PRODUCT MONOGRAPH

Pr Tri-Cira 21

Pr Tri-Cira 28

Norgestimate and Ethinyl Estradiol Tablets

0.18 mg norgestimate and 0.035 mg ethinyl estradiol
0.215 mg norgestimate and 0.035 mg ethinyl estradiol
0.25 mg norgestimate and 0.035 mg ethinyl estradiol

Apotex Standard

Oral Contraceptive

Apotex. Inc.
150 Signet Drive
Toronto Ontario
M9L 1T9

Date of Preparation:
November 17, 2020

Submission Control No.: 230304

TABLE OF CONTENTS

PRODUCT MONOGRAPH

Pr Tri-Cira 21

Pr Tri-Cira 28

Norgestimate and Ethinyl Estradiol Tablets

0.18 mg norgestimate and 0.035 mg ethinyl estradiol
0.215 mg norgestimate and 0.035 mg ethinyl estradiol
0.25 mg norgestimate and 0.035 mg ethinyl estradiol

Apotex Standard

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**All Nonmedicinal Ingredients**
Oral	Tablets, 0.18 mg norgestimate and 0.035 mg ethinyl estradiol	Hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.
	Tablets, 0.215 mg norgestimate and 0.035 mg ethinyl estradiol	FD&C Blue No.1 Aluminum Lake, FD&C Blue No.2 Aluminum Lake, FD&C Yellow No. 5 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.
	Tablets, 0.25 mg norgestimate and 0.035 mg ethinyl estradiol	FD&C Blue No.1 Aluminum Lake, FD&C Blue No.2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.

INDICATIONS AND CLINICAL USE

Tri-Cira 21 and 28 tablets are indicated for:

- Conception control.
- The treatment of moderate acne vulgaris in females, ≥ 15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, and have achieved menarche.

CONTRAINDICATIONS

- History of or actual thrombophlebitis or thromboembolic disorders.
- Known thrombophilic conditions.
- History of or actual cerebrovascular disorders.
- History of or actual myocardial infarction or coronary arterial disease.
- History of or actual prodromi of a thrombosis (e.g., transient ischemic attack, angina pectoris).
- Active liver disease or history of or actual benign or malignant liver tumours.
- Use with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see **WARNINGS AND PRECAUTIONS**).
- Known or suspected carcinoma of the breast.
- Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia.
- Undiagnosed abnormal vaginal bleeding.
- Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
- When pregnancy is suspected or diagnosed.
- Valvular heart disease with complications.
- Steroid-dependent jaundice, cholestatic jaundice or history of jaundice of pregnancy.
- Current or history of migraine with focal aura.
- History of or actual pancreatitis if associated with severe hypertriglyceridemia.
- Presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
    - persistent blood pressure values ≥160 mm Hg systolic or ≥100 mm Hg diastolic
    - hereditary or acquired predisposition for venous or arterial thrombosis, such as Factor V Leiden mutation and activated protein C (APC-) resistance, antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia (e.g., due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
    - 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.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious cardiovascular events from 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 Tri-Cira 21 and 28, 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 COCs is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes. Other examples of medical conditions which have been associated with adverse circulatory events e.g., systemic lupus erythematosus[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 COCs with higher formulations of estrogen and progestogens than those in common use today. The effect of long-term use of COCs with lower doses of both estrogen and progestogen administered orally remains to be determined.

Carcinogenesis and Mutagenesis

Breast Cancer

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

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

Cervical Cancer

The most important risk factor for cervical cancer is persistent human papilloma virus (HPV) infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to 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.

Cardiovascular

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular events and mortality from combination oral contraceptive (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs, including Tri-Cira 21 and 28, 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 significant and persistent elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary and an alternate method of contraception should be prescribed (see **CONTRAINDICATIONS**).

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

Gastrointestinal

Published epidemiological studies indicate a possible association of combination oral contraceptives 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 mcg 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 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
Tri-Cira 21 and 28 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 or without dasabuvir to obtain further information about restarting Tri-Cira 21 and 28.

Immune

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema[24-27].

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 Disease

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

Ocular Lesions

There have been clinical 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.

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.

Sexual Function/Reproduction

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.

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

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

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

Special Populations

Pregnant Women:
Tri-Cira 21 and 28 are contraindicated during pregnancy. If pregnancy occurs during treatment with Tri-Cira 21 and 28, further intake must be stopped. However, if conception accidentally occurs while taking the

pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child.

Nursing Women:
Contraceptive steroids and/or their metabolites may be excreted in breast milk. In addition, combination hormonal contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. If possible, the nursing mother should be advised not to use Tri-Cira 21 and 28 or other combination hormonal contraceptives but to use other forms of contraception until the child is fully weaned.

Pediatrics (<16 years of age):
Safety and efficacy of norgestimate and ethinyl estradiol tablets have been established in women of reproductive age. Use of this product before menarche is not indicated.

Geriatrics (> 65 years of age):
Tri-Cira 21 and 28 are 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 must be ruled out if any members of the family have suffered from thromboembolic diseases (e.g., deep vein thrombosis, stroke, myocardial infarction) at a young age. Breasts, liver, extremities, and pelvic organs should be examined. A Papanicolaou (PAP) smear should be taken if the patient has been sexually active.

The first follow-up visit should be three months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year, or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on Periodic Health Examination. Their suggestion was that, for women who had two consecutive negative PAP smears, screening could be continued every three years up to the age of 69.

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
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
	Depression
	Headache
	Nervousness
	Dizziness
	Changes in libido
	Chorea
Metabolic:	Reduced tolerance to carbohydrates
	Change in weight (increase or decrease)
	Changes in appetite
Gastro-intestinal Tract:	Gastrointestinal symptoms (such as abdominal cramps and bloating)
	Colitis
	Pancreatitis
Hepatobiliary:	Cholestatic jaundice
	Budd-Chiari syndrome
Eyes:	Intolerance to contact lenses
	Change in corneal curvature (steepening)
	Cataracts
	Optic neuritis
	Retinal thrombosis
Urinary:	Impaired renal function
	Hemolytic uremic syndrome
	Cystitis-like syndrome
Others:	Rhinitis
	Auditory disturbances

Clinical Trial Adverse Drug Reactions

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

The safety of norgestimate and ethinyl estradiol tablets was evaluated in 4,826 healthy women of child-bearing potential who participated in 6 clinical trials and received at least 1 dose of norgestimate and ethinyl estradiol tablets for contraception. Two trials were randomized, active-controlled trials and 4 were uncontrolled, open-label trials. In 3 trials, subjects were followed for up to 24 cycles; in 2 trials, subjects were followed for up to 12 cycles; and in 1 trial, subjects were followed for up to 6 cycles. The most frequent Adverse Drug Reactions (ADRs) reported in >5% of subjects were headache, breast pain and vaginal infection. ADRs reported by ≥1% of norgestimate and ethinyl estradiol tablets-treated subjects in these trials are shown in Table 1.

Table 1: Adverse Drug Reactions Reported by ≥1% of Norgestimate and Ethinyl Estradiol Tablets-treated Subjects in 6 Clinical Trials of Norgestimate and Ethinyl Estradiol Tablets

System/Organ Class Adverse Reaction	% **(N=4,826)**
Infections and Infestations	
Vaginal infection	7.1
Metabolism and Nutrition Disorders	
Fluid retention	1.4
Psychiatric Disorders	
Mood altered	2.1
Nervousness	1.8
Depression	1.7
Nervous System Disorders	
Headache	31.7
Migraine	1.9
Gastrointestinal Disorders	
Abdominal pain	3.1
Gastrointestinal pain	2.5
Flatulence	1.5
Skin and Subcutaneous Tissue Disorders	
Rash	1.4
Reproductive System and Breast Disorders	
Breast pain	7.4
Genital discharge	3.2
General Disorders and Administration Site Conditions	
Edema	1.0
Investigations	
Weight increased	2.3

Additional ADRs reported by <1% of norgestimate and ethinyl estradiol tablets -treated subjects (N=4,826) in the above clinical dataset are shown in Table 2.

