oral contraceptive use in women with chronic medical conditions. *Nurse Pract* 1989;14(9):9-10, 12-13, 16.
9. Gross U, Honcamp M, Daume E, Frank M, Dusterberg B, Doss MO. Hormonal oral contraceptives, urinary porphyrin excretion and porphyrias. *Horm Metab Res* 1995;27(8):379-83.
10. Petri M, Robinson C. Oral contraceptives and systemic lupus erythematosus. *Arthritis Rheum* 1997;40(5):797-803.
11. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Hemolytic uremic syndrome. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 211-8.
12. Galimberti D. Chorea induced by the use of oral contraceptives. Report of a case and review of the literature. *Ital J Neurol Sci* 1987;8(4):383-6.
13. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Sydenham's chorea. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 415-9.
14. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Herpes gestationis. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 367-70.
15. Morgan JK. Herpes gestationis influenced by an oral contraceptive. *Br J Dermatol* 1968;80(7):456-8.
16. Knijff SCM, Goorissen EM, Velthuis-te Wierik EJM, Korver T, Grimes DA. Otosclerosis. In: Summary of contraindications to oral contraceptives. New York: Parthenon Publishing Group; 2000. p. 387-91.
17. Boyko EJ, Theis MK, Vaughan TL, Nicol-Blades B. Increased risk of inflammatory bowel disease associated with oral contraceptive use. *Am J Epidemiol* 1994;140(3):268-78.

18. Godet PG, May GR, Sutherland LR. Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. *Gut* 1995;37(5):668-73.
19. Logan RF, Kay CR. Oral contraception, smoking and inflammatory bowel disease--findings in the Royal College of General Practitioners Oral Contraception Study. *Int J Epidemiol* 1989;18(1):105-7.
20. Ramcharan S, Pellegrin FA, Ray R, Hsu J-P, Vessey MP. General summary of findings; general conclusions; implications. In: *The Walnut Creek Contraceptive Drug Study: a prospective study of the side effects of oral contraceptives. Volume III: An interim report: a comparison of disease occurrence leading to hospitalization or death in users and nonusers of oral contraceptives.* NIH Publication No. 81-564. Bethesda (MD): US Department of Health, Education, and Welfare, Center for Population Research; 1981. p. 211-38.
21. Sutherland LR, Ramcharan S, Bryant H, Fick G. Effect of oral contraceptive use on reoperation following surgery for Crohn's disease. *Dig Dis Sci* 1992;37(9):1377-82.
22. Vessey M, Jewell D, Smith A, Yeates D, McPherson K. Chronic inflammatory bowel disease, cigarette smoking, and use of oral contraceptives: findings in a large cohort study of women of childbearing age. *Br Med J (Clin Res Ed)* 1986;292(6528):1101-3.
23. EMEA. CPMP Public assessment report: combined oral contraceptives and venous thromboembolism. London: EMEA Committee for Proprietary Medicinal Products (CPMP); 2001 Sep 28. Report No.: EMEA/CPMP/2201/01/en Final.
24. Binkley KE, Davis A, 3rd. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 2000;106(3):546-50.
25. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. *Am J Med* 2003;114(4):294-8.
26. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med* 2001;161(20):2417-29.
27. Heikkila M, Haukkamaa M, Luukkainen T. Levonorgestrel in milk and plasma of breast-feeding women with a levonorgestrel-releasing IUD. *Contraception* 1982;25(1):41-9.
28. Nilsson S, Nygren KG, Johansson ED. Ethinyl estradiol in human milk and plasma after oral administration. *Contraception* 1978;17(2):131-9.
29. WHO. Medical eligibility criteria for contraceptive use. Geneva: World Health Organization, Reproductive Health and Research; 2009: 14-42.
30. Barditch-Crovo P, Trapnell CB, Ette E, Zacur HA, Coresh J, Rocco LE, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. *Clin Pharmacol Ther* 1999;65(4):428-38.
31. Krauss GL, Brandt J, Campbell M, Plate C, Summerfield M. Antiepileptic medication and oral contraceptive interactions: a national survey of neurologists and obstetricians. *Neurology* 1996;46:1534-39.
32. Riva R, Albani F, Contin M, Baruzzi A. Pharmacokinetic interactions between antiepileptic drugs: clinical considerations. *Clin Pharmacokinet* 1996;31(6):470-93.
33. Ouellet D, Hsu A, Qian J, Locke CS, Eason CJ, Cavanaugh JH, et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol* 1998;46(2):111-6.
34. Mildvan D, Yarrish R, Marshak A, Hutman HW, McDonough M, Lamson M, et al. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when

