COMPLETE PRESCRIBING INFORMATION

TRIPHASIL® 21 and TRIPHASIL® 28

50 µg Levonorgestrel and 30 µg Ethinyl Estradiol Tablets
75 µg Levonorgestrel and 40 µg Ethinyl Estradiol Tablets
125 µg Levonorgestrel and 30 µg Ethinyl Estradiol Tablets

ORAL CONTRACEPTIVE

MONTREAL, CANADA

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TRIPHASIL® 21 AND TRIPHASIL® 28
(Levonorgestrel and Ethinyl Estradiol Tablets)

COMPLETE PRESCRIBING INFORMATION
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NAME OF DRUG

TRIPHASIL® 21 AND TRIPHASIL® 28

(Levonorgestrel and Ethinyl Estradiol Tablets)

THERAPEUTIC CLASSIFICATION

ORAL CONTRACEPTIVE

ACTION

Although the primary mechanism of action is inhibition of ovulation, the effectiveness of Triphasil ® tablets may also result from other mechanisms of action, such as hostility of the cervical mucus to sperm penetration and migration.

INDICATION

Triphasil® tablets are indicated for conception control.

CONTRAINDICATIONS

Combination Oral Contraceptives (COCs) are contraindicated in the following:

1. History of or actual thrombophlebitis or thromboembolic disorders.
2. History of or actual cerebrovascular disorders.
3. History of or actual myocardial infarction or coronary arterial disease.
4. Deep vein thrombosis (current or history).
5. Thrombogenic valvulopathies and Thrombogenic rhythm disorders.
6. Hereditary or acquired thrombophilias.
7. Migraine with focal neurological symptoms, such as aura (current or history).
8. Active liver disease, or history of or actual benign or malignant liver tumours.
9. Known or suspected carcinoma of the breast.
10. Known or suspected estrogen-dependent neoplasia.
11. Undiagnosed abnormal vaginal bleeding.
12. Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
13. When pregnancy is suspected or diagnosed.
14. Hypersensitivity to any of the components of TRIPHASIL®
15. Diabetes with vascular involvement.
16. Uncontrolled hypertension.

WARNINGS

1. Predisposing Factors For Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality from COC use. This risk increases with age and with the extent of smoking. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use in women who 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 COCs 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.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in COC users older than 35 years of age. Women should be counseled not to smoke.

2. Discontinue medication at the earliest manifestation of the following:

A. Venous and arterial thrombosis and thromboembolism

Use of COCs is associated with an increased risk of venous and arterial thrombotic and thromboembolic events. For any particular estrogen/progestin combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestin that is compatible with a low failure rate and the needs of the individual patient.

New users of COCs should be started on preparations containing less than 50 μg of estrogen.

- Venous thrombosis and thromboembolism

Use of COCs increases the risk of venous thrombotic and thromboembolic events. Reported events include deep venous thrombosis, thrombophlebitis, pulmonary embolism and mesenteric thrombois. For information on retinal vascular thrombosis see **PRECAUTIONS** (Ocular Disease).

The use of any oral contraceptives carries an increased risk of venous thrombotic and thromboembolic events compared with no use. The excess risk is highest during the first year a woman ever uses a combined oral contraceptive. This increased risk is less than the risk of venous thrombotic and thromboembolic events associated with pregnancy which is estimated as 60 cases per 100,000 woman-years. Venous thromboembolism is fatal in 1-2% of cases.

The risk of venous thrombotic and thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism. Caution must be exercised when prescribing COCs for such women.

- Arterial thrombosis and thromboembolism

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

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

B. Conditions that Predispose to Venous Thrombosis and thromboembolism (e.g. obesity, surgery or trauma with increased risk of thrombosis, immobilization after accidents or confinement to bed during long-term illness, recent delivery or second-trimester abortion [see Special Notes on Administration]). Other nonhormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **PRECAUTIONS**.

Examples of risk factors for arterial thrombotic and thromboembolic events are smoking, hypertension, hyperlipidemias, obesity and increasing age.

C. Visual Defects – Partial or Complete

D. Papilledema or Ophthalmic Vascular Lesions

E. Severe Headache of Unknown Etiology, Worsening of Pre-existing Migraine or Development of New Migraine (particularly migraine with Aura). Women with migraine who take COCs may be at increased risk of stroke.

3. A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using COCs compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of COC use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to an earlier detection of breast cancer in COC users (due to more regular clinical monitoring), the biological effects of COCs or a combination of both. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

PRECAUTIONS

1. Physical Examination and Follow-up

Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic

organs should be examined and a Papanicolaou smear should be taken if the patient has been sexually active.

The first follow-up visit should be 3 months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Workshop on Screening for Cancer of the Cervix. Their suggestion was that, for women who had two consecutive negative Pap smears, screening could be continued every three years to the age of 69.

2. Pregnancy

Oral contraceptives should not be taken by pregnant women. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the COC will damage the developing child.

3. Breast-feeding

In breast-feeding women, the use of COCs results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of COCs is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality

of the milk. Some adverse effects on the child have been reported, including jaundice and breast enlargement.

The use of COCs is generally not recommended until the nursing mother has completely weaned her child.

4. Hepatic Function

Patients who have had jaundice, including a history of cholestatic jaundice during pregnancy, or a history of COC-related cholestasis, are more likely to have this condition with COC use and, they should be given COCs with great care and under close observation. If these patients receive a COC they should be carefully monitored and, if the condition recurs, the COC should be discontinued.