Table 2: Adverse Drug Reactions Reported by <1% of Norgestimate and Ethinyl Estradiol Tablets -treated Subjects in 6 Clinical Trials of Norgestimate and Ethinyl Estradiol Tablets

System/Organ Class Adverse Reaction
Metabolism and Nutrition Disorders
Increased appetite, Decreased appetite, Weight fluctuation, Appetite disorder

Table 2: Adverse Drug Reactions Reported by <1% of Norgestimate and Ethinyl Estradiol Tablets -treated Subjects in 6 Clinical Trials of Norgestimate and Ethinyl Estradiol Tablets

Psychiatric Disorders
Libido disorder
Vascular Disorders
Hypertension
Skin and Subcutaneous Tissue Disorders
Alopecia, Rash popular, Skin discolouration, Erythema
Reproductive System and Breast Disorders
Breast enlargement, Breast discharge, Menstruation irregular, Menstrual disorder
Investigations
Weight decreased

In the above trials with norgestimate and ethinyl estradiol tablets, details for specific ADRs, namely nausea, vomiting, gastrointestinal disorder (reported as nausea or vomiting), dysmenorrhea, metrorrhagia, abnormal withdrawal bleeding, amenorrhea and premenstrual syndrome, were solicited or determined from bleeding pattern or cycle characteristics data on a by-cycle basis, e.g., using menstrual calendars or diary cards. These ADRs are not included in Tables 1 and 2, as the incidence of each ADR was reported separately by treatment cycle only and no overall subject incidence for the whole trial was reported. In general, solicited events are associated with higher reporting rates than events spontaneously reported by subjects.

By-cycle ADRs reported by ≥1% of norgestimate and ethinyl estradiol tablets -treated subjects in cycle 1 are shown in Table 3. With the exception of premenstrual syndrome and dsymenorrhea, the incidence of these ADRs was highest in cycle 1 and decreased over time with further treatment cycles. Premenstrual syndrome remained relatively stable over time and dysmenorrhea remained relatively stable, with a slight decrease over time (based on incidence data from cycles 1, 3, 6, 12 and 24).

Table 3: Adverse Drug Reactions Reported by ≥1% of Norgestimate and Ethinyl Estradiol Tablets -treated Subjects in Cycle 1 in 6 Clinical Trials (Except Where Specified) of Norgestimate and Ethinyl Estradiol Tablets

System/Organ Class Adverse Reaction	**Total Subjects[1] (N)**	**Cycle 1 (%)**
Gastrointestinal Disorders		
Gastrointestinal disorder[2,3]	1,779	25.9
Nausea[4]	850	19.1
Vomiting[4]	850	5.3

Reproductive System and Breast Disorders		
Dysmenorrhea[5]	2,675	37.0
Premenstrual syndrome[5]	2,673	32.0
Metrorrhagia	2,912	22.7
Abnormal withdrawal bleeding	2,912	14.8
Amenorrhea[4]	2,334	1.1

[1] Number of subjects with available data for cycle 1.

[2] Based on data from 2 trials.

[3] Reported as nausea or vomiting.

[4] Based on data from 3 trials.

[5] Based on data from 5 trials.

Post-Market Adverse Drug Reactions

Adverse drug reactions first identified during post-marketing experience with norgestimate/ethinyl estradiol (NGM/EE) are included in Table 4.

Table 4: Adverse Drug Reactions Identified During Post-Marketing Experience with NGM/EE from Spontaneous Reports

Infections and Infestations
Urinary tract infection
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)
Breast cancer, Cervical dysplasia, Benign breast neoplasm, Hepatic adenoma, Focal nodular hyperplasia, Fibroadenoma of breast, Breast cyst
Immune System Disorders
Anaphylactic reaction, Hypersensitivity
Metabolism and Nutrition Disorders
Dyslipidaemia
Psychiatric Disorders
Anxiety, Insomnia
Nervous System Disorders
Cerebrovascular accident, Syncope, Convulsion, Paraesthesia, Dizziness
Eye Disorders
Retinal vascular thrombosis, Visual impairment, Dry eye, Contact lens intolerance
Ear and Labyrinth Disorders
Vertigo
Cardiac Disorders
Myocardial infarction, Tachycardia, Palpitations

Table 4: Adverse Drug Reactions Identified During Post-Marketing Experience with NGM/EE from Spontaneous Reports

Vascular Disorders
Arterial thromboembolism, Deep vein thrombosis, Hot flush, Venous thrombosis[1]
Respiratory, Thoracic and Mediastinal Disorders
Pulmonary embolism, Dyspnea
Gastrointestinal Disorders
Pancreatitis, Abdominal distension, Diarrhea, Constipation
Hepatobiliary Disorders
Hepatitis
Skin and Subcutaneous Tissue Disorders
Angioedema, Erythema nodosum, Hirsutism, Night sweats, Hyperhidrosis, Photosensitivity reaction, Urticaria, Pruritus, Acne
Musculoskeletal, Connective Tissue, and Bone Disorders
Muscle spasms, Pain in extremity, Myalgia, Back pain
Reproductive System and Breast Disorders
Ovarian cyst, Suppressed lactation, Vulvovaginal dryness
General Disorders and Administration Site Conditions
Chest pain, Asthenic conditions

[1] The bundled terms for venous thrombosis include Budd Chiari Syndrome and hepatic vein thrombosis.

DRUG INTERACTIONS

Overview

The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent (see Tables 5 and 6). 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.

Drug-Drug Interactions

Table 5: 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 mcg 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	

Class of Compound	Drug	Proposed Mechanism	Suggested Management
		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.
CYP3A inhibitors given in combination with HIV/AIDS drugs	Cobicistat	May reduce the efficacy of estrogen-based contraceptives	Use another drug combination 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.
HIV Protease Inhibitors	Nelfinavir Ritonavir Ritonavir-boosted protease inhibitors	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Non-nucleoside Reverse Transcriptase Inhibitors	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates	Induction of hepatic microsomal	For short course, use additional method or

Class of Compound	Drug	Proposed Mechanism	Suggested Management
	Chloral hydrate Glutethimide Meprobamate	enzymes.	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 6: 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	Use with caution.

Class of Compound	Drug	Modification of Drug Action	Suggested Management
		acetaldehyde.	
Alpha-II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	OCs increase clotting factors, decrease efficacy. However, OCs may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Fluid retention may increase risk of seizures.	Use another method.
	Lamotrigine	Significantly decreased lamotrigine levels (due to induction of lamotrigine glucuronidation) may lead to breakthrough seizures.	Adjust dose of drug if necessary.
Antidiabetic Drugs	Oral hypoglycemics and Insulin	OCs may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin OC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen OC or use another method.
	Beta blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.

Class of Compound	Drug	Modification of Drug Action	Suggested Management
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	Salicylic acid	Plasma levels may be decreased (due to induction of glucuronidation).	Use with caution.
	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.
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.

Class of Compound	Drug	Modification of Drug Action	Suggested Management
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.

Class of Compound	Drug	Modification of Drug Action	Suggested Management
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 co-administration 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-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.

A.	*Liver Function Tests*	
	Bromsulphthalein Retention Test (BSP)	Moderate increase
	AST (SGOT) and GGT	Minor increase
	Alkaline Phosphatase	Variable increase
	Serum Bilirubin	Increased, particularly in conditions predisposing to or associated with hyperbilirubinemia
B.	*Coagulation Tests*	
	Factors II, VII, IX, X, XII and XIII	Increased
	Factor VIII	Mild increase
	Platelet Aggregation and Adhesiveness	Mild increase in response to common aggregating agents
	Fibrinogen	Increased
	Plasminogen	Mild increase
	Antithrombin III	Mild decrease
	Prothrombin Time	Increased
C.	*Thyroid Function Tests*	
	Protein-bound Iodine (PBI)	Increased
	Total Serum Thyroxine (T4)	Increased
	Thyroid Stimulating Hormone (TSH)	Unchanged
	T_3 Resin-uptake	Decreased
	Free T4 Concentration	Unchanged
D.	*Adrenocortical Function Tests*	
	Plasma Cortisol	Increased
E.	*Miscellaneous Tests*	
	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. Tri-Cira 21 and 28 tablets are also used to treat moderate acne in females who are able to take oral contraceptives.

