PRODUCT MONOGRAPH

PrTRIQUILAR® 21

PrTRIQUILAR® 28

0.05 mg levonorgestrel and 0.03 mg ethinyl estradiol tablets
0.075 mg levonorgestrel and 0.04 mg ethinyl estradiol tablets
0.125 mg levonorgestrel and 0.03 mg ethinyl estradiol tablets

USP

Oral Contraceptive

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levonorgestrel and ethinyl estradiol

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1: Product Information Summary

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	0.05 mg levonorgestrel and 0.03 mg ethinyl estradiol tablets 0.075 mg levonorgestrel and 0.04 mg ethinyl estradiol tablets 0.125 mg levonorgestrel and 0.03 mg ethinyl estradiol tablets	Lactose monohydrate. *For a complete listing see* ***DOSAGE FORMS, COMPOSITION AND PACKAGING*** *section.*

INDICATIONS AND CLINICAL USE

TRIQUILAR (levonorgestrel and ethinyl estradiol) is indicated for:

- Conception control

CONTRAINDICATIONS

TRIQUILAR should not be used in women with:

- a history of or actual thrombophlebitis or thromboembolic disorders;
- a history of or actual cerebrovascular disorders;
- a history of or actual myocardial infarction or coronary artery disease;
- a history of or actual prodromi of a thrombosis (eg, transient ischemic attack, angina pectoris)
- presence of severe or multiple risk factor(s) for arterial or venous thrombosis:
  - severe hypertension (persistent values of ≥160/100 mmHg)
  - 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 (eg, due to MTHFR C677T, A1298 mutations), prothrombin mutation G20210A, and antiphospholipid-antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - severe dyslipoproteinemia
  - smoking, if over age 35
  - diabetes mellitus with vascular involvement

    - major surgery associated with an increased risk of postoperative thromboembolism
    - prolonged immobilization
- valvular heart disease with complications;
- concomitant use of the Hepatitis C virus combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** and **DRUG INTERACTIONS, Drug-Drug Interactions**);
- active liver disease, or history of or actual benign or malignant liver tumours;
- known or suspected carcinoma of the breast;
- carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia;
- undiagnosed abnormal vaginal bleeding;
- steroid-dependent jaundice, cholestatic jaundice, history of jaundice of pregnancy;
- any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision, or defect in visual fields;
- known or suspected pregnancy;
- current or history of migraine with focal aura;
- history of or actual pancreatitis if associated with severe hypertriglyceridemia;
- hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, combination oral contraceptives, including TRIQUILAR, should not be used by women who are over 35 years of age and smoke. Women should be counselled not to smoke (see **WARNINGS AND PRECAUTIONS - Cardiovascular** section below).

Patients should be counselled that birth control pills **DO NOT PROTECT** against sexually transmitted infections (STIs) including HIV/AIDS. For protection against STIs, patients should be counselled to use latex or polyurethane condoms **IN COMBINATION WITH** birth control pills.

General

Discontinue Medication at the Earliest Manifestation of:

A. **Thromboembolic and cardiovascular disorders** such as, thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, retinal thrombosis.

B. **Conditions which predispose to venous stasis and to vascular thrombosis** (eg, immobilization after accidents or confinement to bed during long-term illness). Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **WARNINGS AND PRECAUTIONS - Peri-operative Considerations**.

C. **Visual defects, partial or complete.**

D. **Papilledema, or ophthalmic vascular lesions.**

E. **Severe headache of unknown etiology or worsening of pre-existing migraine headache.**

F. **Increase in epileptic seizures.**

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

The use of combination hormonal contraceptives is associated with increased risks of several serious conditions including myocardial infarction, thromboembolism, stroke, hepatic neoplasia and gallbladder disease, although the risk of serious morbidity and mortality is small in healthy women without underlying risk factors. The risk of morbidity and mortality increases significantly if associated with the presence of other risk factors such as hypertension, hyperlipidemias, obesity and diabetes. Other medical conditions which have been associated with adverse circulatory events include, systemic lupus erythematosus, (1) hemolytic uremic syndrome, (2-5) chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis), (6, 7) sickle cell disease, (8) valvular heart disease and atrial fibrillation (9, 10).

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, although a direct association with COC's has not been firmly established: porphyria, (11) systemic lupus erythematosus, (12) hemolytic uremic syndrome, (2) Sydenham's chorea, (13, 14) herpes gestationis, (15, 16) and otosclerosis-related hearing loss (17).

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

Carcinogenesis and Mutagenesis

Malignancies may be life-threatening or may have a fatal outcome.

Breast Cancer

The frequency of diagnosis of breast cancer is very slightly increased among COC users. As breast cancer is rare in women under 40 years of age, the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.

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 at 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 8 years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptives use is small, there is no reason to change prescribing habits at present.

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

Cervical Cancer

The most important risk factor for cervical cancer is persistent human papillomavirus infection (HPV). 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, eg, cervical screening and sexual behaviour including use of barrier contraceptives. (18)

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. A liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement, or signs of intra-abdominal hemorrhage occur in women taking COCs.

See Product Monograph Part II: **PART II: SCIENTIFIC INFORMATION: TOXICOLOGY, Chronic Toxicity** for discussion of animal data.

Cardiovascular

Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, particularly in women over 35 years of age, and with the number of cigarettes smoked. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use by women who smoke. For this reason, combination oral contraceptives, including TRIQUILAR, 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 is well-controlled may be given hormonal contraceptives but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary. An increase in blood pressure has been reported in women taking COCs, and this increase is more likely in older women and with extended duration of use.

Endocrine and Metabolism

Diabetes

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

Lipid and Other Metabolic Effects

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

Gastrointestinal

Published epidemiological studies indicate a possible association of COC use and the development of Crohn's disease and ulcerative colitis, although this has not been firmly established. (19-24)

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

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism, and of cerebrovascular accidents. These events occur rarely.

The use of any combined oral contraceptive carries an increased risk of venous thromboembolism (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman ever uses a combined oral contraceptive or restarts (following a 4-week or greater pill-free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months. VTE is life-threatening and is fatal in 1-2% of cases.

A large, prospective 3-armed cohort study has shown that the frequency of VTE diagnosis ranges from about 8 to 10 per 10,000 woman-years in users of oral contraceptives with low estrogen content (<50 µg ethinyl estradiol). The most recent data suggest that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman-years in nonpregnant, non-COC users and ranges from 20 to 30 per 10,000 woman-years in pregnant women or postpartum.

Overall the risk for VTE in users of oral contraceptives with low estrogen content (<50 µg ethinyl estradiol) is two- to three-fold higher than for nonusers of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

VTE, manifesting as deep venous thrombosis (DVT) and/or pulmonary embolism (PE), may occur during the use of all COCs.

Extremely rarely, thrombosis has been reported to occur in other blood vessels (eg, hepatic, mesenteric, renal, cerebral or retinal veins and arteries in COC users.

Symptoms of DVT can include: unilateral swelling of the leg or along a vein in the leg; pain or tenderness in the leg which may be felt only when standing or walking, increased warmth in the affected leg; red or discolored skin on the leg.

Symptoms of PE can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain which may increase with deep breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. Some of these symptoms (eg, “shortness of breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (eg, respiratory tract infections).

The risk for arterial thromboembolism (ATE) in users of oral contraceptives with low estrogen content (<50 µg ethinyl estradiol) ranges from about 1 to 3 cases per 10,000 woman-years. An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI). Symptoms of a cerebrovascular accident can include: sudden numbness or weakness of the face, arm, or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen.

Symptoms of MI can include: pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats.

Arterial thromboembolic events are life-threatening and may have a fatal outcome.

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 of 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 two 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, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose COCs (<0.05 mg ethinyl estradiol).

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 should be given oral contraceptives only 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 hormonal 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.

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

TRIQUILAR must be discontinued prior to starting therapy with the Hepatitis C virus (HCV) combination drug regimen ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (see **CONTRAINDICATIONS** and **DRUG INTERACTIONS, Drug-Drug Interactions**). During clinical trials with ombitasvir, paritaprevir, ritonavir, with and 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. TRIQUILAR can be restarted approximately 2 weeks following completion of treatment with the HCV combination drug regimen.