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

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

Hepatic nodules (adenomas and focal nodular hyperplasia) have been reported, particularly in long-term users of COCs. 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.

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

5. Hypertension

Patients with essential hypertension whose blood pressure is well-controlled may be given oral 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.

Increases in blood pressure have been reported in women taking COCs. Elevated blood pressure associated with COCs use will generally return to baseline after stopping COCs, and there appears to be no difference in the occurrence of hypertension among ever- and never-users.

6. Diabetes

Glucose intolerance has been reported in COC users . Current low-dose COCs 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. Women who are predisposed to diabetes, with impaired glucose tolerance or who have diabetes mellitus should be carefully monitored if using COCs. 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.

7. Lipid Effects

A small proportion of women will have adverse lipid changes while taking oral contraceptives. Nonhormonal contraception should be considered in women with uncontrolled dyslipidemias. Persistent hypertriglyceridemia may occur in a small proportion of COCs users. Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Women who are being treated for hyperlipidemias should be followed closely if they elect to use COCs.

8. Ocular Disease

Patients who are pregnant or are taking COCs, 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.

With use of COCs, there have been reports of retinal vascular thrombosis which may lead to partial or complete loss of visions. If there are signs or symptoms such as visual changes, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, the COC should be discontinued and the cause immediately evaluated.

9. Breasts

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

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.

10. Cervix

Some studies suggest that COC use may be associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women.

However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

11. Fibroids

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

12. Emotional Disorders

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an 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.

13. Laboratory Tests

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

A. **Liver function tests**

Bromsulphthalein Retention Test (BSP)	Moderate increase
AST (SGOT) and GGT	Minor increase
Alkaline Phosphatase	Variable increase
Serum Bilirubin	Increased, particularly in conditions predisposing to or associated with hyperbilirubinemia

B. **Coagulation tests**

Factors II, VII, IX, X, XII and XIII	Increased
Factor VIII	Mild increase
Platelet aggregation and adhesiveness	Mild increase in response to common aggregating agents
Fibrinogen	Increased
Plasminogen	Mild increase
Antithrombin III	Mild decrease

Prothrombin Time	Increased

C. **Thyroid function tests**

Protein-bound Iodine (PBI)	Increased
Total Serum Thyroxine (T_3 and T_4)	Increased
Thyroid Stimulating Hormone (TSH)	Unchanged
Free T3 Resin Uptake	Decreased

D. **Adrenocortical function tests**

Plasma Cortisol	Increased
Cortisol Binding Globulin	Increased
Dehydroepiandrosterone sulfate (DHEAS)	Decreased

<u>Renal Function</u>

Plasma Creatinine	Increased
Creatinine Clearance	Increased

E. **Miscellaneous Tests**

Serum Folate	Occasionally decreased
Glucose Tolerance Test	Variable increase with return to normal after 6 to 12 months
Insulin Response	Mild to moderate increase
c-Peptide Response	Mild to moderate increase

14. Tissue Specimens

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

15. Return to Fertility

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

16. Vaginal Bleeding

In some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has not been taken according to directions prior to the first missed withdrawal bleed, or if two consecutive withdrawal bleeds are missed, tablet-taking should be discontinued and a nonhormonal back-up method of contraception should be used until the possibility of pregnancy is excluded.

Breakthrough bleeding/spotting may occur in women taking COCs, especially during the first three months of use. If this bleeding persists or recurs, nonhormonal causes should be considered and adequate diagnostic measures may be indicated to rule out pregnancy, infection, malignancy, or other conditions. Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology. If pathology has been excluded, (see also PRECAUTIONS: Cervix) continued use of the COC or a change to another formulation may solve the problem.

17. Amenorrhea

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.

18. Other

Patients should be counseled that this product does not protect against HIV infection (AIDS) or other sexually transmitted diseases. Diarrhea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations.

19. Thromboembolic Complications - Post-surgery

There is an increased risk of thromboembolic complications in COC users after major surgery. If feasible, COCs should be discontinued and an alternative method substituted at least one month prior to **major** elective surgery and during periods of prolonged immobilization. COC use should not be resumed for at least two weeks after major elective surgery , and only after the first menstrual period has occurred following hospital discharge.

20. Drug Interactions

The concurrent administration of oral contraceptives with other substances may result in an altered response to either agent. Decreased ethinyl estradiol (EE) serum concentration may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the oral contraceptive.

During concomitant use of EE-containing products and substances that may lead to decreased EE serum concentration, it is recommended that a nonhormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of Triphasil. In the case of prolonged use of such substances COCs should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased EE serum concentrations, use of a nonhormonal back-up method is recommended for at least 7 days. Longer use of a back-up method is advisable after discontinuation of substances that have lead to induction of hepatic microsomal enzymes, resulting in decreased EE serum concentrations. It may sometimes take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use and rate of elimination of the inducing substance.

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.

Examples of substances that may decrease serum EE concentrations:

- Any substance that reduces gastrointestinal transit time
- Hypericum perforatum, also known as St. John's wort, and ritonavir (possibly by induction of hepatic microsomal enzymes).
- Substances that induce hepatic microsomal enzymes, such as rifampicin, rifabutin, dexamethasone, modafinil, some protease inhibitors, topiramate.