- administered concurrently to HIV-infected women. *J Acquir Immune Defic Syndr* 2002;29(5):471-7.
35. Drugs Directorate Guidelines. Directions for Use of Estrogen-Progestin Combination Oral Contraceptives. 1994.
 36. Francis, W.G. and Dalzeil, D.: Accidental Ingestion of Oral Contraceptives by Children. *Can Med Assoc J* 1965; 92:191.
 37. Jones, R.C. and Edgren, R.A.: The Effects of Various Steroids on the Vaginal Histology in the Rat. *Fertil Steril* 1973; 24:284-291.
 38. Edgren, R.A., Jones, R.C., and Peterson, D.L.: A Biological Classification of Progestational Agents. *Fertil Steril* 1967; 18:238-256.
 39. Kincl, F.A., Birch, A.V., and Dorfman, R.I.: Pituitary Gonadotrophic Inhibitory Activity of Various Steroids in Ovariectomized Intact Female Rats in Parabiosis. *Proc Soc Exp Biol Med* 1964; 117:549-552.
 40. Desaulles, S.H. and Krahenbuhl, C.: Comparison of the Antifertility and Sex Hormonal Activities of Sex Hormones and Their Derivatives. *Acta Endocrinol* 1964; 47:444-456.
 41. McGinty, D.A. and Djerassi, C.: Some Chemical and Biological Properties of 19-nor-17 Ethinyl testosterone. *Ann N Y Acad Sci* 1958; 71:500-515.
 42. Pincus, G., Chang, M.C., Zarrow, M.X., Hafez, E.S.E., and Merrill, A.: Studies of the Biological Activity of Certain 19-nor Steroids in Female Animals. *Endocrinology* 1956; 59:695-707.
 43. Schardein, J.L., Kaump, D.H., Woosley, E.T., and Jellema, M.M.: Long-term Toxicologic and Tumorigenesis Studies on an Oral Contraceptive Agent in Albino Rats. *Toxicol Appl Pharmacol* 1970; 16:10-23.
 44. Committee on the Safety of Medicines: Carcinogenicity Tests of Oral Contraceptives. Her Majesty's Stationery Office, London, 1972.
 45. Fairweather, F.A.: Toxicological Requirements of Oral Contraceptives. *J Reprod Fertil Suppl* 1968; 5:47-49.
 46. Djerassi, C.: Steroid Contraceptives in the People's Republic of China. *N Engl J Med* 1973; 289:533-535.
 47. Nelson, J.H.: Selecting the Optimum Oral Contraceptive. *J Reprod Med* 1973; 11:135-141.
 48. Bingel, A.S. and Benoit, P.S.: Oral Contraceptives: Therapeutics Versus Adverse Reactions, with an Outlook for the Future I. *J Pharm Sci* 1973; 62:179-200.
 49. Bingel, A.S. and Benoit, P.S.: Oral Contraceptives: Therapeutics Versus Adverse Reactions, with an Outlook for the Future II. *J Pharm Sci* 1973; 62:349-362.
 50. Pearl, R.: Contraception and Fertility in 2000 Women. *Hum Biol* 1932; 4:363-407.
 51. Potter, R.G.: Application of Life Table Techniques to Measurement of Contraceptive Effectiveness. *Demography* 1966; 3:297-304.
 52. McGuire, J.L., Bariso, C.D., Yuliano, E., Hume, R.J., and Pasquale, S.A.: Effects of Low Dose Oral Contraceptives Containing Norethindrone and Ethinyl Estradiol on Serum Levels of Progesterone and Pituitary Gonadotropins. *Contraception* 1975; 11(3):329-338.
 53. Pasquale, S.A. and Yuliano, E.: Clinical Results with a New Low Dose Oral Contraceptive Utilizing Norethindrone/ Ethinyl Estradiol. *Contraception* 1975; 12(5):495-503.
 54. Tyrer L. (1994). *Fertility Control* 2nd Ed. Pearl River NY: Parthenon Publishing. Oral Contraceptive practice. p. 97-113.
 55. Guillebaud J. (1999). *Contraception: Your Questions Answered*. 3rd Edition. Edinburg, UK: Churchill Livingstone. p. 234-254.