Immune

Angioedema

Exogenous estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema. (25-27)

Neurologic

Migraine and Headache

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

Ophthalmologic

Ocular Disease

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

Ocular Lesions

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

Peri-operative Considerations

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

Psychiatric

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made, which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

Renal

Fluid Retention

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

Sexual Function/Reproduction

Return to Fertility

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

Amenorrhea

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

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

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

Reduced Efficacy

The efficacy of COCs may be reduced in the event of missed tablets, gastrointestinal disturbances or concomitant medication (see **DOSAGE AND ADMINISTRATION** **and** **DRUG INTERACTIONS**).

Skin

Chloasma may occasionally occur with use of COCs, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

Special Populations

Pregnant Women

Oral contraceptives should not be taken by pregnant women. If pregnancy occurs during treatment with TRIQUILAR, further intake must be stopped. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child.

Nursing Women

In breastfeeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. (28) Published studies have indicated that during lactation, 0.1% of the daily maternal dose of levonorgestrel (29) and 0.02% of the daily maternal dose of ethinyl estradiol (30) could be transferred to the newborn via milk. Adverse effects on the child have been reported, including jaundice and breast enlargement. The nursing mother should be advised not to use oral contraceptives but to use other forms of contraception until she has completely weaned her child. There have been no formal studies of TRIQUILAR in nursing women.

Pediatrics

Safety and efficacy of TRIQUILAR has not been established in women under the age of 16 years. Use of this product before menarche is not indicated.

Geriatrics

TRIQUILAR is not indicated for use in postmenopausal women. Oral contraceptives may mask the onset of the climacteric.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

- arterial and venous thromboembolic events
- being diagnosed with breast cancer
- benign and malignant hepatic tumors

- cerebral hemorrhage
- cerebral thrombosis
- congenital anomalies
- gallbladder disease
- hypertension
- mesenteric thrombosis
- myocardial infarction
- neuro-ocular lesions (eg, retinal thrombosis)
- pulmonary embolism
- thrombophlebitis

The following other adverse reactions have also been reported in patients receiving oral contraceptives:

Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10% or fewer of patients during the first cycle. The following other reactions, as a general rule, are seen less frequently or only occasionally:

- abdominal pain
- amenorrhea during and after treatment
- angioedema (exogenous estrogens may induce or exacerbate symptoms of angioedema in women with hereditary angioedema)
- auditory disturbances
- breakthrough bleeding
- breast changes (tenderness, enlargement, and secretion)
- cataracts
- changes in appetite
- change in corneal curvature (steepening)
- changes in glucose tolerance or effect on peripheral insulin resistance
- changes in libido
- change in menstrual flow
- change in weight (increase or decrease)
- chloasma or melasma which may persist
- cholestatic jaundice
- chorea
- Crohn's disease
- cystitis-like syndrome
- mental depression
- diarrhea
- dizziness
- dysmenorrhea
- edema
- endocervical hyperplasia
- erythema multiforme
- erythema nodosum

- gallstone formation[a]
- gastrointestinal symptoms (such as abdominal cramps and bloating)
- headache
- hemolytic uremic syndrome
- hemorrhagic eruption
- herpes gestationis[a]
- hirsutism
- hypersensitivity
- hypertension
- hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- impaired renal function
- increase in size of uterine leiomyomata
- intolerance to contact lenses
- jaundice related to cholestasis[a]
- liver function disturbances
- loss of scalp hair
- migraine
- nervousness
- optic neuritis
- otosclerosis-related hearing loss[a]
- pancreatitis
- porphyria
- possible diminution in lactation when given immediately postpartum
- premenstrual-like syndrome
- pruritus related to cholestasis[a]
- rash (allergic)
- Raynaud's phenomenon
- reduced tolerance to carbohydrates
- retinal thrombosis
- rhinitis
- spotting
- Sydenham's chorea[a]
- Systemic lupus erythematosus[a]
- temporary infertility after discontinuation of treatment
- ulcerative colitis
- urticaria
- vaginal candidiasis
- vaginal discharge
- vaginitis

[a] Occurrence or deterioration of conditions for which association with COC use is not conclusive

Clinical Trial Adverse Drug Reactions

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

The most frequently reported adverse events in the 8,748 patients (50,793 cycles) monitored during clinical trials have been tabulated below (see Table 2). The reported frequencies are the numbers of patients exhibiting a certain symptom per total number of cycles monitored.

Table 2: Clinical Trial Adverse Drug Reactions with a Reported Frequency of >1%

Adverse Events	Frequency of Observations per Cycle (%)
Gastrointestinal disorders	
Nausea and/or vomiting	4.2
Nervous system disorders	
Headache	5.6
Migraine	2.0
Psychiatric disorders	
Libido, increase-decrease	2.0
Depression	2.0
Reproductive system and breast disorders	
Dysmenorrhea	6.5
Spotting	5.8
Breast tension or pain	4.2
Breakthrough bleeding	1.8
Skin and subcutaneous tissue disorders	
Acne	2.3
Chloasma	1.8
Vascular disorders	
Varicose veins	3.5

In all studies, there was a decline in the incidence of symptoms with time. Most side effects were observed in the first three months of therapy, particularly such symptoms as nausea, dizziness, breast tension, headache and changes in libido occurred more frequently during Cycles 1 to 3 than during the pretreatment phase. However, from Cycles 4 to 24, the frequencies of all symptoms were lower than the pretreatment values.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

General disorders and administration site condition: Edema
Investigations: Weight increased
Metabolism and nutrition disorders: Increased appetite
Reproductive system and breast disorders: Amenorrhea
Vascular disorders: Thrombophlebitis

Intermenstrual Bleeding

The incidence of intercyclic bleeding irregularities (defined as either spotting or breakthrough bleeding) was higher during the first cycle. The frequency of intercyclic bleeding episodes decreased with time, so that after the 12th cycle with TRIQUILAR bleeding irregularities were rarely encountered.

In the patient population studied, bleeding irregularities occurred during 8.5% of all cycles monitored. However, bleeding irregularities for those cycles associated with admitted pill errors were generally much higher (25.6%) (see Table 3). Overall the incidence of spotting was greater than that of breakthrough bleeding in most cycles.

Table 3: Intermenstrual Bleeding

	Spotting	Breakthrough Bleeding	Spotting & Breakthrough Bleeding
Pill error – 1211 cycles	187 (14.6%)	107 (9.0%)	27 (2.2%)
All cycles – 50,793 cycles	2946 (5.8%)	901 (1.8%)	455 (0.9%)

DRUG INTERACTIONS

Overview

The concurrent administration of oral contraceptives with other drugs may lead to breakthrough bleeding and/or may result in an altered response to either agent (see Table 4 and Table 5). Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low-dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before oral contraceptives are prescribed.

Drug-Drug Interactions

Table 4: Drugs Which May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Antibiotics (31, 32)	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional non-hormonal method of contraception or use another drug. For long course, use another non-hormonal method of contraception.
	Rifampin Rifabutin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another non-hormonal method of contraception.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional non-hormonal method of contraception or use another drug. For long course, use another non-hormonal method of contraception.

Table 4: Drugs Which May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
	Troleandomycin	May retard metabolism of oral contraceptives, increasing the risk of cholestatic jaundice.	
Anticonvulsants (33-39)	Carbamazepine Ethosuximide Felbamate Lamotrigine Oxcarbazepine Phenobarbital Phenytoin Primidone Topiramate	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose oral contraceptives (50 µg ethinyl estradiol), another drug or another non-hormonal method of contraception.
Antifungals (40)	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another non-hormonal method of contraception.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces oral contraceptive efficacy.	Use another non-hormonal method of contraception.
HCV Protease Inhibitors	Boceprevir Telaprevir	Remains to be confirmed.	Use another drug or another non-hormonal method of contraception.
HIV Protease Inhibitors (41)	Ritonavir	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.
Non-nucleoside reverse transcriptase inhibitors (28, 42)	Nevirapine	Induction of hepatic microsomal enzymes.	Use another drug or another non-hormonal method of contraception.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional non-hormonal method of contraception or another drug. For long course, use another non-hormonal method of contraception or higher dose oral contraceptives.
Other Drugs	Analgesics Antihistamines Antimigraine preparations Phenylbutazone Vitamin E	Reduced oral contraceptive efficacy has been reported. Remains to be confirmed.	

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy, enzyme induction may be sustained for about 4 weeks.

Strong and moderate CYP3A4 inhibitors such as azole antifungals (eg, ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (eg, clarithromycin, erythromycin), diltiazem, and grapefruit juice can increase plasma concentrations of the estrogen or the progestin or both.