Examples of substances that may increase serum EE concentrations:

- atorvastatin

- Competitive inhibitors for sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and acetaminophen.
- Substances that inhibit cytochrome P 450 3A4 isoenzymes such as indinavir, fluconazole, and troleandomycin.

Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with COCs.

Ethinyl estradiol may interfere with the metabolism of other drugs byinhibiting hepatic microsomal enzymes, or by inducing hepatic drugconjugation, particularly glucuronidation. Accordingly,

plasma and tissue concentrations of some drugs may either be increased (eg. cyclosporine, theophylline, corticosteroids) or decreased (eg. lamotrigine) by ethinyl estradiol.

For possible drug interactions with OCs see Tables I and II.

TABLE I*

Drugs that May Decrease The Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	Carbamazepine Ethosuximide Phenobarbital Phenytoin Primidone	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose Ocs (50μg ethinyl estradiol), another drug or another method.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces OC efficacy.	Use another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.

Other Drugs	Phenylbutazone** Antihistamines** Analgesics** Antimigraine Preparations** Vitamin E	Reduced OC efficacy has been reported. Remains to be confirmed.	

* Adapted from Dickey, R.P., ed.: *Managing Contraceptive Pill Patients*, 5th edition Creative Informatics Inc., Durant, OK, 1987.

** Refer to Oral Contraceptives 1994, A report by the Special Advisory Committee on Reproductive Physiology to the Drugs Directorate Health Protection Branch, Health Canada.

TABLE II*

Modification of Other Drug Action by Oral Contraceptives

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

TABLE II (continued)

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 OCs. OCs 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		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		OCs have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All Phenothiazines, Reserpine and similar drugs	Estrogen potentiates the hyperprolactinemia effect of these drugs.	Use other drugs or lower dose OCs. If galactorrhea or hyperprolactinemia occurs, use other method.
Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic Anti-depressants	Clomipramine (possibly others)	Increased side effects: i.e., depression.	Use with caution.
Vitamin B_{12}		OCs have been reported to reduce serum levels of Vitamin B_{12}.	May need to increase dietary intake, or supplement.

* Adapted from Dickey, R.P., ed.: *Managing Contraceptive Pill Patients*, 5th edition Creative Informatics Inc., Durant, OK, 1987.

NON-CONTRACEPTIVE BENEFITS OF ORAL CONTRACEPTIVES

Several health advantages other than contraception have been reported.

- Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.
- Oral contraceptives reduce the likelihood of developing benign breast disease.
- Oral contraceptives reduce the likelihood of development of functional ovarian cysts.
- Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
- 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.
- Other non-contraceptive benefits are outlined in *Oral Contraceptives 1994*, Health Canada.

Oral contraceptives **do not protect** against sexually transmitted diseases including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **in combination with** oral contraceptives.

ADVERSE REACTIONS

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

- Thrombophlebitis
- Pulmonary embolism
- Mesenteric thrombosis
- Neuro-ocular lesions (e.g. retinal thrombosis)
- Myocardial infarction
- Cerebral thrombosis
- Cerebral hemorrhage
- Hypertension
- Benign hepatic tumours
- Gallbladder disease, including gallstones*
- Stroke
- Transient ischemic attack
- Venous thrombosis
- Cervical intraepithelial neoplasia

- Cervical cancer
- Being diagnosed with breast cancer

* COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

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

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

Other Adverse Reactions:

The following adverse reactions have been reported in patients receiving COCs and are believed to be drug related:

- Gastrointestinal symptoms (such as abdominal pain, cramps and bloating)
- Breakthrough bleeding
- Spotting
- Change in menstrual flow

- Amenorrhea
- Dysmenorrhea
- Temporary infertility after discontinuance of treatment
- Fluid retention/Edema
- Chloasma (melasma) which may persist
- Breast changes: pain, tenderness, enlargement, and secretion
- Change in weight (increase or decrease)
- Change in cervical ectropion and secretion
- Diminution in lactation when given immediately postpartum
- Cholestatic jaundice
- Headache, including migraines
- Rash (allergic)
- Mood changes, including depression
- Reduced tolerance to carbohydrates
- Vaginitis including candidiasis
- Change in corneal curvature (steepening)
- Intolerance to contact lenses
- Retinal vascular thrombosis

The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted:

Congenital anomalies

Premenstrual syndrome

Cataracts

Optic neuritis**

Changes in appetite (increase or decrease)

Cystitis-like syndrome

Nervousness

Dizziness

Hirsutism

Alopecia

Loss of scalp hair

Erythema multiforme.

Erythema nodosum

Hemorrhagic eruption

Vaginitis

Exacerbation of porphyria

Impaired renal function

Hemolytic uremic syndrome

Budd-Chiari syndrome

Acne

Changes in libido

Colitis

Sickle-cell disease

Cerebral-vascular disease with mitral valve prolapse

Lupus-like syndrome

Anaphylactic (anaphylactoid reactions, including very rare cases of urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms)

Exacerbation of systemic lupus erythematosus

Exacerbation of Chorea

Aggravation of varicose veins

Pancreatitis

Hepatic adenomas

Hepatocellular Carcinomas

Changes in Serum Lipid levels, including hypertriglyceridemia

Decrease in serum folate levels***

** Optic neuritis may lead to partial or complete loss of vision.

***Serum folate levels may be depressed by COC therapy.

SYMPTOMS AND TREATMENT OF ACUTE OVERDOSAGE

Symptoms of COC overdosage in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females. There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms.

