Product Monograph

Including Patient Medication Information

PrTRI-CIRA 21

PrTRI-CIRA 28

Norgestimate and Ethinyl Estradiol Tablets

For oral use

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.
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Date of Authorization:
2025-08-21

Control Number: 294283

Recent Major Label Changes

None at time of the most recent authorization	

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

TRI-CIRA 21 and TRI-CIRA 28 (Norgestimate and Ethinyl Estradiol 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.

1.1. Pediatrics

Pediatrics (< 16 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TRI-CIRA 21 and TRI-CIRA 28 in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. See 7.1.3 Pediatrics.

1.2. Geriatrics

Geriatrics (> 65 years of age): TRI-CIRA 21 and TRI-CIRA 28 are not indicated for use in post-menopausal women. See 7.1.4 Geriatrics.

2. Contraindications

TRI-CIRA 21 and TRI-CIRA 28 are contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.
- 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 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).
- 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

3. Serious Warnings and Precautions Box

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 TRI-CIRA 28, should not be used by women who are over 35 years of age and smoke (see 7 Warnings and Precautions, Cardiovascular).

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.

4. Dosage and Administration

4.1. Dosing Considerations

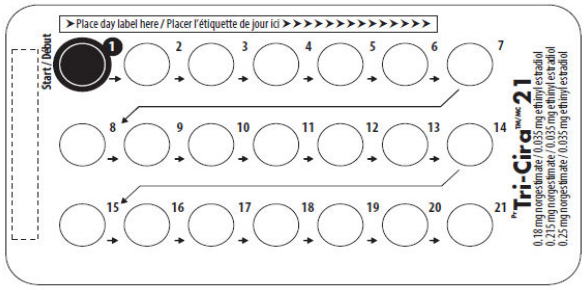
INFORMATION TO PATIENTS ON HOW TO TAKE THE BIRTH CONTROL PILL

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:

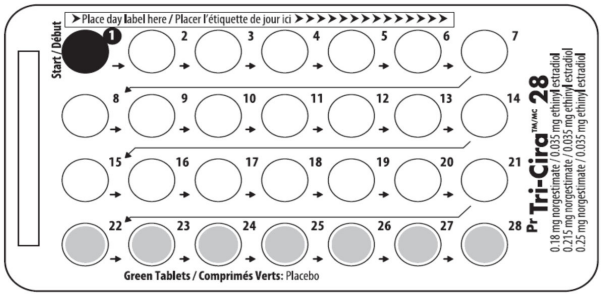
- **21-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week or
- **28-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

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 healthcare professional 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 healthcare professional 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 healthcare professional or clinic.
10. **IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW**, talk to your healthcare professional 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 HEALTHCARE PROFESSIONAL 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 healthcare professional 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.

4.2. Recommended Dose and Dosage Adjustment

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 healthcare professional. You will always begin taking your pill on this day of the week. Your healthcare professional 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.

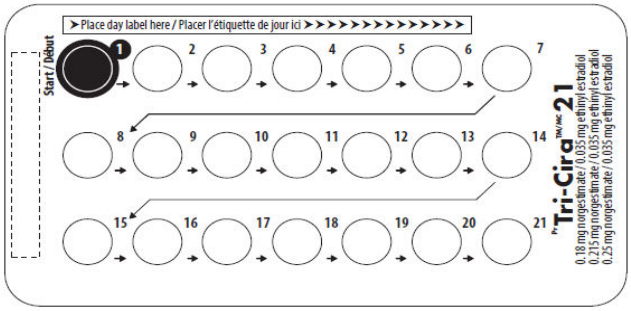
FOLLOW THESE INSTRUCTIONS CAREFULLY:

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.

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

21-Day Pill Pack

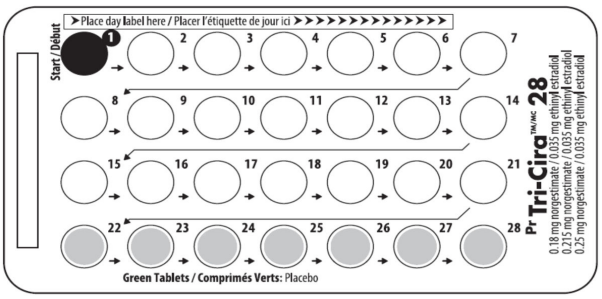


example, if your first day of menstruation is Saturday, place the day label that starts with **WED** in the space provided.

OR

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

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 DAYUNTIL 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.

4.4. Administration

Special Notes on Administration

Use after childbirth:

TRI-CIRA 21 and TRI-CIRA 28 should be started no earlier than 4 weeks postpartum in women who elect not to breastfeed due to increased risk of thromboembolism (see 7 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 TRI-CIRA 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 TRI-CIRA 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.

4.5. Missed Dose

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 HEALTHCARE PROFESSIONAL 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 HEALTHCARE PROFESSIONAL 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.	**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 HEALTHCARE PROFESSIONAL OR CLINIC.	**IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR HEALTHCARE PROFESSIONAL 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 HEALTHCARE PROFESSIONAL OR CLINIC about ways to make pill-taking easier or about using another method of birth control.

5. Overdose

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

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-Medicinal Ingredients
Oral	WHITE Tablets, 0.18 mg of norgestimate and 0.035 mg of ethinyl estradiol	Hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.
	LIGHT BLUE Tablets, 0.215 mg of norgestimate and 0.035 mg of 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.
	BLUE Tablets, 0.25 mg of norgestimate and 0.035 mg of 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.
	GREEN Tablets	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

Description

TRI-CIRA 21 and TRI-CIRA 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.