56. Hatcher R, Stewart F, Trussell J, Kowal D, Guest F, Stewart GK, Cates W. (1998). *Contraceptive Technology* 17th Rev. Ed. New York NY: Ardent Media Inc. p. 413-424.
57. Bork K, Fischer B, DeWald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. *Am J Med* 2003;114:294-298.
58. Borawski M, Aymes A. Review of Urticaria and Angioedema Observed With Postmarketing use of Norethindrone/Ethinyl Estradiol Tablets. (ORTHO-NOVUM® 1-35) 24 January 2007.
59. Boston Collaborative Drug Surveillance Programme: Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gallbladder Disease, and Breast Tumors. *Lancet* 1973;1:1399-1404.
60. Bradley, D.D., Wingerd, J., Petitti, D.B., Krauss, R.M., and Ramcharan, S.: Serum High-Density-Lipoprotein Cholesterol in Women Using Oral Contraceptives, Estrogens and Progestins. *N Engl J Med* 1978; 299(1):17-20.
61. Chobanian et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 2003;42:1206-1252.
62. Collaborative Group for the Study of Stroke in Young Women: Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis. *N. Engl. J. Med.* 288(17):871-878, 1973.
63. Collaborative Group for the Study of Stroke in Young Women: Oral Contraceptives and Stroke in Young Women. Associated Risk Factors. *JAMA* 1975; 231(7):718-722.
64. Greene, G.R. and Sartwell, P.E.: Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection. *Am J Pub Health* 1972; 62(5):680-685.
65. Guillebaud J. *Contraception: Your questions answered*. 3rd ed. Edinburg, UK: Churchill Livingstone. 1999:97-110, 124-136, 157-171, 216-222, 226-231, 234-254.
66. Inman, W.H.W. and Vessey, M.P.: Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age. *Brit Med J* 1968; 2:193-199.
67. Kannel, W.B., Castelli, W.P., and Gordon, T.: Cholesterol in the Prediction of Atherosclerotic Disease. New Perspectives Based on the Framingham study. *Am Intern Med* 1979; 90:85-91.
68. McEvoy GK et al. (Eds.). *AHFS Drug Information*. Bethesda: American Society of Health-System Pharmacists, Inc. 2000.
69. Nora, J.J., Nora, A.H.: Birth Defects and Oral Contraceptives. *Lancet* 1973; 1:941-942.
70. Pasquale, S.A., Murphy, R.J., Norwood, P.K., and McBride, L.C.: Results of a Study to Determine the Effects of Three Oral Contraceptives on Serum Lipoprotein Levels. *Fertil Steril* 1982; 38(5):559-563.
71. Royal College of General Practitioners: *Oral Contraceptives and Health* 1974; Pitman, London, 1-100.
72. Royal College of General Practitioners: *Oral Contraception and Thromboembolic Disease*. *J Coll Gen Pract* 1967; 13:267-279.
73. Sartwell, P.E., Masi, A.T., Arthes, F.G., Green, G.R., and Smith, H.E.: Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study. *Am J Epidemiol* 1969; 90:365-380.