DOSAGE AND ADMINISTRATION

TRIPHASIL® 21 TABLETS REGIMEN

Each cycle consists of 21 days on medication and a 7-day interval without medication (three weeks on, one week off).

The 21-day regimen is comprised of the first six days of pale brown tablets, followed by five days of white tablets, followed by ten days of yellow tablets.

For the first cycle of medication, the patient is instructed to take one Triphasil® tablet daily for 21 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1.) The tablets are then discontinued for seven days (one week). Withdrawal bleeding should usually occur during the period that the patient is off the tablets.

The patient begins her next and all subsequent 21-day courses of Triphasil® tablets (following the same 21 days on, 7 days off) on the same day of the week that she began her first course. She begins taking her tablets seven days after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.

TRIPHASIL® 28 TABLETS REGIMEN

Each cycle consists of 21 days of Triphasil® tablets followed by 7 days of inert tablets (three weeks on Triphasil®, one week on inert tablets).

The 28-day regimen is comprised of the first six days of pale brown tablets, followed by five days of white tablets, followed by ten days of yellow tablets, followed by seven days of inert green tablets.

For the first cycle of medication, the patient is instructed to take one tablet for 28 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1.) Withdrawal bleeding should usually occur during the week the patient is taking the inert green tablets.

The patient begins her next and all subsequent 28-day courses of tablets on the same day of the week that she began her first course. She continues her next course of 28 tablets immediately

after the last course, regardless of whether or not a period of 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".

SPECIAL NOTES ON ADMINISTRATION

It is recommended that Triphasil® tablets be taken at the same time each day, preferably after the evening meal or at bedtime.

Triphasil® is effective from the first day of therapy if the tablets are begun as described under "DOSAGE AND ADMINISTRATION".

If Triphasil® tablets administration is initiated after Day 1 of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on Triphasil® until after the first seven consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered. Therefore, nonhormonal methods of contraception (such as condoms and spermicide) should be used for the first 7 days of tablet taking. In the nonlactating mother, Triphasil® may be prescribed in the postpartum period either immediately or at the first postpartum examination, whether or not menstruation has resumed.

If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding usually is transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician.

The patient should be instructed to use the following chart if she misses one or more of her birth control pills. She should be told to match the number of pills with the appropriate starting time for her type of pill.

SUNDAY START	OTHER THAN SUNDAY START
MISS ONE PILL	**MISS ONE PILL**
Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 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 2 pills in one day.
MISS TWO PILLS IN A ROW	**MISS TWO PILLS IN A ROW**
First 2 Weeks: 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. **Third Week**: 1. Keep taking 1 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 nonhormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS 2 PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**	**First 2 Weeks**: 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. **Third Week**: 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a nonhormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS 2 PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**
MISS THREE OR MORE PILLS IN A ROW	**MISS THREE OR MORE PILLS IN A ROW**
Anytime in the Cycle: 1. Keep taking 1 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 nonhormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **IF YOU MISS 2 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 nonhormonal back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS 2 PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**

Contraceptive reliability may be reduced if active tablets are missed and particularly if the missed tablets extend the tablet-free interval. If active tablets were missed and intercourse took place in the week before the tablets were missed, the possibility of pregnancy should be considered.

Advice in case of vomiting

If vomiting occurs within 3-4 hours after tablet-taking, absorption may not be complete. In such event, advice concerning the Management of Missed Tablet is outlined in the above chart**.**

The woman must take the extra active tablet(s) needed from a backup pack.

No preceding hormonal contraceptive use (in the past month)

Tablet-taking should start on day 1 of the woman's natural cycle (ie, the first day of her menstrual bleeding). Starting on days 2-7 (eg. Sunday start) is allowed, but for the first 7 days of tablet-taking during the first cycle, a nonhormonal back-up method of birth control (such as condoms and spermicide) is recommended.

Changing from another oral contraceptive pill

The woman should start TRIPHASIL preferably on the day after the last active tablet of her previous oral contraceptive, but at the latest, on the day following the usual tablet-free or inactive tablet interval of her previous oral contraceptive.

Changing from a progestin only method (progestin-only pill, injection, implant)

The woman may switch any day from the progestin-only pill and should begin TRIPHASIL the next day. She should start TRIPHASIL on the day of an implant removal or, if using an injection, the day the next injection would be due. In all of these situations, the woman should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking.

Following first-trimester abortion

The woman may start TRIPHASIL immediately. Additional contraceptive measures are not needed.