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

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 7 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, hemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn’s disease or ulcerative colitis), sickle cell disease, valvular heart disease and atrial fibrillation.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COCs has not been firmly established: porphyria, systemic lupus erythematosus, hemolytic uremic syndrome, Sydenham’s chorea, herpes gestationis and otosclerosis-related hearing loss.

The information contained in this section is principally from studies carried out in women who used 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 Genotoxicity

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 TRI-CIRA 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 2 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 2 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.

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 to 2% of cases.

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 4.4 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 4.4 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 TRI-CIRA 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 2 Contraindications and 9 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 TRI-CIRA 28.

Immune

Angioedema
Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

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.

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 2 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.

Perioperative 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.

Reproductive Health

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 9 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.

7.1. Special Populations

7.1.1. Pregnancy

TRI-CIRA 21 and TRI-CIRA 28 are contraindicated during pregnancy. If pregnancy occurs during treatment with TRI-CIRA 21 and TRI-CIRA 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.

7.1.2. Breastfeeding

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 TRI-CIRA 28 or other combination hormonal contraceptives but to use other forms of contraception until the child is fully weaned.

7.1.3. Pediatrics

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.

7.1.4. Geriatrics

Geriatrics (> 65 years of age): TRI-CIRA 21 and TRI-CIRA 28 are not indicated for use in post-menopausal women.

8. Adverse Reactions

8.1. Adverse 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:

Cardiac Disorders:	Edema
	Slight rise of blood pressure
Ear and Labyrinth Disorders:	Auditory disturbances
Eye Disorders:	Intolerance to contact lenses
	Change in corneal curvature (steepening)
	Cataracts
	Optic neuritis
	Retinal thrombosis
Gastrointestinal Disorders:	Gastrointestinal symptoms (such as abdominal cramps and bloating)
	Colitis
	Pancreatitis
Hepatobiliary Disorders:	Cholestatic jaundice
	Budd-Chiari syndrome
Metabolism and Nutrition Disorders:	Reduced tolerance to carbohydrates
	Change in weight (increase or decrease)
	Changes in appetite
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps):	Malignant hepatic tumours
	Cervical cancer
	Increase in size of uterine leiomyomata
	Breast cancer
Nervous System Disorders:	Migraine
	Depression
	Headache
	Nervousness

	Dizziness
	Changes in libido
	Chorea
Renal and Urinary Disorders:	Impaired renal function
	Hemolytic uremic syndrome
	Cystitis-like syndrome
Reproductive System and Breast Disorders:	Breast pain, tenderness, enlargement, and secretion
	Possible diminution in lactation when given immediately Postpartum
	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
Respiratory, Thoracic and Mediastinal Disorders:	Rhinitis
Skin and Subcutaneous Tissue Disorders:	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

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

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

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.

8.3. Less Common Clinical Trial Adverse Reactions

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 4.

Table 4 - 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
Investigations Weight decreased
Metabolism and Nutrition Disorders Increased appetite, Decreased appetite, Weight fluctuation, Appetite disorder
Psychiatric Disorders Libido disorder
Reproductive System and Breast Disorders Breast enlargement, Breast discharge, Menstruation irregular, Menstrual disorder

Skin and Subcutaneous Tissue Disorders Alopecia, Rash popular, Skin discolouration, Erythema
Vascular Disorders Hypertension

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 2 and 4, 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.

8.5. Post-Market Adverse Reactions

Adverse drug reactions first identified during post-marketing experience with norgestimate/ethinyl estradiol (NGM/EE) are included in Table 5.

Table 5 - Adverse Drug Reactions Identified During Post-Marketing Experience with NGM/EE from Spontaneous Reports

System/Organ Class Adverse Reaction
Cardiac Disorders Myocardial infarction, Tachycardia, Palpitations
Ear and Labyrinth Disorders Vertigo
Eye Disorders Retinal vascular thrombosis, Visual impairment, Dry eye, Contact lens intolerance
Gastrointestinal Disorders Pancreatitis, Abdominal distension, Diarrhea, Constipation
General Disorders and Administration Site Conditions Chest pain, Asthenic conditions
Hepatobiliary Disorders Hepatitis
Immune System Disorders Anaphylactic reaction, Hypersensitivity
Infections and Infestations Urinary tract infection
Metabolism and Nutrition Disorders

System/Organ Class Adverse Reaction
Dyslipidaemia
Musculoskeletal, Connective Tissue, and Bone Disorders
Muscle spasms, Pain in extremity, Myalgia, Back pain
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
Nervous System Disorders
Cerebrovascular accident, Syncope, Convulsion, Paraesthesia, Dizziness
Psychiatric Disorders
Anxiety, Insomnia
Reproductive System and Breast Disorders
Ovarian cyst, Suppressed lactation, Vulvovaginal dryness
Respiratory, Thoracic and Mediastinal Disorders
Pulmonary embolism, Dyspnea
Skin and Subcutaneous Tissue Disorders
Angioedema, Erythema nodosum, Hirsutism, Night sweats, Hyperhidrosis, Photosensitivity reaction, Urticaria, Pruritus, Acne
Vascular Disorders
Arterial thromboembolism, Deep vein thrombosis, Hot flush, Venous thrombosis[1]

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

9. Drug Interactions

9.1. Serious Drug Interactions

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 2 Contraindications and 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).

9.2. Drug Interactions Overview

The concurrent administration of oral contraceptives with other drugs may result in an altered response

to either agent (see Tables 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.