74. Spellacy WN, Wynn V. Progestogens and the Cardiovascular System: Am J Obstet Gynecol 1982; 142B-2:717-816.
75. The Medical Letter: Oral Contraceptives and the Risk of Cardiovascular Disease, 1983; 25:69-70.
76. Vessey, M.P. and Doll, R.: Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Brit Med J 1969; 2:651-657.
77. Vandembroucke JP, Rosing J, Bloemenkamp KW, Middeldorp S, Helmerhorst FM et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med 2001;344:1527-35.
78. Wahl, P., Wladen, C., Knopp, R., Hoover, J., Wallace, R., Heiss, G., and Rifkind, B.: Effect of Estrogen/Progestin Potency on Lipid/Lipoprotein Cholesterol. N Engl J Med 1983; 308:862-867.
79. Wu O, Robertson L, Langhorne P, Twaddle S, Lowe GD et al. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. Thromb Haemost 2005;94:17-25.
80. Zhang H, Cui D, Wang B, Han YH, Balimane P, Yang Z, Sinz M, Rodrigues AD. Pharmacokinetic drug interactions involving 17 α -ethinylestradiol. A new look to an old drug. Clin Pharmacokinet 2007;46(2):133-157.

PART III: CONSUMER INFORMATION

PrORTHO® 1/35

norethindrone and ethinyl estradiol Tablets

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ORTHO® 1/35. 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® 1/35 is a birth control pill (oral contraceptive) that contains two female sex hormones (norethindrone 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.

Do not use ORTHO® 1/35 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 (chest pain) 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
- you are taking ombitasvir, paritaprevir, ritonavir, with or

- without dasabuvir for the treatment of Hepatitis C
- allergic reaction to norethindrone, ethinyl estradiol or to any of the other ingredients in ORTHO[®] 1/35 (see **What the nonmedicinal ingredients are**).

What the medicinal ingredients are:

Norethindrone and ethinyl estradiol

What the nonmedicinal ingredients are:

D&C Yellow #10 Lake, FD&C Blue #2 Lake, lactose, magnesium stearate, microcrystalline cellulose, Red Ferric Oxide, starch and Yellow Ferric Oxide.

What dosage forms it comes in:

ORTHO[®] 1/35 (norethindrone and ethinyl estradiol) Tablets are available in a 21-day regimen and a 28-day regimen.

21-day DISCREET Package contains: 21 PEACH tablets each containing 1.0 mg norethindrone and 0.035 mg ethinyl estradiol.

28-day DISCREET Package contains: 21 PEACH tablets each containing 1.0 mg norethindrone and 0.035 mg ethinyl estradiol and 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[®] 1/35, should not be used by women who are over 35 years of age and smoke.

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

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

Do not use if you are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir for the treatment of Hepatitis C. Using these drugs at the same time as ORTHO[®] 1/35 has the potential to cause problems with your liver, such as an increase in the ALT liver enzyme. Consult with your doctor or pharmacist about restarting ORTHO[®] 1/35 after finishing your Hepatitis C treatment (see ABOUT THIS MEDICATION - When it should not be used).

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[®] 1/35, talk to your doctor or

pharmacist if the following apply to you:

- have a history of 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
- have or have had ‘pregnancy spots’. These are yellowish-brown patches or spots, especially on your face (called ‘chloasma’). These spots may not go away completely, even after you stop using ORTHO[®] 1/35. Protect your skin from sunlight or ultraviolet radiation. This may help prevent you from getting these spots or help prevent them from getting worse.
- 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
- gallbladder or pancreatic disease
- hereditary angioedema or have had episodes of swelling in body parts such as hands, feet, face, or airway passages
- 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.

ORTHO[®] 1/35 is **NOT** to be used before menarche (your first menstrual period) or in postmenopausal women.

If you see a different doctor, inform him or her that you are using ORTHO[®] 1/35.

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[®] 1/35 four weeks before surgery and not using ORTHO[®] 1/35 for a time period after surgery or during bed rest.