Following delivery or second-trimester abortion

Since the immediate post-partum period is associated with an increased risk of thromboembolism, COCs should be started no earlier than day 28 after delivery in the nonlactating mother or after second-trimester abortion. The woman should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman must wait for her first menstrual period.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

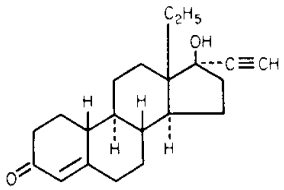
Proper Names: Levonorgestrel

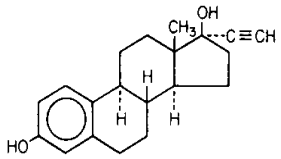
Ethinyl Estradiol

Chemical Names: Levonorgestrel: 18,19-Dinorpregn-4-en-20-yn-3-one,13-ethyl-17-hydroxy-,(17α)-(-)-

Ethinyl Estradiol: 19-Norpregna-1,3,5(10)-trien-20-yne-3, 17-diol,(17α)-

Structural Formulae:





LEVONORGESTREL ETHINYL ESTRADIOL

Molecular Formulae: Levonorgestrel: $C_{21}H_{28}O_2$

	Ethinyl Estradiol:	$C_{20}H_{24}O_2$
Molecular Weights:	Levonorgestrel:	312.46
	Ethinyl Estradiol:	296.41

Solubility: (USP Classification)

Levonorgestrel:	Slightly soluble in alcohol, insoluble in water.
Ethinyl Estradiol:	Insoluble in water, soluble in alcohol, chloroform, ether, in vegetable oils and in solutions of fixed alkali hydroxides.

Melting Point:	Levonorgestrel:	232° - 239°C
	Ethinyl Estradiol:	180° - 186°C

Biological Properties:

Levonorgestrel:	A unique, totally synthetic progestogen. Levonorgestrel is the International Non-proprietary Name for the biologically active d-enantiomer of norgestrel.
Ethinyl Estradiol:	A semi-synthetic estrogen. The presence of the ethinyl group at C 17 on ring D of the steroid nucleus prevents enzymatic degradation of the estradiol molecule and results in an orally active compound.

COMPOSITION

Non-Medicinal Ingredients: Each Triphasil® tablet contains: Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Microcrystalline Cellulose, Polacrilin Potassium,Polyethylene Glycol, Titanium Dioxide and Wax E.

In addition, each brown tablet contains synthethic red iron oxide and synthetic yellow iron oxide; each yellow tablet contains synthetic iron oxide; and each green tablet (inert tablets in the 28-day regimen) contains FD&C Blue No.1 aluminum lake and synthetic yellow iron oxide.

AVAILABILITY OF DOSAGE FORMS

PrTRIPHASIL® tablets are available in 21-day and 28-day Tablet Dispenser units.

Each pale brown tablet contains 50 μg levonorgestrel plus 30 μg ethinyl estradiol.

Each white tablet contains 75 μg levonorgestrel plus 40 μg ethinyl estradiol.

Each yellow tablet contains 125 μg levonorgestrel plus 30 μg ethinyl estradiol.

In the 28-day regimen, each green tablet contains inert ingredients.

INFORMATION FOR THE CONSUMER

A. INFORMATION TO PATIENTS ON HOW TO TAKE THE BIRTH CONTROL PILL

1. **READ THESE DIRECTIONS**

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

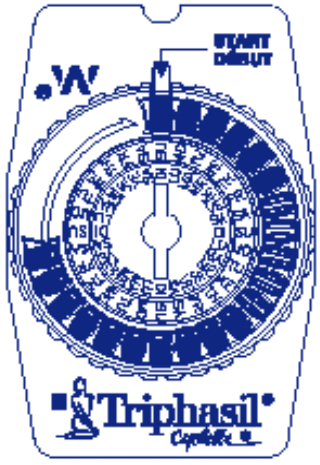
2. **LOOK AT YOUR PILL PACK** to see if it has 21 or 28 pills:

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

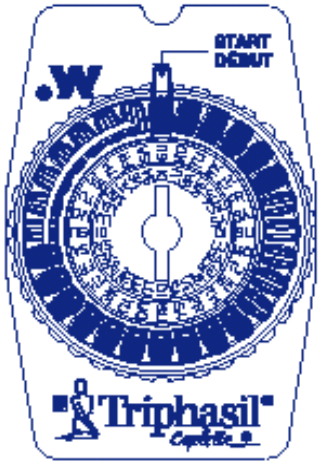
     or

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

ALSO CHECK:



Triphasil® 21



Triphasil® 28

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

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

5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL.** If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

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

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

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

8. **ALWAYS BE SURE YOU HAVE READY:**

   - **ANOTHER KIND OF BIRTH CONTROL** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
   - **AN EXTRA, FULL PACK OF PILLS.**

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

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

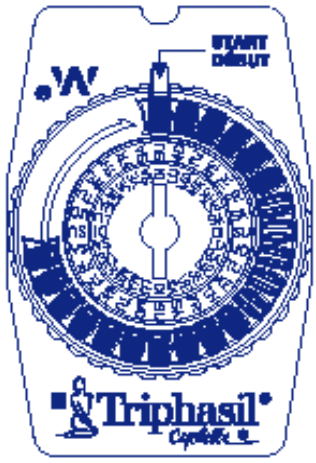
11. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

WHEN TO START THE *FIRST* PACK OF PILLS

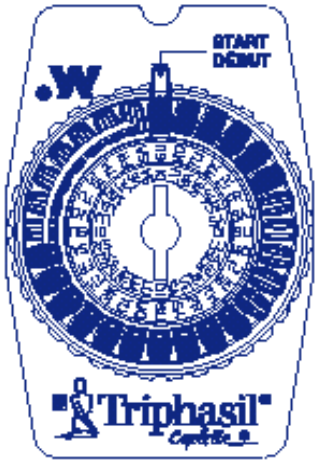
BE SURE TO READ THESE INSTRUCTIONS:

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

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



Triphasil® 21 tablets



Triphasil® 28 tablets

A. **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. If TRIPHASIL® tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on TRIPHASIL® until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet taking.