9.4. Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6 – Established or Potential Drug-Drug Interactions

Non-proprietary name of the drug products	Effect	Clinical comment
Alcohol	Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II Adrenoreceptor Agents Clonidine	Sedation effect increased.	Use with caution.
Tizanidine	May lead to an increase in tizanidine plasma levels (due to CYP inhibition).	Use with caution.
Antacids	Decreased intestinal absorption of progestins.	Dose two hours apart.
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.

Non-proprietary name of the drug products	Effect	Clinical comment
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.
Lamotrigine	Significantly decreased lamotrigine levels (due to induction of lamotrigine glucuronidation) may lead to breakthrough seizures.	Adjust dose of drug if necessary.
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.	
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.

Non-proprietary name of the drug products	Effect	Clinical comment
Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
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.
Antifungals Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Voriconazole	May lead to an increase in voriconazole plasma levels (due to CYP inhibition).	Use with caution.
Antihypertensive Agents Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen OC or use another method.
Beta blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
Antipyrine	Impaired metabolism.	Decrease dose of drug.
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	Adjust dose of drug as necessary.

Non-proprietary name of the drug products	Effect	Clinical comment
	decreased response to these drugs.	Discontinuing OCs can result in excessive drug activity.
Bosentan	Induction of hepatic microsomal enzymes.	Consider switching to a non-hormonal contraceptive method or adding a barrier method to oral contraceptive therapy.
Caffeine	The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine.	Use with caution.
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.
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.
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.
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

Non-proprietary name of the drug products	Effect	Clinical comment
Folic Acid	OCs have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
(fos)aprepitant	Induction of hepatic microsomal enzymes.	Use 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.
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.
Non-nucleoside Reverse Transcriptase Inhibitors Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another method.
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.
Phenylbutazone **Antihistamines** **Analgesics** **Antimigraine preparations** **Vitamin E** **Modafinil**	Reduced OC efficacy has been reported. Remains to be confirmed.	

Non-proprietary name of the drug products	Effect	Clinical comment
Proton Pump Inhibitors Omeprazole	May lead to an increase in omeprazole plasma levels (due to CYP inhibition).	Use with caution.
Sedatives and Hypnotics Benzodiazepines Barbiturates Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.
Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
Temazepam	Decreased temazepam plasma level (due to induction of glucuronidation).	Use with caution.
Selegiline	May lead to an increase in selegiline plasma levels (due to CYP inhibition).	Avoid concomitant use.
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.

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 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)

9.5. Drug-Food Interactions

Grapefruit juice may increase the plasma levels of ethinyl estradiol if co-administered.

9.6. 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.

9.7. 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.

10. Clinical Pharmacology

10.1. Mechanism of Action

Oral Contraception

The primary mechanism of action of TRI-CIRA 21 and TRI-CIRA 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.

10.2. 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.

Oral Contraception

Norgestimate, alone and in combination with ethinyl estradiol, is an effective antiovulatory agent. It is moderately potent in the standard *in vivo* progestational assay which measures endometrial proliferation in rabbits, and it effectively blocks ovulation in rats, hamsters and rabbits. In rats, this

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

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.

10.3. 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:

Table 7 – Pharmacokinetic Parameters of Norgestimate and Ethinyl Estradiol

		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 - Ethinyl Estradiol	6.5 hr 7.3 hr	7.6 hr 4.3 hr	5.3 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), elimination is primarily renal.

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 TRI-CIRA 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.

11. Storage, Stability, and Disposal

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 reach and sight of children.

Part 2: Scientific Information

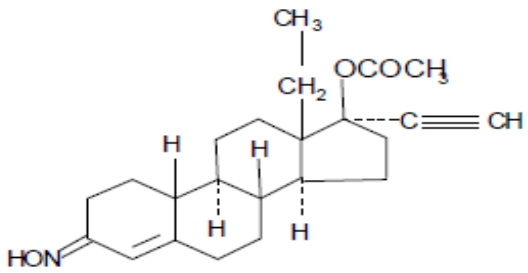
13. Pharmaceutical Information

(i) Drug Substance

Norgestimate:

Non-proprietary name of the drug substance:	Norgestimate
Chemical name:	18,19-dinor-17-pregn-4-en-20-yn-3-one, 17-(acetyloxy)-13-ethyl-, oxime, (17α)-(+)-
Molecular formula and molecular mass:	C_{23} H_{31} NO_3 and 369.50 g/mol

Structural formula:



Physicochemical properties: Norgestimate is a white or almost white powder.
Melting range/point: 214°C and 218°C.

Solubility:

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

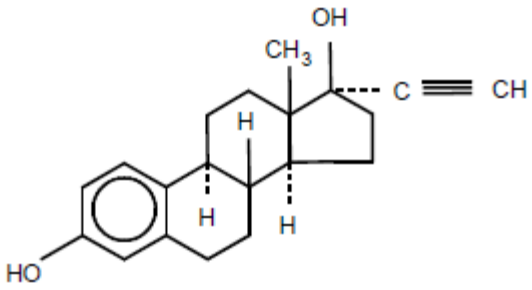
No pKa was determined because of its poor solubility in water.

Optical Rotation: +42.0° and +50.0°

(ii) Drug Substance

Ethinyl Estradiol:

Non-proprietary name of the drug substance:	Ethinyl Estradiol
Chemical name:	19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol
Molecular formula and molecular mass:	$C_{20}H_{24}O_2$ and 296.40 g/mol
Structural formula:	



Physicochemical properties:	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.

14. Clinical Trials

14.1. Clinical Trials by Indication

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 8). 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 8 - 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:

Table 9 - 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.

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.

14.2. Comparative Bioavailability Studies

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.

Table 10 – Summary Table of the Comparative Bioavailability Data - Norgestimate

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.