ORTHO[®] 1/35 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[®] 1/35 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[®] 1/35 outweigh the risks, you should be aware of the following risks:

THE RISKS OF USING ORTHO[®] 1/35

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

Women who use hormonal contraceptives like ORTHO[®] 1/35 have a higher incidence of blood clots compared to non-users. Blood clots are the most common serious side effects of birth control pills. The risk of developing blood clots is especially high during the first year a woman ever uses a hormonal contraceptive or restarts the same or a different hormonal contraceptive after a break of 4 weeks or more. Clots can occur in many areas of the body.

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

- sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung.
- pain and/or swelling in the calf. These symptoms could indicate a possible 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) like ORTHO[®] 1/35 for a long time the chance of getting cervical cancer may be slightly higher. This finding may not be caused by the pill itself but may be related to sexual behavior and other factors.

4. 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[®] 1/35 after childbirth, miscarriage, or therapeutic abortion.

8. Pregnancy after stopping ORTHO[®] 1/35

You will have a menstrual period when you stop taking ORTHO[®] 1/35. 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® 1/35 include:

- drugs used for epilepsy (e.g., primidone, phenytoin, phenobarbital, carbamazepine, lamotrigine, oxcarbazepine, topiramate, rufinamide)
- drugs used for tuberculosis (e.g., rifampin and rifabutin)
- (fos)aprepitant (drug used for nausea)
- selegiline (drug used for Parkinson’s disease)
- tizanidine (drug used for multiple sclerosis [MS])
- drugs used for HIV/AIDS (e.g., atazanavir, indinavir, nelfinavir, ritonavir, ritonavir-boosted protease inhibitors, etravirine, nevirapine)
- drugs used for Hepatitis C virus (HCV) (e.g., boceprevir, telaprevir)
- antibiotics (e.g., penicillins, tetracyclines) for infectious diseases
- salicylic acid
- bosentan (drug used for pulmonary hypertension which is high blood pressure in the blood vessels between the heart and the lungs)
- ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (used to treat Hepatitis C)
- theophylline (drug used for asthma)
- stimulants (e.g., modafinil)
- lipid-lowering drugs (e.g., atorvastatin, rosuvastatin)
- colestevlam
- 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, temazepam)
- pain medication (e.g., meperidine, morphine, acetaminophen)
- antidepressants (e.g., clomipramine)
- some nutritional supplements (e.g., vitamin B₁₂, vitamin C, folic acid)
- antacids (use 2 hours before or after taking ORTHO® 1/35).

Grapefruit juice may interfere with ORTHO® 1/35. ORTHO® 1/35 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® 1/35. 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® 1/35. Talk to your doctor for more information about

drug interactions.

PROPER USE OF THIS MEDICATION

HOW TO TAKE ORTHO® 1/35:

1. READ THESE DIRECTIONS

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

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

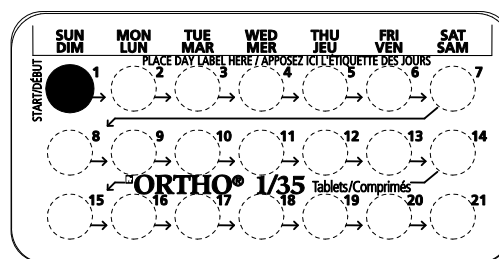
- 21-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week

OR

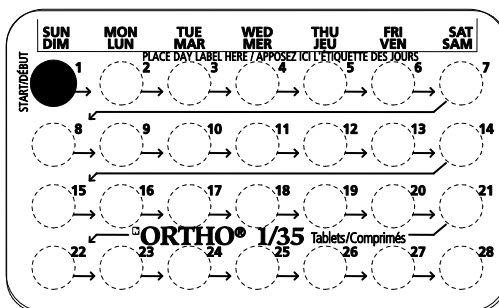
- 28-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

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

21-Day DISCREET Package



28-Day DISCREET Package



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.**

WHEN TO START THE FIRST PACK OF PILLS

BE SURE TO READ THESE INSTRUCTIONS:

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

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

DIRECTIONS FOR 21-DAY AND 28-DAY PILL PACKS

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

on Sunday, start that same day.