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

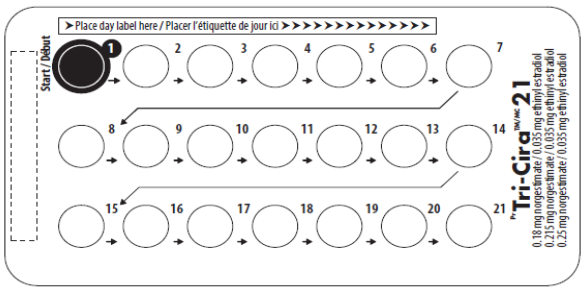
INFORMATION TO PATIENTS ON HOW TO TAKE THE BIRTH CONTROL PILL

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

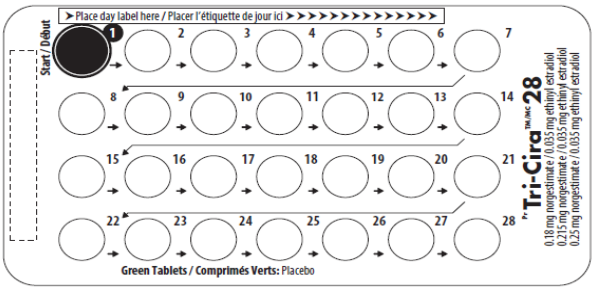
2. **LOOK AT YOUR PILL PACK** to see if it has 21 or 28 pills:
   - **21-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week or
   - **28-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills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



28-Day
Pill Pack



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 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.

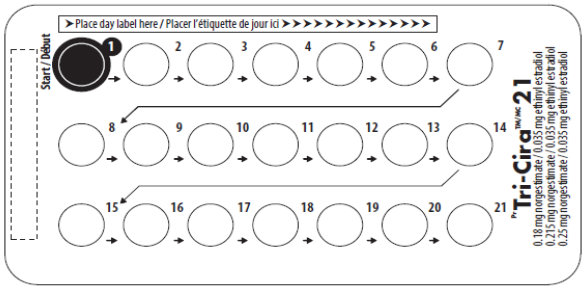
   Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS ON THE PILLS**. Your period should occur during the last seven days of using that pill pack.

INSTRUCTIONS FOR USING YOUR 21-DAY AND 28-DAY PILL PACKS.

FOLLOW THESE INSTRUCTIONS CAREFULLY:

1. **For Day 1 start:** Label the Pill Pack 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.

21-Day Pill Pack



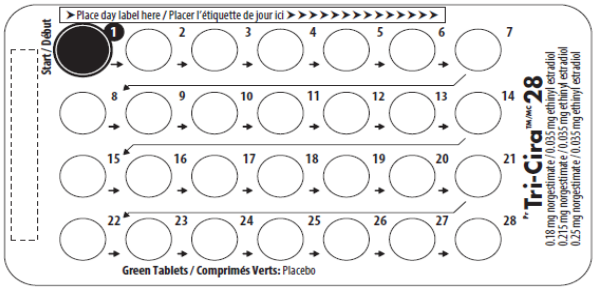
OR

For Day 5 start: Label the Pill Pack 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

<u>For Sunday start:</u> The first Sunday **<u>after</u>** your period begins, or, if your period starts on Sunday, start that **<u>same day</u>**.

28-Day Pill Pack



2. Place the day label in the space where you see the words "Place day label here". Having the Pill Pack 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 Pill Pack.
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**
First Two Weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**	**First Two Weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**
MISS THREE OR MORE PILLS IN A ROW	**MISS THREE OR MORE PILLS IN A ROW**

Any Time in the Cycle	**Any Time in the Cycle**
1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month.	1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month.
IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.	**IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**

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

Always be sure you have on hand:

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

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

Special Notes on Administration

Use after childbirth:

Tri-Cira 21 and 28 should be started no earlier than 4 weeks postpartum in women who elect not to breastfeed due to increased risk of thromboembolism (see **WARNINGS AND PRECAUTIONS, Hematologic**). The possibility of ovulation and conception prior to initiation of medication should also be considered.

Use after abortion or miscarriage:

After an abortion or miscarriage that occurs prior to 20 weeks gestation, Tri-Cira 21 and 28 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, Tri-Cira 21 and 28 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.[28] 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

Oral Contraception

The primary mechanism of action of Tri-Cira 21 and 28 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.

Studies evaluating the effect of the combination on cervical mucus characteristics, hormonal levels and also on the endometrial tissue yielded results that were consistent with the known mechanism of action (i.e., suppression of ovulation) of the combination.

Acne

Acne is an androgen dependent skin condition with a multifactorial etiology. Elevation in serum sex hormone binding globulin (SHBG), the main testosterone-carrier protein in women, is an indicator of the potential anti-androgenic effects associated with oral contraceptives. The combination of ethinyl estradiol and norgestimate has been shown to increase SHBG and decrease free testosterone in healthy women. The combination of ethinyl estradiol and norgestimate in norgestimate and ethinyl estradiol tablets has been associated with a decrease in the severity of facial acne in otherwise healthy women with this skin condition.

Pharmacodynamics

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

Pharmacokinetics

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

Absorption:
Orally administered norgestimate plus ethinyl estradiol in norgestimate and ethinyl estradiol tablets has been shown to be absorbed rapidly. Peak plasma concentrations (C_{max}), areas under the plasma level vs time curve (AUC), time to peak plasma levels (T_{max}), and half-life ($t_{1/2}$) of norgestimate and ethinyl estradiol were as follows:

		0.250 mg Norgestimate (blue) tablet x 2	0.215 mg Norgestimate (light blue) tablet x 2	0.180 mg Norgestimate (white) tablet x 2
C_{max} ±SD	- Norgestimate	278 + 140 pg/mL	529 + 220 pg/mL	778 ± 420 pg/mL
	- Ethinyl Estradiol	119 + 50 pg/mL	113 + 39 pg/mL	117 ± 56 pg/mL
T_{max}	- Norgestimate	1.1 hr	1.2 hr	1.1 hr
	- Ethinyl Estradiol	1.8 hr	1.8 hr	1.9 hr
AUC ± SD	- Norgestimate	1064 + 425 hr•pg/mL	1649 + 604 hr•pg/mL	2264 + 962 hr•pg/mL
	- Ethinyl Estradiol	984 + 476 hr•pg/mL	873 + 489 hr•pg/mL	815 + 450 hr•pg/mL
$t_{1/2}$	- Norgestimate	6.5 hr	7.6 hr	5.3 hr
	- Ethinyl Estradiol	7.3 hr	4.3 hr	5.5 hr

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

Elimination:
The elimination of norgestimate has been shown to be unaffected by ethinyl estradiol. While some biliary excretion and enterohepatic circulation is seen with norgestimate (similar to that seen with other contraceptive steroids),[29,30] elimination is primarily renal.[29-31]

Special Populations and Conditions

Pediatrics
The safety and efficacy of norgestimate and ethinyl estradiol tablets has been established in women of reproductive age. Use of this product before menarche is not indicated.

Geriatrics
Tri-Cira 21 and 28 are not indicated for use in postmenopausal women.

Hepatic Insufficiency
The effects of hepatic impairment on the pharmacokinetics of norgestimate and ethinyl estradiol tablets have not been studied. However, steroid hormones may be poorly metabolized in women with impaired liver function.

Renal Insufficiency
The effects of renal impairment on the pharmacokinetics of norgestimate and ethinyl estradiol tablets have not been studied.

STORAGE AND STABILITY

Store between 15°C to 30°C. Leave contents in protective packaging including carton to protect from light, until time of use. Keep out of the sight and reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tri-Cira 21 and 28 tablets are available in:

21-day Pill Pack that contains:
7 WHITE tablets each containing 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. The tablets are round, biconvex, white tablets engraved “C” on one side and “21” on the other side.
7 LIGHT BLUE tablets each containing 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. The tablets are round, biconvex, light blue tablets engraved “C” on one side and “22” on the other side.
7 BLUE tablets each containing 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. The tablets are round, biconvex, blue tablets engraved “C” on one side and “23” on the other side.