Table 11 – Summary Table of the Comparative Bioavailability Data – Ethinyl Estradiol

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.

16. Non-Clinical Toxicology

General toxicology

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

Acute Toxicity Studies

Mice

In HaM/1CR CD-1 mice oral norgestimate alone and oral norgestimate + ethinyl estradiol (5:1) 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 5 g/kg of the combination than in controls. Ethinyl estradiol alone had an oral LD_{50} of 5.3 g/kg for males and 3.2 g/kg for females. Drug was administered suspended in carboxymethylcellulose.

Dogs

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

<u>Monkeys</u>

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.

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 fib
rosis 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 and developmental toxicology

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.

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 to 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.

17. Supporting Product Monographs

1. PrTRI-CYCLEN® (norgestimate and ethinyl estradiol tablets), control 235045, product monograph, Janssen Inc. 2020-03-03.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTRI-CIRA 21

PrTRI-CIRA 28

Norgestimate and Ethinyl Estradiol Tablets

This patient medication information is written for the person who will be taking **TRI-CIRA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TRI-CIRA**, talk to a healthcare professional.

Serious Warnings and Precautions

- **Smoking Warning:** Cigarette smoking increases the risk of serious heart and blood vessel problems. This risk goes up as you get older, especially if you are over 35 years old and use hormonal birth control like TRI-CIRA. The more you smoke, the higher the risk. Because of this, women over 35 who smoke should not use TRI-CIRA.
- **STI Protection:** Birth control pills like TRI-CIRA do not protect against sexually transmitted infections (STIs), including HIV and AIDS. To protect yourself from STIs, use condoms in addition to your birth control pills.

What TRI-CIRA 21 and TRI-CIRA 28 are used for:

TRI-CIRA 21 and TRI-CIRA 28 are used:

- to prevent pregnancy
- to treat moderate acne

How TRI-CIRA 21 and TRI-CIRA 28 works:

- TRI-CIRA is birth control pill. It is called a combination oral contraceptive because it contains two female hormones: norgestimate and ethinyl estradiol. When taken as directed by your healthcare professional, TRI-CIRA is effective at preventing pregnancy.
- TRI-CIRA helps prevent pregnancy in two ways:
  - it stops your ovaries from releasing an egg each month (this is called ovulation).
  - it changes the mucus in your cervix, making it harder for sperm to move through the uterus (womb).

<u>Effectiveness of Birth Control Pills:</u>
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 ingredients in TRI-CIRA 21 and TRI-CIRA 28 are:

Medicinal ingredients: Norgestimate and ethinyl estradiol

Non-medicinal ingredients:
TRI-CIRA 21 and TRI-CIRA 28:

- **White** tablets: Hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.
- **Light blue** tablets and **Blue** tablets:
    - **Both tablets:** FD&C Blue No.1 Aluminum Lake, FD&C Blue No.2 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium croscarmellose and titanium dioxide.
    - **Light Blue tablets only:** FD&C Yellow No. 5 Aluminum Lake
    - **Blue tablets only:** FD&C Yellow No. 6 Aluminum Lake

TRI-CIRA 28 only:

- **Green** tablets: 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

TRI-CIRA 21 and TRI-CIRA 28 comes in the following dosage forms:

TRI-CIRA 21 and TRI-CIRA 28 comes in two types of packages:

- **21-Day Pill Pack (TRI-CIRA 21)**
- **28-Day Pill Pack (TRI-CIRA 28)**

TRI-CIRA 21 (21-Day Pill Pack) and TRI-CIRA 28 (28-Day Pill Pack)

Each pack contains **21 active tablets**, taken once daily. These tablets come in **three different colors**, each with a slightly different hormone dose:

- **7 white to off-white tablets** – each contains:
  - 0.18 mg norgestimate
  - 0.035 mg ethinyl estradiol
- **7 light blue tablets** – each contains:
  - 0.215 mg norgestimate
  - 0.035 mg ethinyl estradiol
- **7 blue tablets** – each contains:
  - 0.25 mg norgestimate
  - 0.035 mg ethinyl estradiol

TRI-CIRA 28 (28-Day Pill Pack only)

In addition to the 21 active tablets listed above, this pack includes:

- **7 green tablets** – These are "reminder" (inactive) pills with no hormones. They help maintain the habit of taking a pill every day.

Do not use TRI-CIRA 21 and TRI-CIRA 28 if:

- you are allergic to ethinyl estradiol, norgestimate, or any other ingredient in TRI-CIRA 21 or TRI-CIRA 28 (see The ingredients in TRI-CIRA 21 and TRI-CIRA 28 are:)
- you have serious blood clot, heart or blood vessel problems:
  - you have or had a blood clot in your legs (deep vein thrombosis), lungs (pulmonary embolism), eyes, or elsewhere.
  - you have or had inflammation of a vein (thrombophlebitis).
  - you have had a stroke, heart attack, chest pain (angina), or a condition that may be an early warning sign of a stroke, such as a mini-stroke (transient ischemic attack).
  - you have or had heart valve disease with complications.
  - you have a blood clotting disorder.
  - you have trouble seeing due to a blood vessel problem in the eye.
  - you have severe high blood pressure or high blood pressure that is not under control.
- you are over 35 and smoke (this increases your risk of serious heart problems).
- you have very high levels of fat in your blood, such as cholesterol or triglycerides.
- you have unusual levels of fat-carrying proteins (lipoproteins) in your blood.
- you are scheduled for major surgery or will be on bed rest for a long time.
- you have or had migraine with visual or sensory symptoms (like flashing lights or tingling).
- you have liver or pancreas problems:
  - liver disease, including hepatitis C, or a history of liver growths (tumors).
  - jaundice (yellowing of the skin or eyes).