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

21-DAY Pill Pack:

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

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

28-DAY Pill Pack:

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

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

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

1. **For Day 1 start:** Label the DISCREET Package by selecting the day label that starts with Day 1 of your menstrual period (the first day of menstruation is Day 1). For example, if your first day of menstruation is Tuesday, attach the day label that begins with **TUE** in the space provided.

OR

For Day 5 start: Label the DISCREET Package by selecting the day label that starts with the day that is 5 days after your period begins. (Count 5 days including the first day of menstruation.) For example, if your first day of menstruation is Saturday, place the day label that starts with **WED** in the space provided.

OR

For Sunday start: No day label is required. The DISCREET Package is printed for a Sunday start. (The first Sunday **after** your period begins, or, if your period starts on Sunday, start that **same day.**)

2. Place the day label in the space where you see the words "Place day label here". Having the DISCREET Package labelled with the days of the week will help remind you to take your pill every day.
3. To begin taking your pills, start with the pill inside the red circle (where you see the word **START**). This pill should correspond to the day of the week that you are taking your first pill. To remove the pill, push through the back of the DISCREET Package.
4. On the following day, take the next pill in the same row, always proceeding from left to right (→). Each row will always begin

on the same day of the week.

WHAT TO DO DURING THE MONTH

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

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

2. WHEN YOU FINISH A PACK

- **21 PILLS**
WAIT SEVEN DAYS to start the next pack. You will have your period during that week.
- **28 PILLS**
Start the next pack **ON THE NEXT DAY**. Take one pill every day. Do not wait any days between packs.

Overdose:

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.

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

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

<p>First Two Weeks</p> <ol style="list-style-type: none"> 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. <p>Third Week</p> <ol style="list-style-type: none"> 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. <p>If you miss two periods in a row, call your doctor or clinic.</p>	<p>First Two Weeks</p> <ol style="list-style-type: none"> 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. <p>Third Week</p> <ol style="list-style-type: none"> 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. <p>If you miss two periods in a row, call your doctor or clinic.</p>
<p>MISS THREE OR MORE PILLS IN A ROW</p> <p>Any Time in the Cycle</p> <ol style="list-style-type: none"> 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. <p>If you miss two periods in a row, call your doctor or clinic.</p>	<p>MISS THREE OR MORE PILLS IN A ROW</p> <p>Any Time in the Cycle</p> <ol style="list-style-type: none"> 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. <p>If you miss two periods in a row, call your doctor or clinic.</p>

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.

taking hormonal contraceptives in general:

- difficulty wearing contact lenses
- vaginal irritation or infections
- change in skin pigmentation (can be permanent)
- 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects reported in women taking hormonal contraceptives in general are nausea and vomiting.

Side effects reported with combination oral contraceptives (COCs) such as ORTHO[®] 1/35 include:

Common side effects: vaginal discharge, edema, breast tenderness, abdominal cramps, bloating, acne, headache, dizziness, depression, nervousness, high blood pressure, irritable and fluid retention.

Uncommon side effects: vaginal candidiasis (yeast infection), spotting, absence of withdrawal bleeding, breast pain, intolerance to contact lenses, loss of scalp hair, rash, hirsutism (unwanted excess hair), darkening of the skin, migraine, changes in libido (sex drive), mood changes, change in weight (increase or decrease) and changes in appetite.

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. If these side effects continue, consult your doctor. 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

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 seek immediate medical help
		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			✓
	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)			✓	

This is not a complete list of side effects. For any unexpected effects while taking ORTHO® 1/35, contact your doctor or pharmacist.

HOW TO STORE IT

Store in original packaging, between 15°C - 30°C. Keep out of the sight and 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 MedEffect® (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 1908C
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

For more information, please contact your health professional or pharmacist. This document plus the full product monograph, prepared for health professionals, can be found at: www.janssen.com/canada or by contacting the manufacturer, Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by Janssen Inc. Toronto, Ontario M3C 1L9

Last revised: March 14, 2017
All trademarks used under license.