2. Take one pill at approximately the same time every day for 21 days, **THEN TAKE NO PILLS FOR SEVEN DAYS**. Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period.)

B. **28-DAY COMBINATION**

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

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** 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. If TRIPHASIL® tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on PrTRIPHASIL® until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet taking.

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

WHAT TO DO DURING THE MONTH

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

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

2. **WHEN YOU FINISH A PACK:**

- **21 PILLS**

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

- **28 PILLS**

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

WHAT TO DO IF YOU MISS PILLS

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

SUNDAY START	OTHER THAN SUNDAY START
Miss One Pill	**Miss One Pill**
Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.
Miss Two Pills in a Row	**Miss Two Pills in a Row**
First two weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**First two weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**
Miss Three or More Pills in a Row	**Miss Three or More Pills in a Row**

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 nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**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 nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **IF YOU MISS TWO PERIODS IN A ROW, CALL YOUR DOCTOR OR CLINIC.**

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

Always be sure you have on hand

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

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

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B. PACKAGE INSERT FOR PATIENTS USING ORAL CONTRACEPTIVES

(BIRTH CONTROL PILLS)

A supplementary information booklet that describes the benefits and risks of taking birth control pills (oral contraceptives) is available from your doctor or pharmacist. Be sure to obtain a copy and read it carefully before you start taking these pills.

Triphasil® is a birth control pill (oral contraceptive) which contains two female sex hormones, levonorgestrel and ethinyl estradiol. Each pale brown tablet contains 50 μg levonorgestrel and 30 μg ethinyl estradiol. Each white tablet contains 75 μg levonorgestrel and 40 μg ethinyl estradiol. Each yellow tablet contains 125 μg levonorgestrel and 30 μg ethinyl estradiol. Each green tablet (contained in Triphasil® 28 tablets only) is inert. 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.

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 always should be supervised by your doctor.

You should not use birth control pills if you have or have had any of the following conditions:

- unusual vaginal bleeding that has not yet been diagnosed;
- blood clots in the legs, lungs, eyes or elsewhere;
- a stroke, heart attack, or chest pain (angina pectoris);
- hereditary or acquired blood clotting disorders;
- migraines with neurological symptoms, such as aura;
- heart valve or heart rhythm disorders that may be associated with formation of blood clots;
- partial or complete loss of vision or other vision problems caused by a vascular disease;
- known or suspected cancer of the breast or sex organs;
- liver tumour associated with the use of the pill or other estrogen-containing products; and/or
- jaundice or liver disease if still present
- diabetes affecting your circulation;
- uncontrolled high blood pressure;
- allergy or hypersensitivity to any of the components of Triphasil (including levonorgestrel and ethinyl estradiol).

The pill should not be taken if you are pregnant or if pregnancy is suspected.

If you decide to take birth control pills

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

1. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users over 35 years of age. Women should not smoke.

2. 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.

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

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

   - sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung;
   - pain in the calf. This symptom could indicate a possible blood clot in the leg;

- crushing chest pain or heaviness. This symptom could indicate a possible heart attack;
- sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke;
- sudden partial or complete loss of vision. This symptom could indicate a possible blood clot in the eye;
- severe pain or lump in the abdomen. These symptoms could indicate a possible tumour of the liver;
- severe depression;
- yellowing of the skin (jaundice);
- unusual swelling of the extremities; and/or
- breast lumps. **ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTION ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.**

5. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing.

6. You will have a menstrual period when you stop taking birth control pills. You should delay pregnancy until another menstrual period occurs within four to six weeks. Contact your doctor for recommendations on alternative methods of contraception during this time.

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

8. The hormones in birth control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. If birth control pills are not resumed until nursing is established, however, the quantity and quality of breast milk does not seem to be affected. There is no evidence that birth control pills are harmful to the nursing infant. The use of COCs is generally not recommended until the nursing mother has completely weaned her child.

9. Should you require **MAJOR** surgery, inform your surgeon that you are using birth control pills.

10. **If you see a different doctor, inform him or her that you are taking birth control pills.** Tell the doctor that your birth control pills are **Triphasil®**.

11. **Inform your doctor if you are taking or if you start to take other medications. This applies to both prescription and non-prescription drugs.** These medications may change the effectiveness and/or cycle control of your birth control pills. **You may need to use a back-up method of birth control.**

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

13. Birth control pills **DO NOT PROTECT** against sexually transmitted diseases (STDs), including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

HOW TO TAKE BIRTH CONTROL PILLS

1. **READ THESE DIRECTIONS**

- before you start taking your pills, and

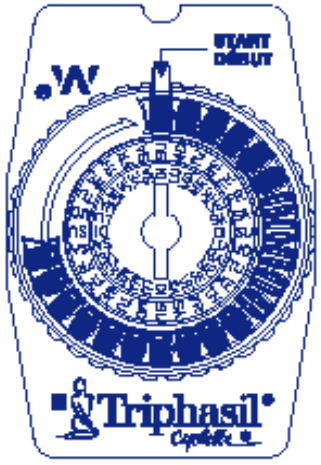
- any time you are not sure what to do.