    - pancreatitis (inflammation of the pancreas) with high triglyceride levels (a type of fat in the blood).
- you have or think you have breast cancer, cancer of the uterus lining (endometrium), or any hormone-sensitive cancer.
- you have unusual vaginal bleeding without a known reason.
- you have diabetes with complications (affecting your kidneys, eyes, nerves, or blood vessels).
- you are pregnant or think you might be.
- you are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (used to treat hepatitis C). Do **not** use TRI-CIRA if you are taking the medications listed above for Hepatitis C. Taking these together can cause serious liver problems, including increased liver enzymes. Your healthcare professional will tell you when it is safe to start, stop or restart TRI-CIRA 21 or TRI-CIRA 28.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRI-CIRA 21 and TRI-CIRA 28. Talk about any health conditions or problems you may have, including if you:

- have or had breast problems (like lumps) or if a close relative (like a parent or sibling) had breast cancer
- have diabetes
- have high blood pressure
- have high cholesterol or triglycerides
- are very overweight
- smoke
- get migraine headaches
- have heart or kidney disease
- have epilepsy (seizures)
- have depression
- have fibroids (non-cancerous growths) in your uterus
- wear contact lenses
- are pregnant or breastfeeding
- have lupus
- have bowel disease like Crohn's disease or ulcerative colitis
- have hemolytic uremic syndrome – a condition that can cause low blood cells and kidney problems
- have sickle cell disease – a blood disorder where red blood cells are shaped like a sickle
- have heart valve problems and/or an irregular heartbeat
- have hereditary angioedema – a condition you are born with that causes sudden swelling in areas like the face, hands, feet, stomach, or throat
- have gallbladder or pancreas problems
- have or had jaundice (yellowing of the skin or eyes) or liver disease
- have or had chloasma (brown patches on the skin, especially during pregnancy). If so, avoid sunlight and UV rays
- have close relatives (like a parent or sibling) who had blood clots, heart attacks, or strokes
- are lactose intolerant or have rare conditions like:
    - galactose intolerance
    - lapp lactase deficiency
    - glucose-galactose malabsorption

TRI-CIRA 21 and TRI-CIRA 28 contain lactose

Other warnings you should know about:

- **Blood clots in legs, lungs, heart, eyes or brain**
  - some women who use hormonal birth control (like the pill, patch, or ring) have a higher chance of developing blood clots, especially during the first year of use.
  - blood clots are a rare but serious side effect.
  - they can form in different parts of the body and may lead to vision problems or blindness. damage or loss of a limb, in rare cases, death
  - while you are taking TRI-CIRA 21 or TRI-CIRA 28, contact your healthcare professional right away if you notice any of these signs of a blood clot:
    - sharp chest pain
    - coughing up blood
    - sudden shortness of breath
    - pain and/or swelling in your calf
    - crushing chest pain or chest heaviness
    - sudden severe or worsening headache
    - dizziness or fainting
    - changes in vision
    - changes in speech
    - weakness or numbness in an arm or leg
    - sudden pain, swelling, and blue discoloration of an arm or leg
- **Cancer Risks**

Using birth control pills may increase the risk of certain cancers, like breast, cervical, and liver cancer.

- **Breast Cancer**
  - your risk of breast cancer increases with age and if you have a family history (mother or sister with breast cancer). Other risk factors include being overweight, never having children, or having your first full-term pregnancy later in life.
  - do not use birth control pills if you currently have or have had breast cancer. The hormones in the pills can affect some cancers.
  - some women who use birth control pills may have a higher risk of developing breast cancer before menopause, especially if they started using the pill at a young age or used it for more than 8 years.
  - In a few women, the pill may speed up the growth of a breast cancer that has not been found yet.
  - the overall risk is small, but it's important to have your breasts checked by a healthcare professional at least once a year.
  - while taking TRI-CIRA, check your breasts regularly and contact your healthcare professional if you notice:
    - dimpling or sinking of the skin
    - changes in the nipple
    - any lumps you can see or feel
- **Cervical Cancer**
  - women who use birth control pills may have a higher chance of getting cervical cancer.

        - this may be linked to other factors, like infection with HPV (Human Papillomavirus), which is a major cause of cervical cancer. However, the pill itself may also play a role in increasing this risk.
    - **Liver Cancer**
        - birth control pills may be linked to rare cases of liver cancer or liver tumors.
        - the risk increases the longer you use the pill, but these tumors are very rare.
        - do not use TRI-CIRA if you have a history of liver tumors (cancerous or non-cancerous).
        - contact your healthcare professional right away if you feel severe abdominal pain or notice a lump in your abdomen
- **Gallbladder disease**
    - women who take birth control pills have a higher chance of getting gallbladder disease that may need surgery.
    - the risk is:
        - highest in the first year of using the pill.
        - increases the longer the pill is used.
- **Vaginal Bleeding**
    - some women may have breakthrough bleeding or spotting (light bleeding between periods) while using birth control pills like TRI-CIRA 21 and TRI-CIRA 28.
        - this is most common in the first 3 months after starting the pill.
        - if the bleeding is heavy or doesn't stop, contact your healthcare professional.
    - while taking TRI-CIRA 21 or TRI-CIRA 28, you may not get your period every month.
        - if you miss a period and did not take the pill as directed, take a pregnancy test to make sure you are not pregnant.
    - if you go more than 6 months without a period, talk to your healthcare professional —especially if you also notice breast discharge.
- **Pregnancy, Breastfeeding, Miscarriage and Abortions**
    - **Use during pregnancy**
        - do not take birth control pills if you think you might be pregnant.
        - the pill will not stop a pregnancy that has already started.
        - there is no strong evidence that taking the pill by mistake early in pregnancy will harm the baby.
        - always check with your healthcare professional about any medications you are taking during pregnancy.
    - **Use after pregnancy, miscarriage or an abortion**
        - your healthcare professional will tell you when it is safe to start using TRI-CIRA after childbirth, miscarriage, or an abortion.
    - **Pregnancy after stopping TRI-CIRA 21 or TRI-CIRA 28**
        - when you stop taking TRI-CIRA 21 or TRI-CIRA 28, you will usually have a menstrual period.
        - wait until after your next period—usually in about 4 to 6 weeks—before trying to get pregnant.
        - talk to your healthcare professional about other birth control options you can use while you wait
    - **Use while breast-feeding**
        - if you are breast-feeding, talk to your healthcare professional before starting birth control pills.