28-day Pill Pack that contains:
7 WHITE tablets each containing 0.18 mg norgestimate and 0.035 mg ethinyl estradiol. The tablets are round, biconvex, white tablets engraved “C” on one side and “21” on the other side.
7 LIGHT BLUE tablets each containing 0.215 mg norgestimate and 0.035 mg ethinyl estradiol. The tablets are round, biconvex, light blue tablets engraved “C” on one side and “22” on the other side.
7 BLUE tablets each containing 0.25 mg norgestimate and 0.035 mg ethinyl estradiol. The tablets are round, biconvex, blue tablets engraved “C” on one side and “23” on the other side.
7 GREEN tablets with inert ingredients. The tablets are plain, round, biconvex, green tablets.

Each white Tri-Cira 21 and 28 tablet contains 0.18 mg norgestimate plus 0.035 mg ethinyl estradiol. Each white tablet also contains hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.

Each light blue Tri-Cira 21 and 28 tablet contains 0.215 mg norgestimate plus 0.035 mg ethinyl estradiol. Each light blue tablet also contains FD&C Blue No.1 Aluminum Lake, FD&C Blue No.2 Aluminum Lake, FD&C Yellow No. 5 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.

Each blue Tri-Cira 21 and 28 tablet contains 0.25 mg norgestimate plus 0.035 mg ethinyl estradiol. Each blue tablet also contains FD&C Blue No.1 Aluminum Lake, FD&C Blue No.2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.

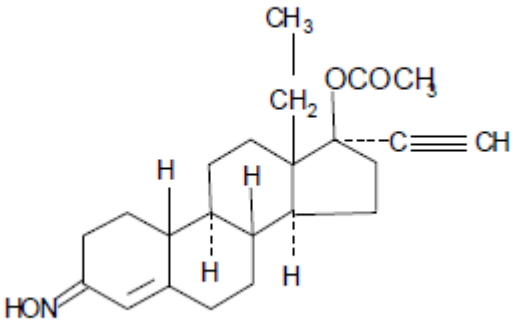
Each green tablet contains inert ingredients FD&C Blue No. 2 Aluminum Lake, hydroxypropyl methylcellulose, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate, sodium croscarmellose, titanium dioxide and triacetin.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

(i) DRUG SUBSTANCE

Norgestimate:
Chemical Name: 18,19-dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)-
Structural Formula:



Molecular Weight: 369.50 g/mol Molecular Formula: $C_{23}H_{31}NO_3$

Description:
Norgestimate is a white or almost white powder.

Melting range/point: 214ºC and 218ºC.

Solubility:

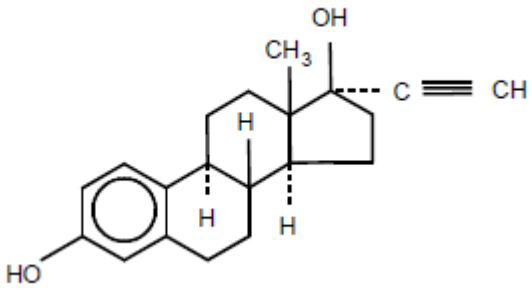
Solvent	Solubility value (mg/kg)
Water	Practically insoluble
Hexane	< 290
Diethyl ether	< 5000
Methanol	< 3000

No pKa was determined because of its poor solubility in water.

Optical Rotation: +42.0° and +50.0°

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

Structural Formula:



Molecular Weight: 296.40g/mol Molecular Formula: C_{20} H_{24} O_2

Description:
Ethinyl estradiol is a white or slightly yellowish-white, crystalline powder. It is practically insoluble in water and freely soluble in ethanol (96%). It dissolves in solutions of fixed alkali hydroxides.

CLINICAL TRIALS

Comparative Bioavailability Study

A randomized, single dose, 3-way crossover comparative bioavailability study of Tri-Cira (Apotex Inc.) and Tri-Cyclen® (Janssen Inc.) was conducted in healthy female volunteers under fasting conditions. Comparative bioavailability data from subjects that were included in the statistical analysis (N=20 for norgestimate, N=19 for ethinyl estradiol) are summarized in the following tables.

Norgestimate (2 x 0.250 mg norgestimate/ 0.035 mg ethinyl estradiol) Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference[†]	Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg•h/mL)	88.2 94.0 (36.7)	92.8 100.8 (51.9)	95.1	86.8 - 104.0
AUC_I (pg•h/mL)	101.5 107.2 (33.3)	106.5 114.9 (49.9)	95.3	85.7 -105.9
C_{max} (pg/mL)	66.0 72.8 (45.2)	65.0 70.0 (42.2)	101.5	87.9 - 117.3
T_{max}[§] (h)	0.67 (0.37 – 1.67)	0.67 (0.25-3.00)		
$T_{1/2}$[€] (h)	0.59 (29.73)	0.71 (34.08)		

* Tri-Cira (norgestimate/ ethinyl estradiol) tablets, 0.250/ 0.035 mg (Apotex Inc.)

[†] Tri-Cyclen® (norgestimate/ ethinyl estradiol) tablets, 0.250/ 0.035 mg (Janssen Inc., Canada)

[#] Based on Geometric Least Squares Means.

[§] Expressed as median (range)

[€] Expressed as arithmetic means (CV%) only.

Ethinyl Estradiol (2 x 0.250 mg norgestimate/ 0.035 mg ethinyl estradiol) Geometric Mean[#] Arithmetic Mean (CV%)				
Parameter	Test*	Reference[†]	Ratio of Geometric Means	90% Confidence Interval
AUC_T (pg•h/mL)	1513.9 1563.9 (28.8)	1604.2 1655.7 (28.7)	94.4	89.4 - 99.6
AUC_I (pg•h/mL)	1586.9 1641.1 (29.1)	1682.1 1738.2 (29.1)	94.3	89.1 - 99.8
C_{max} (pg/mL)	165.8 175.0 (35.2)	166.6 175.8 (34.7)	99.5	92.3 - 107.3
T_{max}[§] (h)	1.33 (1.00-1.67)	1.67 (1.00-3.00)		
$T_{1/2}$[€] (h)	17.55 (30.06)	18.21 (26.64)		

* Tri-Cira (norgestimate/ ethinyl estradiol) tablets, 0.250/ 0.035 mg (Apotex Inc.)

† Tri-Cyclen® (norgestimate/ ethinyl estradiol) tablets, 0.250/ 0.035 mg (Janssen Inc., Canada)

Based on Geometric Least Squares Means.

§ Expressed as median (range)

€ Expressed as arithmetic means (CV%) only.

Clinical Efficacy of Norgestimate and Ethinyl Estradiol Tablets

Contraception

In four major clinical trials with norgestimate and ethinyl estradiol tablets, 4,756 subjects completed 45,244 cycles and a total of 42 pregnancies were reported. This represents an overall use-efficacy (typical user efficacy) pregnancy rate of 1.11 per 100 woman-years. This rate includes patients who did not take the drug correctly. The Pearl Rates for the individual studies ranged from 0.63 to 1.36.

Acne

In two double-blind, placebo-controlled, multicentre clinical trials, norgestimate and ethinyl estradiol tablets showed a statistically significantly greater improvement for all primary efficacy measures: inflammatory lesion count, total lesion count, and investigator's global assessment (Table 7). In the secondary efficacy measures, norgestimate and ethinyl estradiol tablets also showed a statistically greater improvement for the end-of-therapy subject's self-assessment. The adverse reaction profile of norgestimate and ethinyl estradiol tablets from these two controlled clinical trials is consistent with what has been noted from previous studies involving norgestimate and ethinyl estradiol tablets and the known risks associated with oral contraceptives.