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

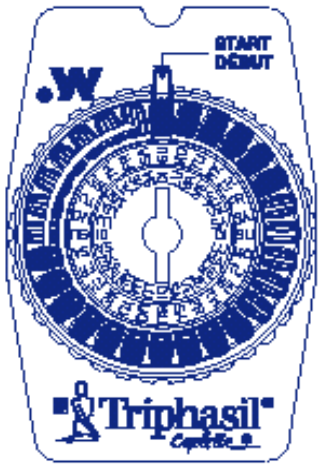
- **21-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week or

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

ALSO CHECK:



Triphasil® 21



Triphasil® 28

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

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

5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL.** If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

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

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

- when you start a pack late, or

- when you miss pills at the beginning or at the very end of the pack.

8. **ALWAYS BE SURE YOU HAVE READY:**

- **ANOTHER KIND OF BIRTH CONTROL** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
- **AN EXTRA, FULL PACK OF PILLS.**

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

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

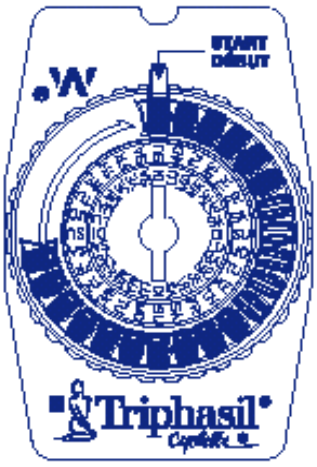
11. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

WHEN TO START THE *FIRST* PACK OF PILLS

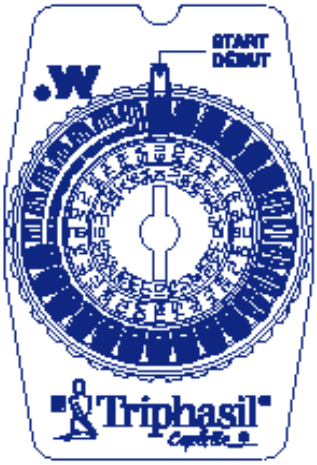
BE SURE TO READ THESE INSTRUCTIONS:

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

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



Triphasil® 21 tablets



Triphasil® 28 tablets

A. **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. If TRIPHASIL® tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on TRIPHASIL® until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet taking.

2. Take one pill at approximately the same time every day for 21 days, **THEN TAKE NO PILLS FOR SEVEN DAYS**. Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period).

B. **28-DAY COMBINATION**

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

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** 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. If TRIPHASIL® tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on TRIPHASIL® until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet taking.

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

WHAT TO DO DURING THE MONTH

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

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

2. **WHEN YOU FINISH A PACK:**

- **21 PILLS**

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

- **28 PILLS**

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

WHAT TO DO IF YOU MISS PILLS

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

SUNDAY START	OTHER THAN SUNDAY START
Miss One Pill	**Miss One Pill**
Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.
Miss Two Pills in a Row	**Miss Two Pills in a Row**
First two weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**First two weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**
Miss Three or More Pills in a Row	**Miss Three or More Pills in a Row**

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 nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**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 nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**

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

Always be sure you have on hand:

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

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

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C. SUPPLEMENTARY INFORMATION BOOKLET

FOR PATIENTS CONSIDERING THE USE OF ORAL CONTRACEPTIVES

(BIRTH CONTROL PILLS)

Introduction

This booklet will give you information to make an informed choice on the use of oral contraceptives. Oral contraceptives are also known as birth control pills or "the pill."

You should read this booklet if you are thinking about any method of birth control. If you have decided to take birth control pills, this booklet will help you understand both the risks and the benefits. It also will give you information on how to use birth control pills.

When taken as directed, birth control pills are a very effective way to prevent pregnancy. Only sterilization is more effective. The pill is convenient and has many benefits other than birth control. Most women do not develop serious and unpleasant side effects from using birth control pills.

The pill has important advantages over other methods of birth control. It also has certain risks that no other method has. Your doctor is the best person to explain the consequences of any possible risks.

You can help your doctor prescribe birth control pills as safely as possible. Tell your doctor about yourself, and be alert for the earliest signs of possible trouble.

Read this booklet carefully and discuss its contents with your doctor.

Types of birth control pills

There are two types of birth control pills:

1. The "combination pill" is the most common type. It contains two female sex hormones - an estrogen and a progestin. The amounts and types of estrogen and progestin differ from one preparation to another. The amount of estrogen is more important. The effectiveness and some dangers of birth control pills are related mainly to the amount of estrogen.

2. The "mini-pill" is the second type. It contains only one female sex hormone - a progestin.

How birth control pills work

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 mini-pill (progestin only) is slightly less effective than combination birth control pills.

Other ways to prevent pregnancy

Other methods of birth control are available to you. They are usually less effective than birth control pills. 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.

Who should not use birth control pills

You should not use birth control pills if you have or have had any of the following conditions:

- unusual vaginal bleeding that has not yet been diagnosed;
- blood clots in the legs, lungs, eyes, or elsewhere;
- a stroke, heart attack or chest pain (angina pectoris);
- hereditary or acquired blood clotting disorders;
- migraines with neurological symptoms, such as aura;
- heart valve or heart rhythm disorders that may be associated with formation of blood clots;
- partial or complete loss of vision or other vision problems caused by a vascular disease;
- known or suspected cancer of the breast or sex organs;
- liver tumour associated with the use of birth control pills or other estrogen-containing products; and/or
- jaundice or liver disease if still present
- diabetes affecting your circulation;
- uncontrolled high blood pressure;
- allergy or hypersensitivity to any of the components of Triphasil (including levonorgestrel and ethinyl estradiol).