        - other types of birth control may be a better choice while you are breastfeeding.
        - the hormones in the pill can sometimes reduce how much breast milk you make.
        - some side effects have been reported in breastfed babies, like yellowing of the skin (called jaundice) and breast swelling.
        - it is best to wait until you have completely weaned your baby before starting TRI-CIRA 21 or TRI-CIRA 28.
- **Skin Conditions**
    - while using TRI-CIRA 21 or TRI-CIRA 28, you may develop chloasma—yellowish-brown patches on your skin, especially on your face.
    - this is more likely if you had chloasma during pregnancy, also called the "mask of pregnancy."
    - if you have or had chloasma:
        - avoid sun exposure while using TRI-CIRA 21 or TRI-CIRA 28.
        - sunlight contains ultraviolet (UV) rays that can make the patches worse or burn the skin
        - use sunscreen, wear protective clothing, and stay in the shade when possible**.**
- **Surgery or medical treatment**
    - always tell any healthcare professional that you are taking this birth control.
    - let your healthcare team know if you are scheduled for lab tests—this medication can affect some results.
    - before major surgery, talk to your healthcare team. You may need to stop the pill 4 weeks before and wait to restart it after recovery or bed rest.
- **Check-Ups and Tests**
    - before starting TRI-CIRA 21 or TRI-CIRA 28, your healthcare professional will:
        - do a physical exam, including checking your breasts, liver, arms, and legs.
        - perform a pelvic exam.
        - ask about your personal and family health history.
        - measure your blood pressure and may order blood tests.
    - while taking TRI-CIRA 21 or TRI-CIRA 28, you will need regular check-ups:
        - your first check-up should be about 3 months after starting TRI-CIRA 21 or TRI-CIRA 28.
        - after that, you will usually have a check-up once a year.
        - these visits may include:
            - a physical and internal exam.
            - blood pressure checks and blood tests.
    - If you are scheduled for any lab tests, tell your healthcare professional you are taking TRI-CIRA 21 or TRI-CIRA 28. Birth control pills can affect some test results.
- **When TRI-CIRA 21 and TRI-CIRA 28 may Not work as well**

  TRI-CIRA may not prevent pregnancy as well if you:
    - miss pills or take them late.
    - do not follow the instructions from your healthcare professional
    - have stomach problems like vomiting or diarrhea.
    - take certain medications that interfere with how the pill works.

  If any of these happen, talk to your healthcare professional. You may need to use a backup method like condoms

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious Drug Interactions with TRI-CIRA 21 and TRI-CIRA 28

- Do **not** use TRI-CIRA 21 if you are taking certain medications for **Hepatitis C**, such as **ombitasvir, paritaprevir, ritonavir, with or without dasabuvir**. Taking these together can cause **serious liver problems**, including increased liver enzyme levels.
- Your healthcare professional will tell you when it is safe to **start, stop, or restart** TRI-CIRA 21 and TRI-CIRA 28

The following may also interact with TRI-CIRA 21 and TRI-CIRA 28:

- medicines for seizures, like primidone, phenytoin, phenobarbital, carbamazepine, lamotrigine, oxcarbazepine, topiramate, rufinamide
- medicines for tuberculosis, like rifampin and rifabutin
- antibiotics, like penicillins and tetracyclines
- medicines for nausea, like fosaprepitant
- medicines for parkinson's disease, like selegiline
- medicines for multiple sclerosis, like tizanidine
- medicines for HIV/aids, such as atazanavir, indinavir, nelfinavir, ritonavir, ritonavir-boosted protease inhibitors, etravirine, nevirapine, or combination medicines with cobicistat
- medicines for hepatitis C virus including ombitasvir, paritaprevir/ritonavir, with or without dasabuvir, telaprevir
- medicines to treat allergies
- medicines to prevent blood clots
- medicines for asthma, like theophylline
- stimulants (energy-boosting medications), like modafinil
- cholesterol-lowering medicines, like atorvastatin, rosuvastatin, cholestyramine, clofibrate, colesevelam
- medications that lower your immune system, like cyclosporine
- medicines for heartburn, like omeprazole
- antifungals, like griseofulvin, voriconazole, itraconazole, fluconazole, ketoconazole
- herbal remedies, like St. John's wort
- medicines for high blood pressure
- medicines for diabetes and insulin
- anti-inflammatory medicines, like prednisone and prednisolone
- medicines to help you relax and sleep aids, like benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate, temazepam
- pain relievers, like meperidine, morphine, acetaminophen
- antidepressants, like clomipramine
- medicines for mental health conditions, including schizophrenia
- nutritional supplements, like vitamin B12, vitamin C, and folic acid
- antacids (take 2 hours before or after TRI-CIRA)
- medicines to prevent blood clots
- medicines for fever and pain, like acetaminophen, antipyrine, ASA
- medicines for bleeding conditions after surgery, like aminocaproic acid
- medicines for heart failure, like isoproterenol
- grapefruit juice
- antacids, like TUMS
    - can affect how your body absorbs the pill.