Table 7: Acne Vulgaris Indication Combined Results: Two Multicentre, Placebo-Controlled Trials Primary Efficacy Variables: Evaluable-for-Efficacy Population

	Norgestimate and Ethinyl Estradiol Tablets	PLACEBO	
	N=163	N=161	
Mean Age at Enrollment	27.3 years	28.0 years	
Inflammatory Lesions - Mean Percent Reduction	56.6	36.6	p=0.0001
Total Lesions - Mean Percent Reduction	49.6	30.3	p=0.0001
Investigator's Global Progress of Treatment			
- Percent of Subjects improved	88.3	64.0	p<0.001
- Percent of Subjects not improved	11.7	36.0	

Clinical Safety of Norgestimate and Ethinyl Estradiol Tablets

U.S. Multicentre, Comparative, Phase III Study

In the major comparative U.S. study, 8.6% (182 of 2115) of the norgestimate and ethinyl estradiol tablets subjects discontinued due to adverse experiences, while 6.8% (145 of 2132) of subjects receiving the norgestrel-containing product discontinued due to adverse experiences. The difference between the groups was not statistically significant and the adverse experiences were characteristic of those expected among women taking low-dose combination oral contraceptives.

Among all patients, 70.50% (1491 of 2115) receiving norgestimate and ethinyl estradiol tablets and 67.64% (1442 of 2132) receiving Triphasil reported at least one adverse experience during the trial. The most common adverse experiences in the norgestimate triphasic regimen were headaches (29.3%), upper respiratory infection (12.2%), dysmenorrhea (11.6%), and nausea (10.87%). The incidences of such experiences in the norgestrel regimen were 29.5%, 11.9%, 11.9%, and 10.32% respectively.

U.S. Multicentre, Non-comparative, Phase III Studies

In the two non-comparative, U.S. studies combined, 296 of 1,783 (16.6%) subjects discontinued for medical use-related reasons. Only 77 (4.3%) discontinued treatment due to bleeding events.

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

SUBJECT FREQUENCY OF ADVERSE EXPERIENCES CAUSING DISCONTINUATION
(COMBINED NON-COMPARATIVE STUDIES, N=1783)

Adverse Experience	Number (Percent)
Breakthrough Bleeding or Spotting	77 (4.32)
Headache	54 (3.03)
Nausea and/or Vomiting	39 (2.19)
Menstrual Disturbances Other than Amenorrhea, Breakthrough Bleeding or Spotting	38 (2.13)
Mood Alterations	28 (1.57)
Weight Gain	23 (1.29)
Fluid Retention	21 (1.18)
Gastrointestinal Disorders	19 (1.07)
Lab Abnormalities	16 (0.90)
Hypertension	13 (0.73)
Other OB/Gyn	13 (0.73)
Skin Problems	8 (0.45)
Eye Abnormalities	8 (0.45)
Amenorrhea*	4 (0.22)
All Other	41 (2.30)

*The statistical definition of amenorrhea is two consecutive valid cycles with no bleeding or spotting. According to this definition, no norgestimate and ethinyl estradiol tablets subjects had amenorrhea.

Laboratory Tests

A broad range of clinical laboratory data have been collected in a number of studies. Statistically significant laboratory changes were generally clinically insignificant and consistent with use of low-dose oral contraceptives.

Lipid profile changes are relevant due to their relationship to cardiovascular disease.
Norgestimate and ethinyl estradiol tablets are associated with minimal adverse effect on triglycerides, LDL, and total cholesterol. Uncharacteristic of most currently approved products, norgestimate and ethinyl estradiol tablets are associated with a salutary increase in HDL and HDL/LDL ratios.[36]

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

Liver function test mean values generally decreased with time on therapy and, consistent with results from other low-dose products, showed no adverse clinical impact.

No unusual findings for thyroid function, kidney function, or hematology values were noted with norgestimate and ethinyl estradiol tablets and normal coagulability of the blood was maintained.

Norgestimate and ethinyl estradiol tablets also exhibited minimal androgenicity. Sex hormone binding

globulin levels were increased and testosterone was not readily displaced from its binding sites by norgestimate.

As both progestins and estrogens may modify carbohydrate metabolism, this area was investigated. No clinically significant changes were observed in fasting serum or blood glucose levels and associated blood insulin levels of subjects receiving norgestimate and ethinyl estradiol tablets. Measurement of glycosylated hemoglobin confirmed these results demonstrating that there was no adverse change in carbohydrate metabolism.

DETAILED PHARMACOLOGY

Oral Contraception

Norgestimate, alone and in combination with ethinyl estradiol, is an effective antiovulatory agent.[29] It is moderately potent in the standard *in vivo* progestational assay which measures endometrial proliferation in rabbits, and it effectively blocks ovulation in rats, hamsters and rabbits. In rats, this blockade correlates well with suppression of the proestrus LH surge and the antiovulatory activity of norgestimate is overcome by LHRH. The blockade appears, like that of other progestational agents, to be the result of inhibition of the hypothalamic/pituitary axis. Norgestimate is an active progestin when administered either orally or parenterally and binds to progestational receptors *in vitro*. Like other progestins, norgestimate inhibits the action of estrogen but is not estrogenic itself. Studies measuring the stimulation of ventral prostate growth in rats, the ability to bind to human SHBG *in vitro,* and the effects on serum SHBG levels in rabbits demonstrate that in contrast to levonorgestrel, norgestimate is not androgenic. It also does not inhibit the action of androgen in rats. No adverse effects on the reproductive, thyroid or adrenal endocrine systems were seen in rats given norgestimate orally for 7 days at doses up to 100 times the clinical dose. *In vitro* studies indicate that norgestimate does not directly alter ovarian aromatase activity. Norgestimate does not exhibit central nervous system or autonomic nervous system activities in rats and does not interfere with autonomic-mediated responses of the cardiovascular system in dogs. *In vitro* studies indicate that norgestimate does not possess antimicrobial activity against diverse pathogenic microorganisms. Ethinyl estradiol is a potent estrogen, which stimulates the uterus and the vagina. Its preclinical pharmacology is well established.[30,32]

Acne

Acne is an androgen dependent skin condition with a multifactorial etiology. Elevation in serum sex hormone binding globulin (SHBG), the main testosterone-carrier protein in women, is an indicator of the potential anti-androgenic effects associated with oral contraceptives. The combination of ethinyl estradiol and norgestimate has been shown to increase SHBG and decrease free testosterone in healthy women. The combination of ethinyl estradiol and norgestimate in norgestimate and ethinyl estradiol tablets has been associated with a decrease in the severity of facial acne in otherwise healthy women with this skin condition.

TOXICOLOGY

Toxicology studies have evaluated norgestimate alone as well as in combination with ethinyl estradiol in the mouse, rat, rabbit, dog and monkey.[29] Ethinyl estradiol has also been evaluated both alone and in

combination with synthetic steroidal progestogens in the rat, rabbit, dog and monkey.[29, 33-35] Compound-related gross and microscopic lesions have been minimal and show the typical pathological changes that are known to occur with the administration of progestogen and estrogen.

Acute Toxicity Studies

Mice

In HaM/1CR CD-1 mice oral norgestimate alone and oral norgestimate + ethinyl estradiol (5:1) each had an LD_{50} greater than 5 g/kg body weight. Norgestimate alone at 5 g/kg caused no overt signs of toxicity while the combination caused transient changes in behaviour and one death (one female out of 10 females and 10 males) at 5 g/kg. Oral ethinyl estradiol alone at 5 g/kg caused a transient period of depression and slightly laboured breathing (in males only) with no mortality. The drug was given as a single dose, suspended in carboxymethylcellulose or carboxymethylcellulose and sesame oil.

Rats

In hooded Long-Evans rats no deaths or toxic signs were seen at 5 g/kg or 6.2 g/kg orally of norgestimate alone. Norgestimate in combination with ethinyl estradiol (5:1) orally at 5 g/kg caused no deaths or overt signs of toxicity other than a slight decrease in body weight compared to controls. At autopsy prostate, seminal vesicles and testes were smaller in animals receiving 5g/kg of the combination than in controls. Ethinyl estradiol alone had an oral LD_{50} of 5.3 g/kg for males and 3.2 g/kg for females. Drug was administered suspended in carboxymethylcellulose.