Several of the anti-HIV/HCV protease inhibitors (eg, ritonavir, telaprevir, boceprevir) and non-nucleoside reverse transcriptase inhibitors (eg, nevirapine) have been studied with co-administration of oral combination hormonal contraceptives; significant changes (increase or decrease) in the mean AUC of the estrogen or progestogen have been noted in some cases. The efficacy and safety of oral contraceptive products may be affected. Health care professionals should refer to the label of the individual anti-HIV/HCV protease inhibitor for further drug-drug interaction information.

In vitro, ethinyl estradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing ethinyl estradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (eg, midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (eg, theophylline) or moderately (eg, melatonin and tizanidine).

Oral contraceptives may also interfere with the metabolism of other drugs (see Table 5). Accordingly, plasma and tissue concentrations may either increase (eg, cyclosporine) or decrease (eg, lamotrigine).

Table 5: Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde	Use with caution.
Alpha-II adrenoreceptor agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	Oral contraceptives increase clotting factors, decrease efficacy. However, oral contraceptives may potentiate action in some patients.	Use another non-hormonal method of contraception.
Anticonvulsants	All	Estrogens may increase risk of seizures.	Use another non-hormonal method of contraception.
	Lamotrigine	Decreased lamotrigine levels may lead to breakthrough seizures.	Use another non-hormonal method of contraception.
Antidiabetic drugs	Oral hypoglycemics and insulin	Oral contraceptives may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin oral contraceptive or another non-hormonal method of contraception. Monitor blood glucose.
Antihypertensive agents	Guanethidine and methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen oral contraceptive or use another non-hormonal method of contraception.
	Beta blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of oral contraceptives.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic acid		Theoretically, a hypercoagulable state may occur because oral contraceptives augment clotting factors.	Avoid concomitant use.
Betamimetic agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing oral contraceptives can result in excessive drug activity.
Caffeine		The actions of caffeine may be enhanced as oral contraceptives may impair the hepatic metabolism of caffeine.	Use with caution.

Table 5: Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Cholesterol lowering agents	Clofibrate	Their action may be antagonized by oral contraceptives. Oral contraceptives may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine (43)		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Direct-acting antiviral (DAA) medicinal products	Ombitasvir, Paritaprevir, Ritonavir, with and without Dasabuvir	Has 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.	see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.**
Folic acid		Oral contraceptives have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine tranquilizers	All phenothiazines, reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose oral contraceptives. If galactorrhea or hyperprolactinemia occurs, use other non-hormonal method of contraception.
Sedatives and hypnotics	Chlordiazepoxide Diazepam Lorazepam Oxazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic antidepressants	Clomipramine (possibly others)	Increased side effects: ie, depression	Use with caution.
Vitamin B_{12}		Oral contraceptives have been reported to reduce serum levels of Vitamin B_{12}	May need to increase dietary intake, or supplement.

No formal drug-drug interaction studies have been conducted with TRIQUILAR.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

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

Drug-Laboratory Test Interactions

Results of laboratory tests should be interpreted with the knowledge that the patient is on oral contraceptives. The following laboratory tests are modified:

Liver Function Tests

Aspartate serum transaminase (AST) - variously reported elevations
Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated

Coagulation Tests

Minimal elevation of test values reported for such parameters as prothrombin and Factors VII, VIII, IX and X.

Thyroid Function Tests

Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T_3 resin uptake.

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 two weeks after discontinuing the use of oral contraceptives before measurements are made.

Glucose Tolerance

Glucose tolerance may be decreased.

Tissue Specimens

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

Drug-Lifestyle Interactions

No studies on the effects of TRIQUILAR on the ability to drive or use machines have been performed.

Noncontraceptive Benefits of Oral Contraceptives

Several health advantages other than contraception have been reported.

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

DOSAGE AND ADMINISTRATION

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. The patient may begin using TRIQUILAR (levonorgestrel and ethinyl estradiol) on Day 1 of her menstrual cycle (ie, the first day of menstrual flow), on Day 5, or on the first Sunday after her period begins. If the patient's period begins on Sunday, she should start that same day. An additional (barrier) method of birth control is recommended for the first seven days of use.

TRIQUILAR 21 (21-day Regimen)

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

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

TRIQUILAR 28 (28-day Regimen)

Tablet taking is continuous. One tablet is to be taken daily for 28 consecutive days. Withdrawal bleeding usually occurs within 2 to 3 days of starting the placebo tablets (ie, while the patient is taking the last row of the slightly larger, hormone-free white tablets).

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

Management of Missed Tablets:

The patient should be instructed to use the following chart if she misses one or more of her birth control pills (see Table 6). She should be told to match the number of tablets missed with the appropriate starting time for her dosing regimen. The risk of pregnancy increases with each hormone-containing light brown, white or ochreous tablet missed.

Table 6: Management of Missed Hormone-containing Light Brown, White or Ochreous Tablets

Sunday Start	**Other than Sunday Start**
Miss One Light Brown, White or Ochreous Tablet At Any Time	**Miss One Light Brown, White or Ochreous Tablet At Any Time**
Take it as soon as you remember, and take the next tablet at the usual time. This means that you might take two tablets in one day.	Take it as soon as you remember, and take the next tablet at the usual time. This means that you might take two tablets in one day.
Miss Two Light Brown, White or Ochreous Tablets in a Row	**Miss Two Light Brown, White or Ochreous Tablets in a Row**
First Two Weeks: 1. Take two tablets the day you remember and two tablets the next day. 2. Then take one tablet a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets.	**First Two Weeks:** 1. Take two tablets the day you remember and two tablets the next day. 2. Then take one tablet a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets.
Third Week 1. Keep taking one tablet a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**

Table 6: Management of Missed Hormone-containing Light Brown, White or Ochreous Tablets

Sunday Start	**Other than Sunday Start**
Miss Three or More Light Brown, White or Ochreous Tablets in a Row	**Miss Three or More Light Brown, White or Ochreous Tablets in a Row**
Anytime in the cycle 1. Keep taking one tablet a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Anytime in the cycle** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the tablets. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**

Patients taking TRIQUILAR 28

If the patient forgets any of the seven slightly larger, hormone-free white tablets in Week 4, she should be advised to safely dispose of the tablets she missed, and then to keep taking one tablet each day until the pack is empty. A backup method of birth control is not required.

Special Notes on Administration

Switching from Another Combined Hormonal Contraceptive (Combined Oral Contraceptive (COC), Vaginal Ring or Transdermal Patch)

The patient should start TRIQUILAR on the day she would normally start her next pack of combination oral contraceptives. In case a vaginal ring or transdermal patch has been used, the woman should start using TRIQUILAR preferably on the day of removal, but at the latest when the next application would have been due.

Switching from a Progestogen-only Method (Mini-Pill, Injection) or from a Progestogen-releasing Intrauterine System (IUS)

The patient may switch from the mini-pill to TRIQUILAR on any day of her cycle. Patients using a progestogen injection should start TRIQUILAR on the day the next injection is due. Patients using an IUS should start TRIQUILAR on the day the IUS is removed. In all cases, the patient should be advised to use an additional (barrier) method for the first 7 days of TRIQUILAR use.

Following First Trimester Abortion

The patient may start using TRIQUILAR immediately. When doing so, she need not take additional contraceptive measures.

Following Delivery or Second Trimester Abortion

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

Withdrawal/Breakthrough Bleeding

Withdrawal bleeding usually occurs within 3 days following the last hormone-containing tablet. If spotting or breakthrough bleeding occurs while taking TRIQUILAR, the patient should be instructed to continue taking TRIQUILAR as instructed and by the regimen described above. She should be instructed that this type of bleeding is usually transient and without significance; however, if the bleeding is persistent or prolonged, the patient should be advised to consult her physician.

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

Advice in Case of Vomiting

If vomiting occurs within 3 to 4 hours after a tablet is taken, absorption may not be complete. In such an event, the advice concerning management of missed tablets is applicable.

OVERDOSAGE

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

Symptoms

With levonorgestrel and ethinyl estradiol, acute doses in excess of clinical levels, when administered to experimental animals, have been shown to have a minimal deleterious effect. In humans, however, the extent of ill effects to be expected following accidental ingestion of a large dose of any oral contraceptive has not been firmly established.

Overdosage may cause nausea and vomiting. Depending upon the amount ingested, liver toxicity, temporary interference with the function of the seminiferous tubules, or in the case of females, possible withdrawal bleeding within a few days of consumption, are theoretically possible. Withdrawal bleeding may even occur in girls before their menarche, if they have accidentally taken the medicinal product. Case histories of both male and female children, some of whom ingested more than half a month's supply of oral contraceptive pills, indicate that the effects are asymptomatic and without immediate consequence. Despite the frequency of nausea and vomiting in adult females during the first few cycles of use, none of these children presented such symptoms.