- If needed, take the antacid 2 hours before or 2 hours after your birth control pill.
- caffeine and alcohol

How to take TRI-CIRA 21 and TRI-CIRA 28:

1. Read these directions

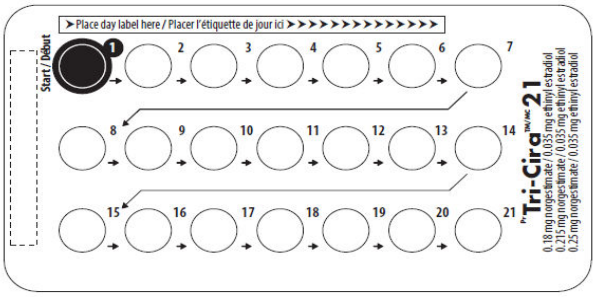
- before you start taking your pills, and
- any time you are not sure what to do.

2. Decide with your healthcare professional what the best day is for you to start taking your first pill. Pick a time of day that will be easy to remember

3. Look at your pill pack

There are two types of pill packs for TRI-CIRA 21 and TRI-CIRA 28

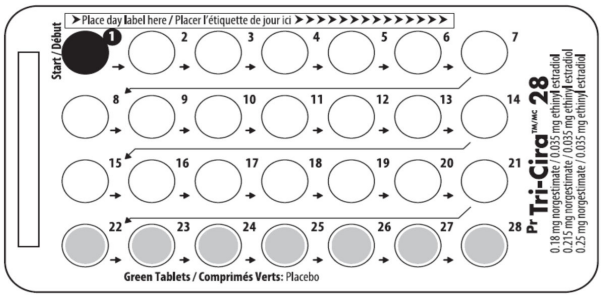
TRI-CIRA 21: 21-Day PILL Package



The TRI-CIRA 21 pack contains 21 active (hormone-containing) tablets, in three different colors:

- 7 white tablets
- 7 light blue tablets
- 7 blue tablets

TRI-CIRA 28: 28-Day PILL Package



The TRI-CIRA 28 pack contains 28 tablets:

- 21 **active tablets** (contain hormones), same as listed above:
  - 7 white tablets
  - 7 light blue tablets
  - 7 blue tablets
- 7 green tablets – These are "reminder" tablets and do not contain hormones.

4. Check the pill pack for:

a. where to start taking pills; and

b. the order to take the pills. Follow the arrows.

5. When to start taking your birth control Pills

- the first day of your period (bleeding) is called Day 1 of your cycle.
- you can start taking your birth control pills any time from Day 1 to Day 6 of your cycle.
- your healthcare professional will help you choose the best day to start

6. Choosing your start day

- Once you choose a start day, you will begin your pills on the **same day of the week each month**. Your healthcare professional might suggest one of these options:
- **Day 1 Start:** Start your pills on the first day of your period.
- **Day 5 Start:** Start your pills on Day 5 of your period.
- **Sunday Start:** Start your pills on the first Sunday after your period begins. If your period starts on a Sunday, start that same day.

7. How to label your pill pack

Choose a **start day** based on your healthcare professional advice**:**

- **Day 1 Start:**
    - Start on the first day of your period.
    - Example if your period starts on Tuesday
        - start your pills on Tuesday
        - place the "TUE" day label on your pill pack where it says "Place day label here."
- **Day 5 Start:**
    - Start on the fifth day after your period begins.
    - Count 5 days starting with the first day of bleeding
    - Example If your period starts on a Saturday:
        - count five days (Sat (1), Sun (2), Mon (3), Tue (4), Wed (5))
        - start your pills on Wednesday
        - place the "WED" day label on your pill pack where it says "Place day label here."
- **Sunday Start:**
    - Start your pills on the first Sunday after your period begins.
    - If your period starts on a Sunday, start your pills that same day.
    - Stick the correct day label (e.g., "SUN") on your pill pack where it says “Place day label here.”

8. Taking your pills

- start with the pill marked “start” (inside the red circle).
- take one pill each day, left to right, following the arrows.
- try to take your pill at the same time every day.
    - link it to a daily habit (like brushing your teeth or eating dinner).
- Do not skip pills, even if:
    - you feel sick.
    - you are bleeding between periods.
    - you are not having sex often.

9. How to take your birth control pills

- **21-Day Pill Package (TRI-CIRA 21)**
    - take 1 pill every day for 21 days.
    - then, stop taking pills for 7 days.
    - you will likely have your period during this break.
    - start a new pack on the 8th day, even if you're still bleeding.
- **28-Day Pill Package (TRI-CIRA 28)**
    - take 1 pill every day for 28 days.

- the first 21 pills have hormones.
- the last 7 pills are reminders (no hormones).
- your period should happen during the last 7 days.
- start a new pack right away—no days off.

10. When you finish a pack

- **21-Day Pill Package (TRI-CIRA 21)**: wait 7 days, then start a new pack.
- **28-Day Pill Package (TRI-CIRA 28)**: start the next pack the very next day—no break.