Dogs

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

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

Subacute Toxicity Studies

Rats

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

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

Dogs

Female beagles were given oral doses of norgestimate up to 5.0 mg/kg/day. No deaths were seen.

Hematological test results were normal as were clinical chemistry values except for a slight depression of cholesterol in higher-dose animals early in the study. Urinalysis results were normal.

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

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

Monkeys

Female Rhesus monkeys given norgestimate orally at doses of 5.0, 1.50, 0.25 and 0 mg/kg/day for 90 days showed no signs of toxicity in their behaviour, body weight, hematology results, urinalysis, or clinical chemistry values.

Histological examination revealed no lesions attributable to the drug. The same was seen for oral norgestimate + ethinyl estradiol (10:1) for doses of 5.5, 1.65, 0.275 and 0 mg/kg/day for 90 days except in high-dose animals. These animals showed hypertrophy of cervical mucus glands and an increase in size and number of mammary acini. Evidence of hyperplasia and epithelial sloughing of uterine endometrium was also noted. There was a dose-dependent stimulation of mucus secretion of the cervix.

Long-Term Toxicity Studies

Rats

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

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

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

Hepatic changes were seen in all groups (including controls) at 2 years. The severity and incidence of these changes were higher in high- and mid-dose groups than in others. These changes were: nodular or generalized hepatocyte hypertrophy and hyperplasia, hyperplasia foci of hepatocyte coagulation necrosis, sinusoidal telangiectasis, and formation of hematocysts. The reproductive organs showed little microscopic

evidence of drug effect, although uterine endometrial hyperplasia was increased in treated animals. The incidence of benign mammary tumours was higher in treated animals than in controls. However, the incidence was statistically significant only in the highest dose group. At 50 to 1000 times the human dose, this combination produced effects remarkably similar to those of other progestin-estrogen combinations.

In a second study, female Long-Evans rats were given norgestimate + ethinyl estradiol (5:1) at 0.150, 0.0375 and 0.01875 mg/kg/day (6.5 to 50 times the human dose), norgestimate alone and ethinyl estradiol alone each at 0.025 mg/kg/day (50 times the human dose) or d-norgestrel at 0.150, 0.075, and 0.0375 mg/kg/day (50 times human dose) for 104 weeks. There were 50 rats in each test group and 100 vehicle controls. Mortality was 55.9% overall with no difference between groups. Minor transient changes were seen for food consumption and body weight early in the study. Periodic hematological examination showed no deviations beyond normal range except for a slight decrease in hematocrit in the high-dose norgestimate + ethinyl estradiol groups. All clinical chemistry parameters measured demonstrated large variations associated with aging in all groups. The only statistically significant changes were a decrease in the cholesterol in ethinyl estradiol only and norgestimate + ethinyl estradiol high-dose groups, and an elevation of triglycerides in all combination groups. There was no significant difference between control and test rats for either benign or malignant tumours.

Dogs

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

No deaths occurred. All animals were in good health at termination and no changes in behaviour were noted. In year 1, estrus was seen in all controls. In year 2, it was seen in 13 of 16 controls and was not seen in any test dog during the study. High-dose dogs had decreased RBCs and hematocrit throughout the study and an increased WBC count from 3 to 18 months of study. Decreased lymphocytes were seen in high- and mid-dose dogs and cholesterol was decreased in the low- and mid-dose dogs. Histologic changes were all estrogenic in nature with minimal evidence of progestational response. In a 7-year study, 15 female beagles/group were given oral doses of 0.1425, 0.057, 0.0057 and 0 mg/kg/day norgestimate + ethinyl estradiol in the 21 days on followed by 7 days off cycle. There were 9 deaths during the study: 2 in the control, 2 in the high-dose, 4 in the mid-dose and 1 in the low-dose group. Daily observation revealed no unexpected adverse effects. Near the end of the study, slight to moderate alopecia and enlarged uteri were palpated in some dogs from the high- and the intermediate-dose groups.

Hysterectomies resulting from pyometra were greatest in high-dose and least in low-dose and control animals. Nodules palpated during mammary exams were greatest in number for the low- dose group followed by controls and lowest in the high-dose groups; none appeared drug-related. Heart rate, blood pressure and ECG intervals were all within normal range and no meaningful differences were seen in mean body weights between treated and control dogs.

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

rates at 84 months were increased, primarily in the high-dose group. However, over the entire study, changes in sedimentation rates noted were related to isolated individual increases observed in all test groups.

Coagulation parameters showed sporadic, statistically significant differences, but in general, values over the study were within normal limits. No trends were observed. Decreases in cholesterol and triglycerides and slight increases in potassium and albumin values occurred during the study in treated dogs.

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

Monkeys

Norgestimate + ethinyl estradiol was given orally to female Rhesus monkeys (20/group except for the high-dose group which had 16) at 0.60, 0.30, 0.06 and 0 mg/kg/day in a 21-day treatment followed by a 7-day no-treatment cycle for 2 years. This dose represents 20 to 200 times the human dose. During the study 1 control, 1 high-dose and 4 mid-dose monkeys died.

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

At autopsy, no drug-related gross or microscopic pathologic lesions were observed in any monkeys, including those that died during the study. Isolated cases of focal hepatic sinusoidal dilation, congestion and/or small hemorrhages were seen at the capsular surfaces. It is believed that they are of little pathological importance due to an absence of any significant liver changes over the 2-year dosing period and the high (up to 200 times the human dose) dose levels of drug. Except for an increase in intralobular stromal tissue in a high-dose monkey, mammary nodules found were focal nodular hyperplasia and these occurred in both control and treated animals. The only organ weight changes seen were decreased ovarian and uterine weights in treated monkeys from the 0.30 and 0.60 mg/kg/day groups.

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

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

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

Clinical chemistry showed a dose-related increase in SGPT. All groups also showed an increase with time, generally lower alkaline phosphatase values for treated monkeys and intermittent slight decreases in serum protein for treated monkeys. BUN for all groups was well within reference range and no difference between groups was noted for glucose. Reports from the literature indicate a dose-related increase in triglycerides and a decrease in cholesterol for the mid-dose group.[32]

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

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

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

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

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

a = Same Animal; b = Same Animal

The previously listed tumours of monkeys are single occurrences and are generally in different organs. Each of these tumour types has been reported in the literature as spontaneous occurrences. It is difficult to make a definitive etiologic association of the single cervical adenocarcinoma in one high-dose monkey.

However, in the absence of any antecedent changes (dysplasia, carcinoma *in situ*) in any of the other 47 treated monkeys, the known spontaneous occurrence (although rare in monkeys) suggests the tumour is probably spontaneous in origin.

REPRODUCTIVE STUDIES

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

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

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

TERATOLOGY AND FETAL TOXICITY

Rat

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

In addition, norgestimate + ethinyl estradiol (5:1) was administered orally to pregnant Long- Evans rats from day 15 of pregnancy through day 21 of lactation at dose levels of 0 (vehicle), 0.03, 0.18, 0.30, and 0.060 mg/kg/day. These levels represent approximately 10, 60, 100, and 200 times the proposed human dose levels. In the F_0 generation, no significant adverse effects were seen on maternal growth, behaviour and reproductive performance. However, there was some evidence of lactational insufficiency at the high-dose level.

In the F_1 generation, viability, growth and reproductive performance were unaffected in the 0.03 mg/kg/day group. At 0.18, 0.30 and 0.60 mg/kg/day, there was a dose-related reduction in female fertility. The remaining drug effects were limited to the high-dose level which showed significantly decreased offspring viability from birth to weaning and depressed pup weight during the mid-lactation period.