Treatment

There is no known antidote to overdosage. Treatment should be symptomatic, based on the knowledge of the pharmacological action of the constituents. Liver function tests should be conducted, particularly transaminase levels, 2 to 3 weeks after consumption.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TRIQUILAR, a triphasic oral contraceptive, contains as active ingredients levonorgestrel and ethinyl estradiol. It acts primarily through the mechanism of gonadotrophin suppression by the estrogenic and progestational activity of the active ingredients. Although the primary activity is inhibition of ovulation, alterations in the genital tract, including changes in the cervical mucus (which make sperm penetration more difficult), and the endometrium (which reduce the likelihood of implantation) may also contribute to contraceptive effectiveness.

Levonorgestrel has been evaluated extensively in women to assess its progestational activity.

In women, the endometrium is transformed by the oral administration of 2.5 mg levonorgestrel given over a period of 10 days (total dose after pretreatment with estrogen). The endometrial transformation dose is 250 μg/day, corresponding to 5 μg/kg.

Levonorgestrel at a dose of 125 μg/day was also shown to be twice as potent as norethindrone in the delay of menstruation test by "Swyer and Greenblatt".

Pharmacodynamics

Effects on central and peripheral function before, during and after the use of TRIQUILAR were evaluated in 5 women.

The first and third cycles under TRIQUILAR differed considerably from the control cycle. Serum LH values remained at the level of the early follicular phase as a sign of central inhibitory effect, furthermore there was no increase at mid-cycle.

The 17 β-estradiol also failed to peak and serum progesterone reflected the absence of ovulation. As a result, cervical function was limited, the spinnbarkeit and degree of crystallization of the secretion were greatly reduced. The Caryopyknotic index ran in waves to achieve 25%. Finally, the basal body temperature increased as a result of the thermogenic effect of the progesterone, although this occurred later and more slowly than with preparations which contain a higher dose of progesterone in the first half of the cycle.

Upon discontinuation of TRIQUILAR after the third cycle of use, the serum values of LH, 17 β-estradiol and progesterone again displayed all signs of a normal ovulatory cycle pattern.

Overall the study results confirm that ovulation is inhibited and a distinct antifertile effect is exerted in the peripheral cycle function during therapy with TRIQUILAR.

Pharmacokinetics

Levonorgestrel

Absorption

Orally administered levonorgestrel is rapidly and completely absorbed. (44-46) Following single ingestion of 0.125 mg levonorgestrel together with 0.03 mg ethinyl estradiol (which represents the combination with the highest levonorgestrel content of the triphasic formulation), peak serum concentrations of 4.3 ng/mL are reached at about one hour after single ingestion. (47) Levonorgestrel is almost completely bioavailable after oral administration. (44, 46, 48)

Distribution

Levonorgestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1.4% of the total serum drug concentrations are present as free steroid, 55% are specifically bound to SHBG and about 44% are non-specifically bound to albumin. (47) The ethinyl estradiol induced increase in SHBG influences the proportion of levonorgestrel bound to the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. (49) The volume of distribution of levonorgestrel (V_z) is about 128 L after single oral administration of the highest levonorgestrel dose of TRIQUILAR. (47)

Metabolism

Levonorgestrel is extensively metabolized. The major metabolites in plasma are the unconjugated and conjugated forms of 3α, 5β-tetrahydrolevonorgestrel (50). Based on in vitro and in vivo studies, CYP3A4 is the main enzyme involved in the metabolism of levonorgestrel (51). The clearance rate from serum is approximately 1.0 mL/min/kg (47).

Elimination

Levonorgestrel serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 22 hours. (47) Levonorgestrel is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 1:1. (45) The half-life of metabolite excretion is about 1 day. (45)

Steady-state Conditions

Levonorgestrel pharmacokinetics are influenced by SHBG levels, which are increased about twofold during the 21-day treatment period with TRIQUILAR. Following daily ingestion drug serum levels increase about fourfold as compared to single oral administration of the highest levonorgestrel dose of TRIQUILAR, reaching steady-state conditions during the second half of a treatment cycle. At steady-state, the volume of distribution and the clearance rate are reduced to 52 L and 0.5 mL/min/kg, respectively, as compared to single oral administration of the highest levonorgestrel dose of TRIQUILAR. (47)

Ethinyl Estradiol

Absorption

Orally administered ethinyl estradiol is rapidly and completely absorbed. (52-54) Peak serum concentrations of about 116 pg/mL are reached within 1.3 hours after single oral ingestion of 0.03 mg ethinyl estradiol in combination with 0.125 mg levonorgestrel. (47) During absorption and first liver passage, ethinyl estradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% with a large inter-individual variation of about 20-65%. (53)

Distribution

Ethinyl estradiol is highly but non-specifically bound to serum albumin (approximately 95-98%), (55) and induces an increase in the serum concentrations of SHBG. (53) An apparent volume of distribution of about 2.8-8.6 L/kg was reported after intravenous administration. (53)

Metabolism

Ethinyl estradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinyl estradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The clearance rate was reported to be 2.3 - 7 mL/min/kg after intravenous administration. (53)

Elimination

Ethinyl estradiol serum levels decrease in two disposition phases characterized by half-lives of about 1 hour and 10-20 hours, respectively. (53) Unchanged drug is not excreted. Ethinyl estradiol metabolites are excreted at a urinary to biliary ratio of 4:6 with a half-life of about 1 day. (54)

Steady-state Conditions

According to the variable half-life of the terminal disposition phase from serum, (53) and the daily ingestion, steady-state serum levels of ethinyl estradiol will be reached after about one week. After three cycles, the maximum ethinyl estradiol concentration of about 132 pg/mL is reached after about 1.3 h. (47)

Special Populations and Conditions

Pediatrics

Safety and efficacy of TRIQUILAR has not been established in women under the age of 16 years. Use of this product before menarche is not indicated.

Geriatrics

TRIQUILAR is not indicated for use in postmenopausal women. Oral contraceptives may mask the onset of the climacteric.

Hepatic Insufficiency

TRIQUILAR is contraindicated in women with active liver diseases (see **CONTRAINDICATIONS**).

Renal Insufficiency

TRIQUILAR has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

STORAGE AND STABILITY

Store in original packaging between 15°C and 30°C. Keep out of reach of children and pets.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability

TRIQUILAR tablets are available:

For 21-day regimens in "TRIQUILAR 21".
For 28-day regimens in "TRIQUILAR 28".

Each pack contains three different combinations of levonorgestrel [(-)-isomer of norgestrel] and ethinyl estradiol. Non-medicinal ingredients: calcium carbonate, maize starch, glycerine, lactose, magnesium stearate, montanglycol wax, polyethylene glycol, polyvinylpyrrolidone, red ferric oxide, sucrose, talc, titanium dioxide and yellow ferric oxide.

"TRIQUILAR 21"

Days 1 - 6	Each hormone-containing light brown tablet contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg.
Days 7 - 11	Each hormone-containing white tablet contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg.
Days 12 - 21	Each hormone-containing ochreous tablet contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg.

"TRIQUILAR 28"

Days 1 - 6	Each hormone-containing light brown tablet contains levonorgestrel 0.05 mg and ethinyl estradiol 0.03 mg.
Days 7 - 11	Each hormone-containing white tablet contains levonorgestrel 0.075 mg and ethinyl estradiol 0.04 mg.
Days 12 - 21	Each hormone-containing ochreous tablet contains levonorgestrel 0.125 mg and ethinyl estradiol 0.03 mg.
Days 22 - 28	Each slightly larger inert white tablet is hormone-free.