11. Helpful tips for using birth control pills

- **use backup protection at first:** For the **first 7 days** of your first pill pack, use a second method of birth control (like condoms and spermicide) just in case you forget a pill while getting used to the routine.
- **always let your** healthcare professional know that you are taking birth control pills before any medical treatment.
- you might have spotting (light bleeding) or feel nauseous during the first 3 months.
    - do not stop taking the pills—these symptoms usually go away.
    - if they do not, talk to your healthcare professional.
- always keep these on hand
    - a backup birth control method (like condoms and spermicide).
    - an extra full pack of pills.
- If you vomit, have diarrhea, or take certain medications
    - your pills might not work as well.
    - use backup protection and check with your healthcare professional
- you do not need to stop taking the pill for a rest period.

Usual dose:

- **TRI-CIRA 21:** 21 active pills (with hormones)
    - Take 1 active pill per day for 21 days. Then take no pills for 7 days.
    - Begin a new pack the next day.
- **TRI-CIRA 28:** 21 active pills (with hormones), 7 green pills (inactive or reminder pills)
    - Take 1 active pill per day. When all 21 active pills are done, take 1 green pill per day for 7 days.
    - Begin a new pack the next day.

Overdose:

If you take too many birth control pills, you might experience: nausea, vomiting or vaginal bleeding. Available data from accidental overdoses in children show that these symptoms are usually not dangerous.

If you think you, or a person you are caring for, have taken too much TRI-CIRA 21 and TRI-CIRA 28, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

- The white, light blue or blue pills in TRI-CIRA 21 or TRI-CIRA 28 contain hormones. **Missing them can lead to pregnancy**. The more pills you miss, the more likely you are to get pregnant.
- Missing pills can also cause:
    - spotting or light bleeding, even if you take the missed pills
    - pregnancy especially if you:
        - start a new pack late, or
        - miss pills at the beginning or end of your pack.

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 healthcare professional 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 healthcare professional 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 healthcare professional 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 healthcare professional or clinic.**

- If you are using a 28-Day Pack (TRI-CIRA 28):
    - the last 7 green pills in the pack (Week 4) are reminder pills — they do not contain hormones.
    - If you forget to take any of these 7 green reminder pills, it is okay:
        - just throw away the missed reminder pills.
        - keep taking one pill each day until the pack is empty.
        - you do not need to use a back-up method of birth control.
- If you are not sure what to do about the pills you have missed call your healthcare professional
- always keep these on hand:
    - a back-up method of birth control (like condoms and spermicide), just in case you miss pills.
    - an extra, full pack of pills.
- if you miss more than one pill two months in a row:
  Talk to your healthcare professional. They can help you:
    - find ways to make pill-taking easier, or
    - discuss other birth control options that might work better for you**.**

Possible side effects from using TRI-CIRA 21 and TRI-CIRA 28:
These are not all the possible side effects you may have when taking **TRI-CIRA 21 and TRI-CIRA 28**. If you experience any side effects not listed here, tell your healthcare professional.

The following side effects have been reported in women taking hormonal contraceptives in general:

- tenderness of the breasts
- nausea and vomiting
- weight gain or loss
- acne
- difficulty wearing contact lenses
- vaginal irritation or infections (discomfort, itching, or notice unusual discharge)
- change in skin color (can sometimes be permanent)
- abdominal or back pain
- hair loss or increase in growth
- urinary tract infections or inflammation
- infections that affect your nose, throat, and airways (include illnesses like colds, bronchitis, runny or stuffy nose, sore throat, etc.)
- severe headaches
- insomnia

- changes in hearing
- flu-like symptoms
- allergy, fatigue, fever, rash
- diarrhea, flatulence

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Uncommon			
Arterial thromboembolism (blood clot in the artery)**, myocardial infarction** (heart attack): chest pain or pressure, a heavy or tight feeling in the chest, or pain that spreads to the shoulder, arm, back, jaw, or stomach. You might also feel very full, like you have indigestion or are choking. Other signs include sweating, nausea, dizziness, shortness of breath, feeling very weak or anxious, or having a fast or irregular heartbeat			✓
Breast changes (breast lumps/breast cancer): pain and tenderness, lumps, nipple discharge		✓	
Blood clot in the eye: sudden partial or complete loss of vision			✓
Deep vein thrombosis (blood clot in the leg): swelling of one leg or one foot, pain or tenderness in the leg, difficulty standing or walking, feeling of warmth in the leg, red or discolored skin on the leg, sudden pain, swelling and slight blue discolouration of an extremity			✓
Depression: Persistent sad mood with difficulty sleeping, weakness, lack of energy, fatigue			✓
Edema: unusual swelling of the extremities		✓	
Gallbladder disease: nausea, vomiting, pain on the upper right side of the abdomen, especially after meals, loss of appetite, fever		✓	
High blood pressure: chest pain,		✓	

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
headaches, vision problems, nosebleeds, irregular heartbeat			
Liver problems including liver tumour, jaundice: abnormal liver test, yellowing of the skin or eyes, dark urine, nausea, vomiting, severe pain or lump in the abdomen, loss of appetite, fever, light-coloured bowel movements			✓
Pancreatitis (inflammation of the pancreas): Abdominal pain, nausea or vomiting or lump in the abdomen			✓
Pulmonary embolism (blood clot in the lung): sharp chest pain, coughing of blood, or sudden shortness of breath			✓
Stroke (bleeding or blot clot in the brain): weakness and/or loss of feeling of limbs or face, difficulty speaking, clumsiness, vision loss			✓
Change in vaginal bleeding: heavier or lighter periods, light bleeding between periods, having periods less often, or not having them at all.		✓	
Vaginal infection (inflammation of the vagina or surrounding area)**:** itching, or unusual or increased vaginal discharge	✓		
Very rare			
Severe allergic reaction: swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

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 (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

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 reach and sight of children.

If you want more information about TRI-CIRA 21 and TRI-CIRA 28:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); 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.

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