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

Rabbit

Female New Zealand white rabbits were given oral doses of 0.5% sodium carboxymethylcellulose

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

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. Sickle 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. Wali M, Aymes A. Review of Urticaria and Angioedema Observed with Post-marketing Use of Norgestimate/Ethinyl Estradiol Tablets. 4 April 2006
28. Francis WG, Dalzeil D. Accidental Ingestion of Oral Contraceptives by Children. Can Med Assoc J 1965;92:191.
29. Data on file, Janssen Inc.
30. Helton ED, Goldzieher JW. The Pharmacokinetics of Ethinyl Estrogens. A Review. Contraception 1977;15(3):255-284.
31. Alton KB, Hetyei NS, Shaw C, Patrick JE. Biotransformation of Norgestimate in Women. Contraception 1984;29(1):19-29.
32. Desaulles SH, Krahenbuhl C. Comparison of the Antifertility and Sex Hormonal Activities of Sex Hormones and their Derivatives. Acta Endocr 1964;47:444-456.
33. Schardein JL, Kaump DH, Woosley ET, Jellema MM. Long-term Toxicologic and Tumorigenesis Studies on an Oral Contraceptive Agent in Albino Rats. Toxicol Appl Pharmacol 1970;16:10-23.
34. Committee on the Safety of Medicines: Carcinogenicity Tests of Oral Contraceptives. Her Majesty's Stationery Office, London 1972.
35. Fairweather FA. Toxicological Requirements of Oral Contraceptives. J Reprod Fertil 1968;(5 Suppl): 47-49.
36. Rossner S, Frankman O, Marsk L. Effects of Various Low Dose Contraceptive Pills On Serum Lipoproteins in Proceedings of Lipoprotein Metabolism and Endocrine Regulation, Workshop, In: Hessel LW, Krans HMJ, editors. Development in Endocrinology. New York: Elsevier/North Holland Biomedical Press,1979;91-98.

RELEVANT LITERATURE

1. Becker H. Supportive European data on a new oral contraceptive containing norgestimate. Acta Obstet Gynecol Scand 1990; Suppl 152: 33-39.
2. Bingel AS, Benoit PS. Oral Contraceptives: Therapeutics Versus Adverse Reactions, with an Outlook for the Future. Int J Pharm Sci 1973;62:179-200.

3. Bingel AS, Benoit PS. Oral Contraceptives: Therapeutics Versus Adverse Reactions, with an Outlook for the Future II. J Pharm Sci 1973;62:349-362.
4. Boston Collaborative Drug Surveillance Programme: Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gallbladder Disease, and Breast Tumors. Lancet 1973;1:1399-1404.
5. Chapdelaine A, Desmarais J, et al. Clinical evidence of the minimal androgenic activity of norgestimate. Int J Fertil 1989; 34(5): 347-352.
6. 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.
7. Collaborative Group for the Study of Stroke in Young Women: Oral Contraception and Increased Risk of Cerebral Ischemia or Thrombosis. N Engl J Med 1973; 288(17):871-878.
8. 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.
9. Committee on the Safety of Medicines. Carcinogenicity Tests of Oral Contraceptives. Her Majesty's Stationery Office, London, 1972.
10. Fairweather FA. Toxicological Requirements of Oral Contraceptives. J Reprod Fertil 1968;(5 Suppl): 47-49.
11. Francis WG, Dalzeil D. Accidental Ingestion of Oral Contraceptives by Children. Can Med Assoc J 1965;92:191.
12. Greene GR, Sartwell PE. Oral Contraceptive Use in Patients with Thromboembolism Following Surgery, Trauma, or Infection. Am J Pub Health 1972;62(5):680-685.
13. 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.
14. Inman WHW, Vessey MP. Investigation of Deaths from Pulmonary, Coronary and Cerebral Thrombosis and Embolism in Women of Child-Bearing Age. Br Med J 1968;2:193-199.
15. Janaud A, Rouffy J, et al. A comparison study of lipid and androgen metabolism with triphasic oral contraceptive formulations containing norgestimate or levonorgestrel. Acta Obstet Gynecol Scand 1992; 71, Suppl 156: 33-38.
16. Kannel WB, Castelli WP, Gordon T. Cholesterol in the Production of Atherosclerotic Disease. New Perspectives Based on the Framingham study. Am Intern Med 1979;90: 85- 91.
17. London RS, Chapdelaine A, et al. Comparative contraceptive efficacy and mechanism of action of the norgestimate-containing triphasic oral contraceptive. Acta Obstet Gynecol Scand 1992; 71, Suppl 156:

9-14.
18. McEvoy GK et al. (Eds.). AHFS Drug Information. Bethesda: American Society of Health- System Pharmacists, Inc. 2000.
19. Nora James J, Nora Audrey H. Birth Defects and Oral Contraceptives. Lancet 1973;1:941- 942.
20. Pearl R. Contraception and Fertility in 2000 Women. Hum Biol 1932;4:363-407.
21. Potter RG. Application of Life Table Techniques to Measurement of Contraceptive Effectiveness. Demography 1966;3:297-304.
22. Royal College of General Practitioners. Oral Contraception and Thromboembolic Disease. J Coll Gen Pract 1967;13:267-279.
23. Royal College of General Practitioners: Oral Contraceptives and Health. Pittman, London 1974;1-100.
24. Sartwell PE, Masi AT, Arthes FG, Green GR, Smith HE. Thromboembolism and Oral Contraceptives: An Epidemiologic Case-Control Study. Am J Epidemiol 1969;90:365-380.
25. Spellacy WN, Wynn V. Progestogens and the Cardiovascular System. Am J Obstet Gynecol 1982;142(B Part 2):717-816.
26. The Medical Letter: Oral Contraceptives and the Risk of Cardiovascular Disease. 25 (Issue 640):69-70.
27. Vandenbroucke 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.
28. Vessey MP, Doll R. Investigation of Relation Between Use of Oral Contraceptives and Thromboembolic Disease. A Further Report. Br Med J 1969;2:651-657.
29. 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.
30. Zhang H, Cui D, Wang B, Han YH, Balimane P, Yang Z, Sinz M, Rodrigues AD. Pharmacokinetic drug interactions involving 17α-ethinylestradiol. A new look to an old drug. Clin Pharmacokinet 2007;46(2):133.157.
31. Rossner S, Frankman O, Marsk L. Effects of Various Low Dose Contraceptive Pills On Serum Lipoproteins in Proceedings of Lipoprotein Metabolism and Endocrine Regulation, Workshop, In: Hessel LW, Krans HMJ, editors. Development in Endocrinology. New York: Elsevier/North Holland Biomedical Press,1979;91-98.
32. Drugs Directorate Guidelines. Directions for Use of Estrogen-Progestin Combination Oral

Contraceptives. 1995.

33. Tyrer L. (1994). Fertility Control 2nd Ed. Pearl River NY: Parthenon Publishing. Oral Contraceptive practice. p. 97-113.
34. World Health Organization: Improving access to quality care in family planning: Medical eligibility criteria for contraceptive use. 2nd Ed. Geneva, Switzerland. 2000. p. 2-10.
35. Guillebaud J. (1999). Contraception: Your Questions Answered. 3rd Edition. Edinburg, UK: Churchill Livingstone. p. 234-254.
36. 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.
37. Product Monograph - PrTRI-CYCLEN® (norgestimate and ethinyl estradiol tablets), Janssen Inc. Submission Control no. 235045, Date of Revision March 3, 2020.

PART III: CONSUMER INFORMATION

Pr Tri-Cira 21

Pr Tri-Cira 28

Norgestimate and Ethinyl Estradiol tablets

Apotex Standard

This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about **Tri-Cira 21 and 28.** 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
- to treat moderate acne

What it does:

Tri-Cira 21 and 28 are a birth control pill (oral contraceptive) that contains two female sex hormones (norgestimate 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 Tri-Cira 21 and 28 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
- 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
- pancreatitis (inflammation of the pancreas) associated with high levels of fatty substance (triglycerides) in your blood
- very high blood cholesterol or triglyceride levels
- pregnant or if pregnancy is suspected
- you are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir for the treatment of Hepatitis C
- allergic reaction to ethinyl estradiol, norgestimate or to any of the other ingredients in Tri-Cira 21 and 28 (see **What the nonmedicinal ingredients are**).

What the medicinal ingredients are:

Norgestimate and ethinyl estradiol

What the nonmedicinal ingredients are:
WHITE tablet: Hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.

LIGHT BLUE tablet: FD&C Blue No.1 Aluminum Lake, FD&C Blue No.2 Aluminum Lake, FD&C Yellow No. 5 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.