PART II: SCIENTIFIC INFORMATION

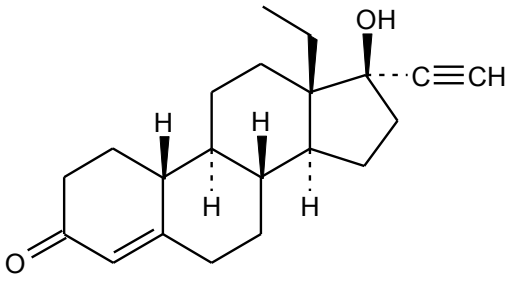
PHARMACEUTICAL INFORMATION

Drug Substance

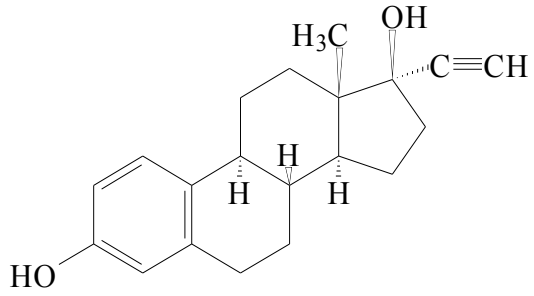
Proper Name: Levonorgestrel
Ethinyl estradiol

Chemical Name:
Levonorgestrel: 18,19-Dinorpregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-,(17α)-(-)
19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)-

Structural Formula:
Levonorgestrel:



Ethinyl estradiol:



Molecular Formula and Molecular Mass:	Levonorgestrel:	$C_{21}H_{28}O_2$	312.45
	Ethinyl estradiol:	$C_{20}H_{24}O_2$	296.41

Physicochemical properties:

Solubility: (USP Classification):

	Levonorgestrel:	Slightly soluble in alcohol; insoluble in water.
	Ethinyl estradiol:	Insoluble in water; soluble in alcohol, chloroform, ether, vegetable oil, and in alkaline solutions.
Melting Points:	Levonorgestrel:	234°C - 240°C
	Ethinyl estradiol:	80°C - 186°C
Biological Properties:	Levonorgestrel:	This entire synthetic progestogen is the (-)-isomer of norgestrel. It is the active form of the racemic norgestrel.
	Ethinyl estradiol:	synthetic estrogen.

CLINICAL TRIALS

Study Demographics and Trial Design

The safety and efficacy of TRIQUILAR were evaluated in eight multicentre, controlled and open clinical trials. The studies were carried out in eleven different countries in Europe and South America.

Two of the studies were controlled, double-blind comparisons of TRIQUILAR versus a monophasic oral contraceptive containing levonorgestrel 150 mcg and ethinyl estradiol 50 mcg. The third study was a double-blind comparison of TRIQUILAR with a monophasic oral contraceptive containing desogestrel 150 mcg and ethinyl estradiol 30 mcg. The remaining five studies were large open evaluations, including a German Phase IV study comprising some 6271 women. A total of 8748 women were included in the studies. All subjects were healthy women of whom the majority had a history of regular menstrual periods. Women with existing or previous contraindications to oral contraceptives were excluded from participating in the trials. A description of the trials is shown in Table 7. Nearly 80% of the women were in the <20 or 20-29 age brackets. The remainder were in their 30's and 40's.

Table 7: Summary of Patient Demographics in TRIQUILAR Pivotal Clinical Efficacy Trials

Study	Trial Design	Number of Subjects	Age Distribution (Years)			
			<20	20-29	30-39	>40
Carlborg	Multicentre, double-blind, controlled vs. levonorgestrel 150 mcg + ethinyl estradiol 50 mcg	417	177	182	58	0
Aydinlik 70015	Multicentre, double-blind, controlled vs. levonorgestrel 150 mcg + ethinyl estradiol 50 mcg	254	49	142	55	8
Lachnit 81182	Multicentre, double-blind, controlled vs. desogestrel 150 mcg + ethinyl estradiol 30 mcg	555	148	248	132	27
Lachnit 1124	Multicentre, open	695	137	366	173	19
Ulstein 79184	Multicentre, open	367	109	193	62	3
Lachnit 70127	Multicentre, open	255	33	142	75	5
Aydinlik 70101	Multicentre, open	210	26	134	46	4
Lachnit 70124	Multicentre, open	6272	2284	2772	973	243
Total		**9025**[1]	**2963**	**4179**	**1574**	**309**

[1] The total number of subjects (9025) includes those in the TRIQUILAR group (8748 subjects) plus the 277 subjects who were on another treatment in Study 81182.

Study Results

In all studies, women were treated with TRIQUILAR for at least six cycles. As shown in Table 8, a total of 6673 patients were treated and monitored for six cycles with TRIQUILAR. In five of the eight studies, women were monitored for up to 12 cycles, and in one study, 54 women were followed for 24 cycles. A total of 50,793 individual cycles were monitored in the course of the eight studies.

Table 8: Duration of Treatment (Cycles)

Study	Patients	6 Cycles	12 Cycles	24 Cycles	Total
Carlborg	417	350	156	-	3194
70015	254	226	-	-	1440
81182	278	235	-	-	1529
1124	696	594	362	-	6628
79184	367	314	245	-	3588
70127	255	193	99	54	3521
70101	210	166	81	-	2252
70124	6271	4595	-	-	28,638
Total	**8748**	**6673**	**943**	**54**	**50,793**

The rate of discontinuation of TRIQUILAR during the trials was carefully assessed. The overall dropout rate was 28%. However, the rate varied considerably from study to study, the lowest rate being 11% and the highest 33%.

Twelve percent (12%) of the patients discontinued for medical reasons and 16% for nonmedical reasons. The most common medical reasons given for dropping out of the trials were headaches, nausea and vomiting, and breakthrough bleeding.

The dropout rate for medical as well as nonmedical reasons was greatly reduced after the 6th cycle.

Table 9: Discontinuation During the First 6 Cycles

Study	Total		Side Effects	
Carlborg	67/417	(16%)	47/417	(11%)
70015	85/254	(33%)	23/254	(9%)
81182	30/258	(11%)	17/258	(6%)
1124	185/696	(27%)	85/696	(12%)
79184	122/367	(33%)	62/367	(16%)
70127	63/258	(24%)	20/258	(8%)
70101	44/210	(22%)	-	
70124	1883/6272	(30%)	824/6272	(13%)
Overall	2479/8732	(28%)	1078/8732	(12%)

In all studies there were patients that admitted to tablet omissions as shown in Table 10. Tablet error was admitted in 1211 cycles during TRIQUILAR administration (2.4%).

Table 10: Tablet Error - Cycles

Study	Total Number of Cycles	Number of Cycles with Tablet Error	
Carlborg	3197	258	(8%)
70015	1440	15	(0.9%)
81182	1529	23	(1.5%)
1124	6628	112	(1.7%)
79184	3588	5	(0.2%)
70127	3521	116	(3.0%)
70101	2252	51	(4.0%)
70124	28,638	631	(2.1%)
Total	**50,793**	**1211**	**(2.4%)**

As shown in Table 11, a total of 21 pregnancies were recorded in the eight studies. Ten of these were considered due to patient failure (errors); however, the remaining eleven pregnancies were considered to be method failures. The results of the Lifetable Analysis and the Pearl Index are presented in Table 12.

Table 11: Pregnancy

Study	Patients	Pregnancy Patient Error	Pregnancy No Error	Total
Carlborg	417	1	-	1
70015	254	0	-	0
81182	278	1	-	1
1124	696	0	-	0
79184	367	4	1	5
70127	255	1	-	1
70101	210	0	-	0
70124	6271	3	10	13
Total	**8748**	**10**	**11**	**21**
Pearl Index = 0.3				

Table 12: Overall Pregnancy Rate

Method	Method Failure + Patient Failure	Method Failure
Lifetable analysis	0.65	0.40
Pearl Index	0.60	0.30

In the large Phase IV multicentre study, there were ten reported pregnancies (method failure). The Pearl Index for this study was 0.4 and the Lifetable Analysis was 0.69.

In the other seven studies, comprising of 2,477 women treated for 22,155 cycles, there was just one method failure pregnancy. The Pearl Index resulting from these studies was 0.06 or approximately five times lower.

Endometrial biopsies obtained at variable times during the cycle were assessed according to the criteria of Noyes. Overall it was shown that this triphasic contraceptive causes a moderate degree of endometrial proliferation during the first phase, followed by premature secretory changes in the second phase, and minimal but continued development and maturation in the third phase that do not approach those seen in a normal cycle.

General Information

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.

Table 13: 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

DETAILED PHARMACOLOGY

Levonorgestrel

Levonorgestrel is a 19-nortestosterone derivative. Investigations with animals (rabbits, rats, mice) and man have shown it to be a very potent progestogen.

In rabbits (Clauberg test), evidence of transformation changes of the endometrium is found after subcutaneous administration of 0.01 mg levonorgestrel, corresponding to 2 µg/kg/day. Transformative effects are also histologically recognisable in the rabbit endometrium when levonorgestrel is administered orally in doses ranging from 0.03 to 0.3 mg/animal, corresponding to approximately 6 to 60 µg/kg/day.

In pregnant rats ovariectomised in the first 4 days after conception, the subcutaneous administration of levonorgestrel of 0.002 mg had a blastocyst-maintaining effect. The anti-estrogenic or progestogenic activity of levonorgestrel has also been demonstrated in various test models in rats and mice. The potency of levonorgestrel is significantly higher than progesterone and about 83 times stronger than chlormadinone acetate.

Levonorgestrel has not demonstrated any estrogenic activity and androgenic effects are only in evidence after large doses. Levonorgestrel also influences the gonadotropic partial function of the anterior lobe of the pituitary gland in all experimental tests (testes inhibition test, parabiosis test, inhibition of ovulation test).

Like other progestogens, relative large doses of levonorgestrel also leads to increases in insulin secretion in rats and dogs.

Ethinyl Estradiol

Ethinyl estradiol is a potent estrogen with qualities similar to estradiol in its oral efficacy. However, the relative oral potency is 3 - 30 times greater than estradiol in peripheral estrogenic effects, antigonadotropic effects and inhibition of ovulation and antifertility effects.

Ethinyl estradiol also exhibited the effects on carbohydrate and lipid metabolism similar to other estrogens, ie, hepatic glycogen content was greatly increased, total glycerin in the serum was increased, serum cholesterol decreased. Phospholipids were also raised after 1 month's treatment.

The effect of ethinyl estradiol on carbohydrate and lipid metabolism also indicates an estrogenic effect on the pituitary/adrenal cortex system, such as increased secretion of ACTH and possibly somatotrophic hormone (STH).

Ethinyl Estradiol/Levonorgestrel

The estrogen/progestogen combinations which have been used in women in ratios varying between (1:1.67 to 1:4.17) are not optimal for use in laboratory testing in animals.

In animals (rats and rabbits) the relative estrogen doses are much lower than the required progestogen doses ie, the optimal estrogen/progestogen doses are further apart. If an estrogen/progestogen combination which is optimal in women is tested in animals the progestogen compound has no or hardly any effect. Thus in the ovulation inhibiting test in the rat the orally effective dose range of ethinyl estradiol is between 30 and 300 μg/animal/day.

Levonorgestrel on the other hand is only slightly effective at dose of 3 mg/animal/day.

In the implantation inhibiting test in the rat, ethinyl estradiol produces a dose-related inhibition of nidation in an oral dose range between 7.6 and 11.4 μg/animal/day. In this test levonorgestrel does not show inhibiting effect below a dose of 2.5 mg/animal/day. In the testes inhibiting test in the rat 0.25 μg/animal/day, ethinyl estradiol (oral) is sufficient to significantly reduce the testicular weight. Levonorgestrel on the other hand has hardly any effect even in the high dose of 125 μg/animal/day orally.

TOXICOLOGY

Acute Toxicity

Acute oral toxicity studies have been carried out with oral, intraperitoneal (i.p.) and subcutaneous (s.c.) doses of levonorgestrel alone, ethinyl estradiol alone and in a combination of 5:1 ratio.

Table 14 represents the findings of these studies:

Table 14: Summary of Acute Toxicity Results

Species	Route of Administration	LD_{50} Levonorgestrel	LD_{50} Ethinyl Estradiol	LD_{50} Levonorgestrel + Ethinyl Estradiol (5:1)
Mice	oral	> 4.0 g/kg	> 2.5 g/kg	> 2.5 g/kg
Mice	i.p.	> 3.9 g/kg	0.69 g/kg	1.32 - 1.65 g/kg
Mice	s.c.	> 4.0 g/kg	> 2.6 g/kg	> 2.5 g/kg
Rats	oral	> 4.0 g/kg	susp. > 5.0 g/kg solu. 1.5 g/kg	> 2 g/kg
Rats	i.p.	> 5.0 g/kg	0.97 g/kg	approx. 2 g/kg
Rats	s.c.	> 4.0 g/kg hair loss		> 2 g/kg
Dogs	oral		> 1.0 g/kg	

Both compounds were found to be almost non-toxic in the acute toxicity studies.

Chronic Toxicity

Table 15: Chronic Toxicity Studies

Species	Drugs, Route of Administration and Dose	Duration of Administration	Symptoms	Histopathology
RAT 16/sex/group	Norgestrel, Oral 0.0001%, 0.0005%, 0.0025%	26 weeks	No signs and symptoms of toxicity.	No histopathological changes.
	Levonorgestrel, Oral 0.00005%, 0.00025%, 0.00125%	26 weeks	Significant less weight gain in low-dose females, no other signs of toxicity.	No abnormal histopathology.
DOG 6/sex/group	Levonorgestrel, Oral 0.05 - 0.1 - 0.5 mg/kg	26 weeks	No estrus in any dog. Mammary enlargement: in all but 2 females and 8 males. Dose related clitoral reddening and enlargement. Significant decrease in cholesterol in all dosage groups.	No drug-related effects on ophthalmology, ECG, hemostatic functions, urinalysis or organ weight.
DOG 16 females/dose	Norgestrel, Oral 0, 3.0, 15.0, 37.5 µg/kg	continuous 7 years	Estrus inhibited in all but low dosage group. Uterine enlargement and endometrial hyperplasia at 15 and 37.5 µg/kg.	Norgestrel 37.5 µg group - many dogs with cysts and absence of luteal phase. 1 dog mammary carcinoma (37.5µg/kg).
	Levonorgestrel, Oral 0.5 mg/kg	cyclic - 7 years	Enlarged clitoris on majority of dogs. Hematocrit and hemoglobin low or SGPT increased significantly. Fibrinogen increased.	Increase in benign mammary adenomas. 1 dog adenocarcinoma. Many vaginal cysts and absence of luteal phase.
RHESUS MONKEY 16 females/dose	Norgestrel, Oral 0 , 3, 15, 75 µg/kg	continuous 10 years (78 months)	Red vaginal discharge less frequent in 15 and 75 µg/kg group.	Mammary nodules in 3 animals at 75 µg/kg. 1 animal at 3 and 15 µg/kg.
	Levonorgestrel, Oral 1 mg/kg	cyclic - (21 days) 10 years (78 months)	Red vaginal discharge more frequent in withdrawal period. Fibrinogen levels increased.	1 animal mammary nodules.

Table 15: Chronic Toxicity Studies

Species	Drugs, Route of Administration and Dose	Duration of Administration	Symptoms	Histopathology
MICE 40/sex/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol (10 + 1) Oral, 0.02 + 0.002 mg/kg; 0.7 + 0.07 mg/kg; 2.0 + 0.2 mg/kg; 3.0 + 0.3 mg/kg	80 weeks	Ethinyl Estradiol depressed weight gain in 3 highest dosage groups. Norgestrel + Ethinyl Estradiol - depressed weight gain in 3 highest dosage groups. Norgestrel - no effects.	Ethinyl Estradiol - significant increase in malignant tumors. Lymphocarcinoma - males interstitial tumors - females. Ethinyl Estradiol + Norgestrel - same. Norgestrel - no significant tumorigenic effect.
RAT 40/sex/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol (10 + 1) Oral, 0.02 + 0.002 mg/kg; 0.5 + 0.05 mg/kg; 2.0+ 0.2 mg/kg	104 weeks	Norgestrel - no effects. Ethinyl Estradiol - dosage related decrease in body weight gain. Norgestrel + Ethinyl Estradiol - dosage related decrease in body weight gain.	Malignant and benign mammary tumors were significantly increased over controls in both males and females at the two highest dosage levels of Ethinyl Estradiol either alone or in combination with Norgestrel. Hematological changes included are one case of Leukemia in low dosage group of Norgestrel + Ethinyl Estradiol.
DOG 12 females/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol Oral - mg/kg I 0.1 - 0.25 II 0.01 III 0.1 + 0.025 0.1 + 0.01 0.25 + 0.025	7 years	Norgestrel - increase in body weight at 0.1 mg/kg. Slight to moderate increase SGPT values in treated groups also increase in fibrinogen in some animals. Norgestrel alone or in combination with Ethinyl Estradiol also suppressed estrus.	Dose related increase in mammary adenomas in the Norgestrel treated groups. Possible indication of an increase in benign adenomas and intraductal papillomas after high doses of Norgestrel.
RHESUS MONKEY 16 females/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol Oral - mg/kg I 0.02, 0.1, 0.5 II 0.002, 0.01, 0.05 III 0.02 + 0.002 0.1 + 0.01 0.5 + 0.05	10 years	Increase in body weight gain in the Norgestrel 0.5 mg/kg group. Fibrinogen levels increased in monkeys receiving Norgestrel alone or in combination with Ethinyl Estradiol. A higher rate with retinal depigmentation in the groups treated with Ethinyl Estradiol alone or in combination with Norgestrel.	No abnormal findings.