BLUE tablet: FD&C Blue No.1 Aluminum Lake, FD&C Blue No.2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.

GREEN tablet: FD&C Blue No. 2 Aluminum Lake, hydroxypropyl methylcellulose, iron oxide yellow, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polysorbate, sodium croscarmellose, titanium dioxide and triacetin.

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

21-day Pill Pack contains: 7 WHITE tablets each containing 0.18 mg norgestimate and 0.035 mg ethinyl estradiol, 7 LIGHT BLUE tablets each containing 0.215 mg norgestimate and 0.035 mg ethinyl estradiol and 7 BLUE tablets each containing 0.25 mg norgestimate and 0.035 mg ethinyl estradiol

28-day Pill Pack contains: 7 WHITE tablets each containing 0.18 mg norgestimate and 0.035 mg ethinyl estradiol, 7 LIGHT BLUE tablets each containing 0.215 mg norgestimate and 0.035 mg ethinyl estradiol, 7 BLUE tablets each containing 0.25 mg norgestimate 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 Tri-Cira 21 and 28, 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 Tri-Cira 21 and 28 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 Tri-Cira 21 and 28 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 Tri-Cira 21 and 28 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 Tri-Cira 21 and 28, 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)
- are very overweight
- cigarette smoking
- migraine headaches
- heart or kidney disease
- epilepsy
- depression
- fibroid tumours of the uterus
- wear contact lenses
- pregnant or breast-feeding
- systemic lupus erythematosus
- inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- hemolytic uremic syndrome
- sickle cell disease
- problems with the valves in your heart and/or have an irregular heart rhythm
- hereditary angioedema or have had episodes of swelling in body parts such as hands, feet, face, or airway passages
- gallbladder or pancreatic disease
- history of jaundice (i.e., yellowing of skin and eyes) or other liver disease
- have or have previously had chloasmas (yellow-brownish patches on your skin, pigment spots during pregnancy, especially on your face). If this happens, avoid sunlight and UV radiation

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

Tri-Cira 21 and 28 are **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 Tri-Cira 21 and 28.

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 Tri-Cira 21 and 28 four weeks before surgery and not using Tri-Cira 21 and 28 for a time period after surgery or during bed rest.

Tri-Cira 21 and 28 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 Tri-Cira 21 and 28 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 Tri-Cira 21 and 28 outweigh the risks, you should be aware of the following risks:

THE RISKS OF USING TRI-CIRA 21 AND 28

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

Women who use hormonal contraceptives like Tri-Cira 21 and 28 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 Tri-Cira 21 and 28 for a long time the chance of getting cervical cancer may be slightly higher. This finding may not be caused by the pill itself but may be related to sexual behaviour and other factors.

4. Gallbladder disease

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

5. Liver tumours

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

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

6. Use during pregnancy

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

7. Use after pregnancy, miscarriage or an abortion

Your doctor will advise you of the appropriate time to start the use of Tri-Cira 21 and 28 after childbirth, miscarriage, or therapeutic abortion.

8. Pregnancy after stopping Tri-Cira 21 and 28

You will have a menstrual period when you stop taking Tri-Cira 21 and 28. 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 Tri-Cira 21 and 28 include:

- drugs used for epilepsy (e.g., primidone, phenytoin, phenobarbital, carbamazepine, lamotrigine, oxcarbazepine, topiramate, rufinamide)
- drugs used for tuberculosis (e.g., rifampin and rifabutin)
- antibiotics (e.g., penicillins, tetracyclines) for infectious diseases
- (fos)aprepitant (used for nausea)
- selegiline (used for Parkinson’s disease)

- tizanidine (used for multiple sclerosis [MS])
- drugs used for HIV/AIDS (e.g., atazanavir, indinavir, nelfinavir, ritonavir, ritonavir-boosted protease inhibitors, etravirine, nevirapine), or HIV/AIDS combination medications that contain cobicistat
- boceprevir, telaprevir (used to treat Hepatitis C)
- ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (used to treat Hepatitis C)
- salicylic acid
- bosentan (used for pulmonary hypertension which is high blood pressure in the blood vessels between the heart and the lungs)
- theophylline (used for asthma)
- stimulants (e.g., modafinil)
- lipid-lowering drugs (e.g., atorvastatin, rosuvastatin,)
- colesevelam
- cyclosporine (an immunosuppressive drug to prevent graft rejection after transplantation)
- omeprazole (used for gastric wound and heart burn)
- 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 (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 Tri-Cira 21 and 28
- grapefruit juice.

Tri-Cira 21 and 28 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 Tri-Cira 21 and 28. 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 Tri-Cira 21 and 28. Talk to your doctor for more information about drug interactions.

PROPER USE OF THIS MEDICATION

HOW TO TAKE TRI-CIRA 21 AND 28:
1. READ THESE DIRECTIONS

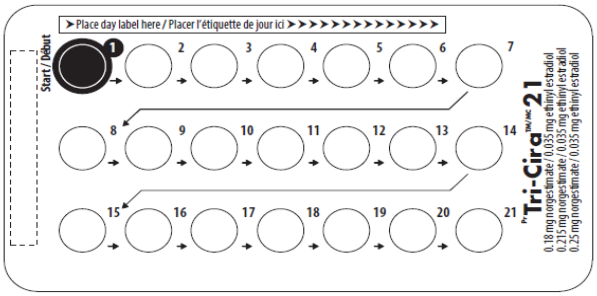
- before you start taking your pills, and
- any time you are not sure what to do.

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

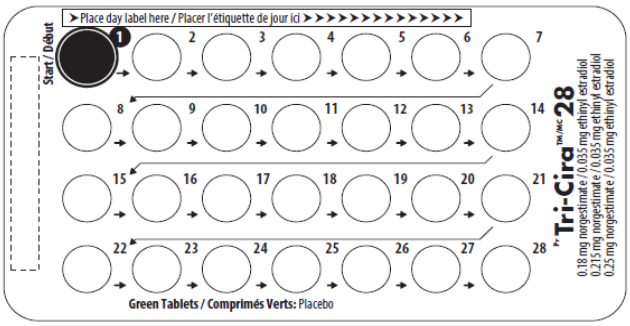
- 21-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week
  OR
- 28-PILL PACK: 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

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

21-Day PILL Package



28-Day PILL 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 21-DAY OR 28-DAY PILL PACKS. FOLLOW THESE INSTRUCTIONS CAREFULLY:

1. **For Day 1 start:** Label the Pill Pack 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 Pill Pack 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: 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 Pill Pack 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 Pill Pack.
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.

If you think you have taken too much Tri-Cira 21 and 28, contact your healthcare professional, 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**
First Two Weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**First Two Weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**
MISS THREE OR MORE PILLS IN A ROW	**MISS THREE OR MORE PILLS IN A ROW**
Any Time in the Cycle 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Any Time in the Cycle** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**

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

Always be sure you have on hand:

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

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

NON-CONTRACEPTIVE BENEFITS OF BIRTH CONTROL PILLS

Several health advantages have been linked to the use of birth control pills.

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

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

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

The following additional symptoms have been reported in women taking hormonal contraceptives in general:

- difficulty wearing contact lenses
- vaginal irritation or infections
- 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, rash
- diarrhea, flatulence
- blood clots in a vein – this can lead to blocked blood vessels in the liver, which cause an enlarged liver, pain and swelling from build-up of fluid around the gut (Budd-Chiari syndrome)

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

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

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

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 get immedia te medi cal help
		Only if severe	In all cases	
	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)			✓

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 get immedia te medi cal help
		Only if severe	In all cases	
Very Rare	A severe allergic reaction which may include swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing.			✓

This is not a complete list of side effects. For any unexpected effects while taking Tri-Cira 21 and 28, contact your doctor or pharmacist.

HOW TO STORE IT

Store in original packaging, between 15°C to 30°C. Leave contents in carton until time of use to protect from light. Keep out of the sight and reach of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Tri-Cira 21 and 28:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp). Find the Consumer Information on the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9

Date prepared: November 17, 2020