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PART III: CONSUMER INFORMATION

PrTRIQUILAR®
(levonorgestrel and ethinyl estradiol tablets USP)

This leaflet is Part III of a three-part "Product Monograph" published when TRIQUILAR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TRIQUILAR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- To prevent pregnancy

What it does:

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

Birth control pills work in two ways:

1. They inhibit the monthly release of an egg by the ovaries.

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

Effectiveness of Birth Control Pills

Combination birth control pills are more than 99 percent effective in preventing pregnancy when:

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

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

The chance of becoming pregnant increases with incorrect use.

Other Ways to Prevent Pregnancy

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

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

Reported Pregnancies per 100 Women per Year:

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

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

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

When it should not be used:

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

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

- blood clots in the legs, lungs, eyes, or elsewhere, or thrombophlebitis (inflammation of the veins)
- stroke, heart attack, or coronary artery disease (eg, angina pectoris), or a condition that may be a first sign of a stroke (such as a transient ischemic attack or small reversible stroke)
- disease of the heart valves with complications
- known abnormalities of the blood clotting system that increases your risk for developing blood clots
- severe high blood pressure
- diabetes with complications
- very high blood cholesterol or triglyceride levels
- you smoke and are over age 35
- migraine headache
- you are scheduled for major surgery
- prolonged bed rest
- you are taking ombitasvir, paritaprevir, ritonavir, with

or without dasabuvir for the treatment of Hepatitis C (an infectious disease that affects the liver, caused by the hepatitis C virus)
- jaundice (yellowing of the eyes or skin), liver disease or liver tumor
- known or suspected cancer of the breast or uterus (womb) or other estrogen-dependent cancer
- unusual vaginal bleeding without a known reason
- loss of vision due to blood vessel disease of the eye
- you are pregnant or suspect you may be pregnant
- pancreatitis (inflammation of the pancreas) associated with high levels of fatty substances in your blood
- allergy (hypersensitivity) to ethinyl estradiol, levonorgestrel or to any of the other ingredients in TRIQUILAR (see **What the Medicinal Ingredients Are** and **What the Nonmedicinal Ingredients Are**)

What the medicinal ingredients are:

levonorgestrel and ethinyl estradiol

What the nonmedicinal ingredients are:

calcium carbonate, cornstarch, glycerine, lactose, magnesium stearate, montanglycol wax, polyethylene glycol, polyvinylpyrrolidone, red ferric oxide, sucrose, talc, titanium dioxide and yellow ferric oxide

What dosage forms it comes in:

TRIQUILAR is a combined oral contraceptive that contains three different combinations of levonorgestrel and ethinyl estradiol as described in the charts below. TRIQUILAR is available in a 21-day or 28-day treatment cycle. Each phase of pills is a different strength and should be taken successively.

TRIQUILAR 21 (21-day Treatment Cycle)

Day	Pill Description	Amount of Levonorgestrel	Amount of Ethinyl Estradiol
1 – 6	light brown	0.05 mg	0.03 mg
7 – 11	white	0.075 mg	0.04 mg
12 – 21	ochreous	0.125 mg	0.03 mg

TRIQUILAR 28 (28-day Treatment Cycle)

Day	Pill Description	Amount of Levonorgestrel	Amount of Ethinyl Estradiol
1 – 6	light brown	0.05 mg	0.03 mg
7 – 11	white	0.075 mg	0.04 mg
12 – 21	ochreous	0.125 mg	0.03 mg
22 – 28	slightly larger, white	no active ingredients	

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

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

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

Do not use TRIQUILAR if you are taking ombitasvir, paritaprevir, ritonavir, with or without dasabuvir for the treatment of Hepatitis C. Using these drugs at the same time as TRIQUILAR has the potential to cause liver problems, such as an increase in the ALT liver enzyme. You can usually start TRIQUILAR about 2 weeks after finishing treatment with this combination of drugs used for Hepatitis C, but always consult with your doctor or pharmacist.

BEFORE you use TRIQUILAR, talk to your doctor or pharmacist if you:

- smoke
- are overweight
- have a history of breast disease (eg, breast lumps) or a family history of breast cancer
- have high blood pressure
- have high cholesterol
- have diabetes
- have heart or kidney disease
- have a history of seizures/epilepsy
- have a history of depression

- have a history of liver disease or jaundice
- wear contact lenses
- have uterine fibroids (benign tumors of the uterus)
- may be pregnant or are breastfeeding
- have systemic lupus erythematosus
- have inflammatory bowel disease such as Crohn's disease or ulcerative colitis
- have hemolytic uremic syndrome
- have sickle cell disease
- have any problems with the valves in your heart and/or have an irregular heart rhythm
- have been told that you have a condition called hereditary angioedema or if you have had episodes of swelling in body parts such as hands, feet, face or airway passages

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

If you see a different doctor, inform him or her that you are using TRIQUILAR.

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

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

TRIQUILAR should be used only under the supervision of a doctor, with regular follow-up to identify side effects associated with its use. Your visits may include a blood pressure check, a breast exam, an abdominal exam and a pelvic exam, including a Pap smear. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year. Use TRIQUILAR only on the advice of your doctor and carefully follow all directions given to you. You must use the birth control pill exactly as prescribed. Otherwise, you may become pregnant.

If you and your doctor decide that, for you, the benefits of TRIQUILAR outweigh the risks, you should be aware of the following:

THE RISKS OF USING TRIQUILAR

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

Women who use hormonal contraceptives have a higher incidence of blood clots. Blood clots are the most common serious side effects of birth control pills. The risk of developing blood clots is especially high during the first year a woman ever uses a hormonal contraceptive or restarts the same or a different hormonal contraceptive. Clots can occur in many parts of the body.

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

- sharp pain in the chest which may increase with deep breathing; coughing blood; sudden shortness of breath or rapid breathing; sense of anxiety; severe light headedness or dizziness; rapid or irregular heartbeat. These symptoms could indicate a possible blood clot in the lung.
- pain and/or swelling in the calf or along a vein in the leg; pain or tenderness in the leg which may be felt only when standing or walking, increased warmth in the affected leg; red or discoloured skin on the leg. These symptoms could indicate a possible blood clot in the leg.
- crushing chest pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; fullness, indigestion or choking feeling; sweating, nausea, vomiting or dizziness; extreme weakness, anxiety, or shortness of breath; rapid or irregular heartbeats. These symptoms could indicate a possible heart attack.
- sudden severe or worsening headache or vomiting; sudden trouble walking, dizziness, loss of balance or coordination; loss of consciousness or fainting with or without seizure; sudden confusion, disturbances of vision, speech or understanding; sudden weakness or numbness of the face, arm or leg. These symptoms could indicate a possible stroke.
- sudden partial or complete loss of vision. This symptom could indicate a blood clot in the eye.
- other signs of a blood clot can include: sudden pain, swelling, slight blue discoloration of an extremity; acute abdomen

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

The risk of clotting seems to increase with higher estrogen doses. **It is important, therefore, to use as low a dosage of estrogen as possible.**

Cancer of the breast, cervix, or liver may be life-threatening or may result in death.

2. Breast cancer

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

Some women who use hormonal contraceptives may be at increased risk of developing breast cancer before menopause, which occurs around age 50. These women may be long-term

users of birth control pills (more than eight years) or women who start using birth control pills at an early age. In a few women, the use of birth control pills may accelerate the growth of an existing but undiagnosed breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to birth control pills seem to be small, however. A yearly breast examination by a health care professional is recommended for all women.

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

3. Cervical cancer

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

4. Liver tumors

The short and long-term use of birth control pills also have been linked with the growth of liver tumors. Such tumors are **extremely** rare.

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

5. Gallbladder disease

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

6. Use in pregnancy

Birth control pills should not be taken by pregnant women. There is no evidence, however, that the birth control pill can damage a developing child. You should check with your doctor about risks to your unborn child from any medication taken during pregnancy.

7. Use after pregnancy, miscarriage or an abortion

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

8. Pregnancy after stopping TRIQUILAR

You will have a menstrual period when you stop using TRIQUILAR. You should delay pregnancy until another menstrual period occurs within four to six weeks. In this way the pregnancy can be more accurately dated. Contact your doctor for recommendations on alternate methods of contraception during this time.

9. Use while breastfeeding

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

INTERACTIONS WITH THIS MEDICATION

There are some medicines you must not take with TRIQUILAR (see **When It Should Not Be Used**). Certain drugs may interact with birth-control pills to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Please inform your doctor or pharmacist if you are taking or have recently taken any other drugs or herbal products, even those without a prescription. Also tell any other doctor or dentist who prescribes another drug (or the dispensing pharmacist) that you use TRIQUILAR. They can tell you if you need to use an additional method of contraception and if so, for how long.

Drugs that may interact with TRIQUILAR include:

- drugs used for the treatment of epilepsy (eg, primidone, phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate); tuberculosis (eg, rifampin, rifabutin), HIV infections (eg, ritonavir, nevirapine), and Hepatitis C Virus infections (eg, boceprevir, telaprevir)
- ombitasvir, paritaprevir, ritonavir, with or without dasabuvir (used to treat Hepatitis C)
- antibiotics (eg, penicillins, tetracyclines, clarithromycin, erythromycin) for infectious diseases
- cyclosporine
- antifungals (eg, griseofulvin, fluconazole, itraconazole, ketoconazole, voriconazole)
- cholesterol-lowering drugs (eg, clofibrate)
- drugs used for the treatment of certain heart diseases or for high blood pressure (eg, diltiazem, verapamil)
- antidiabetic drugs and insulin (for diabetes)
- prednisone
- sedatives and hypnotics (eg, benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate)

- meperidine (pain medication)
- antidepressants (eg, clomipramine)
- tizanidine (drugs used for multiple sclerosis [MS])
- theophylline (drug used for asthma)
- some nutritional supplements (eg, Vit. B_{12}, folic acid)
- antacids (use 2 hours before or after taking TRIQUILAR)

TRIQUILAR may also interfere with the working of other drugs.

Herbal or food products that may interact with TRIQUILAR include:

the herbal remedy St. John's wort (primarily used for the treatment of depressive moods)
grapefruit juice

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

PROPER USE OF THIS MEDICATION

Usual dose:

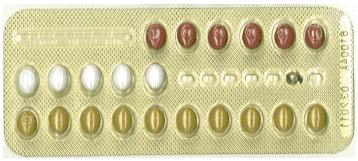
HOW TO TAKE TRIQUILAR

1. **READ THESE DIRECTIONS**

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

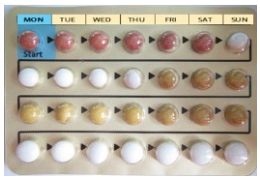
2. **LOOK AT YOUR PILL PACK** to see if it has 21 or 28 pills:

- **21-Pill Pack:** 21 hormone-containing (6 light brown, 5 white, and 10 ochreous) pills taken daily for three weeks, and then no pills taken for one week.



OR

- **28-Pill Pack:** 21 hormone-containing (6 light brown, 5 white and 10 ochreous) pills taken daily for three weeks, and then seven hormone-free "reminder" (slightly larger, white) pills taken daily for one week.



ALSO CHECK the pill pack for: 1) where to start, and 2) direction to take pills in (follow the arrows).

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

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

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

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

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

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

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

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

WHEN TO START THE FIRST PACK OF PILLS

BE SURE TO READ THESE INSTRUCTIONS:

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

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

21-DAY COMBINATION

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.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE**. Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

2. On the back of the pill pack, there is an area shaded in red which reads "I took my first pill on" followed by the days of the week directly below. Under each day of the week, there is a black circle which may be punctured in order to remember the day you first took your pill.

3. Take your first pill starting at the circle shaded in red marked "1."

4. Take one pill each day, following the direction of the arrows.

5. When you have taken all 21pills in this pack, wait seven days and then start a new pack of TRIQUILAR 21. During the seven days when you are not taking any pills, you should have your period.

6. The first pill in every subsequent pack will always be taken on the same day of the week that you first began taking TRIQUILAR 21 pills.

28-DAY COMBINATION

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

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.

2. Select the calendar sticker that is blue coded with the day you take your first pill and discard the rest.

3. Place the selected calendar sticker on the designated area, aligning the blue section with the blue box marked "START."

4. Take your first pill starting at the blue box marked "START."

5. Take one pill each day, following the direction of the arrows. Your period should usually occur during the last week of pills.

6. When you have finished this pack, start a new pack of TRIQUILAR 28 on the next day.

7. The first pill in every subsequent pack will always be taken on the same day of the week that you first began taking TRIQUILAR 28 pills.

WHAT TO DO DURING THE MONTH

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

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

2. **WHEN YOU FINISH A PACK**

- 21 PILLS

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

- 28 PILLS

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

Overdose:

Symptoms of overdose may include nausea, vomiting, or vaginal bleeding. Even girls who have not yet had their first menstrual period but have accidentally taken this medicine may experience such bleeding. Available information from cases of accidental ingestion of oral contraceptives by children indicates no serious effects.

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

Missed dose:

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

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

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

WHAT TO DO IF YOU MISS PILLS

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

Sunday Start	**Other than Sunday Start**
Miss One Light Brown, White or Ochreous Pill At Any Time	**Miss One Light Brown, White or Ochreous Pill At Any Time**
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 Light Brown, White or Ochreous Pills in a Row	**Miss Two Light Brown, White or Ochreous Pills in a Row**
First Two Weeks: 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.	**First Two Weeks:** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills.
Third Week 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**
Miss Three or More Light Brown, White or Ochreous Pills in a Row	**Miss Three or More Light Brown, White or Ochreous Pills in a Row**
Anytime in the cycle 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**	**Anytime in the cycle** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up (barrier) method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If you miss two periods in a row, call your doctor or clinic.**

NOTE: 28-DAY PACK - If you forget any of the seven slightly larger, hormone-free white "reminder" pills in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

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

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

Noncontraceptive Benefits of Birth Control Pills

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

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

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects have been observed in studies of women taking TRIQUILAR:

Common:
painful menstrual periods, spotting, breast pain, increased and decreased libido, breakthrough bleeding, change in skin pigmentation, nausea and/or vomiting, headache, migraine, depression, varicose veins, acne

Uncommon:
increased appetite, swelling, thrombophlebitis (inflammation of veins), weight gain

If you experience new onset of high blood pressure or worsening of high blood pressure, contact your doctor or pharmacist.

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

- difficulty wearing contact lenses
- vaginal irritation or infections
- urinary tract infections or inflammation
- upper respiratory tract infections (colds, bronchitis, runny or stuffy nose, sore throat, etc)
- severe headaches
- depression, insomnia, nervousness
- amenorrhea (lack of a period or breakthrough bleeding)
- back pain
- abdominal pain
- flu-like symptoms
- allergy, fatigue, fever
- diarrhea, flatulence
- rash

Many women have spotting or light bleeding or may feel sick to their stomach during the first three months on the pill. If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

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

Symptom / Possible Side Effect	Talk With Your Doctor or Pharmacist		Stop Taking Drug and Call Your Doctor or Pharmacist
	Only if severe	In all cases	

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

Symptom / Possible Side Effect		Talk With Your Doctor or Pharmacist		Stop Taking Drug and Call Your Doctor or Pharmacist
		Only if severe	In all cases	
Common	Persistent sad mood			✓
Uncommon	Abdominal pain, nausea or vomiting or lump in the abdomen		✓	
	Breast lump		✓	
	Crushing chest pain or heaviness			✓
	Pain or swelling in the leg			✓
	Sharp pain in the chest, coughing blood, or sudden shortness of breath			✓
	Sudden partial or complete loss of vision or double vision			✓
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, or weakness or numbness in the face, arm or leg			✓
	Unexpected vaginal bleeding		✓	
	Unusual swelling of the extremities		✓	
	Yellowing of the skin or eyes (jaundice)			✓

This is not a complete list of side effects. If you have any unexpected effects while taking TRIQUILAR, contact your doctor or pharmacist.

HOW TO STORE IT

Store in original packaging between 15ºC and 30ºC. Keep out of reach of children and pets.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

Canada Vigilance Program

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

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

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

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

MORE INFORMATION

For more information, please contact your health professional or pharmacist first, or Bayer Medical Information at 1-800-265-7382 or canada.medinfo@bayer.com.

This document plus the full Product Monograph, prepared for health professionals can be found at: http://www.bayer.ca or by contacting the manufacturer at the above-mentioned phone number and email address.

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