The pill should not be taken if you are pregnant or if pregnancy is suspected.

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

- breast conditions
    - a strong family history of breast cancer

- breast disorders including pain, discharge from the nipples, thickenings, or lumps. In some circumstances, benefit may be derived from taking the pill; in other cases, adverse effects may follow.

- diabetes
- high blood pressure
- abnormal levels of fats in the bloodstream (high cholesterol or triglycerides)
- cigarette smoking
- migraines with neurological symptoms, such as aura (current and history)
- heart or kidney disease
- epilepsy
- depression
- fibroid tumours of the uterus
- gallbladder or pancreatic disease
- plans for forthcoming surgery
- history of jaundice or other liver disease
- obesity

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

The risks of birth control pills

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

Blood clots are the most common serious side effects of birth control pills. Clots can occur in many areas of the body.

- In the brain, a clot can result in a stroke.

- In a blood vessel of the heart, a clot can result in a heart attack.
- In the legs and pelvis, a clot can break off and travel to the lung resulting in a pulmonary embolus.
- In a blood vessel leading to an arm or leg, a clot can result in damage to or loss of a limb.

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.

Women who use birth control pills have a higher incidence of blood clots. The risk of clotting seems to increase with higher estrogen doses. **It is important, therefore, to use as low a dosage of estrogen as possible.**

> Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users over 35 years of age. Women should not smoke.

2. Breast cancer

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

Some women who use birth control pills may be at increased risk of developing breast cancer before menopause which occurs around age 50. These women may be long-term users of birth control pills (more than eight years) or women who start using birth control pills at an early age. In a few women, the use of birth control pills may accelerate the growth of an existing but undiagnosed breast cancer. Breast cancer has been diagnosed slightly more often in women who use the Pill than in women of the same age who do not use the Pill. This slight increase in the numbers of breast cancer diagnoses gradually disappears during the course of the 10 years after stopping use of the Pill. It is not known whether the difference is caused by the Pill. It may be that the women were examined more often, so that the breast cancer was noticed earlier. 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.

Women with the following conditions should be examined yearly by their doctors no matter what method of contraception they use:

- a strong history of breast cancer in the family;
- breast nodules or thickenings; and/or
- discharge from the nipple.

3. Dangers to a developing child if birth control pills are used during pregnancy

Birth control pills should not be taken by pregnant women. There is no evidence, however, that the pill can damage a developing child.

There is also no evidence that the use of birth control pills immediately before a pregnancy will adversely affect a baby's development. When a woman stops taking birth control pills to become pregnant, however, her doctor may recommend a different method of contraception until she has a period on her own. In this way, the pregnancy can be more accurately dated.

4. Gallbladder disease and liver tumours

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.

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

5. Other side effects of birth control pills

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

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

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

Other side effects may include

- growth of pre-existing fibroid tumours of the uterus
- depression;
- liver problems with jaundice (yellowing of the skin);

- an increase or decrease in hair growth, sex drive and appetite;
- skin pigmentation;
- headaches;
- rash; and/or
- vaginal infections.

Infrequently, there is a need to change contact lens prescription or an inability to use contact lenses.

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

Non-contraceptive benefits of birth control pills

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

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

Birth control pills **DO NOT PROTECT** against sexually transmitted diseases (STDs), including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

Periodic examination

A complete medical and family history is necessary before birth control pills are prescribed. A physical examination should include measuring blood pressure and examining the breasts, abdomen, pelvic organs, and limbs.

A second visit to your doctor should take place three months or sooner after starting birth control pills. During this visit, any side effects should be evaluated and your blood pressure checked again. Afterward, an annual examination similar to the first visit is recommended. A Pap smear is usually taken before starting birth control pills and then at intervals recommended by your doctor.

If you decide to take birth control pills

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

1. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users older than 35 years of age. Women should not smoke.

2. 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.

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

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

- sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung;
- pain in the calf. This symptom could indicate a possible blood clot in the leg;
- crushing chest pain or heaviness. This symptom could indicate a possible heart attack;
- sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke;
- sudden partial or complete loss of vision. This symptom could indicate a possible blood clot in the eye;

- severe pain or lump in the abdomen. These symptoms could indicate a possible tumour of the liver;
- severe depression;
- yellowing of the skin (jaundice);
- unusual swelling of the extremities; and/or
- breast lumps. **ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTION ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.**

5. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing.

6. You will have a menstrual period when you stop taking birth control pills. You should delay pregnancy until another menstrual period occurs within four to six weeks. Contact your doctor for recommendations on alternate methods of contraception during this time.

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

8. The hormones in birth control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. If birth control pills are not resumed until nursing is established, however, the quantity and quality of breast milk does not seem to be affected. There is no evidence that birth control pills are harmful to the nursing infant. The use of OCs is generally not recommended until the nursing mother has completely weaned her child.

9. Should you require **MAJOR** surgery, inform your surgeon that you are using birth control pills.

10. **If you see a different doctor, inform him or her that you are taking birth control pills.** Tell the doctor that your birth control pills are **Triphasil®**.

11. **Inform your doctor if you are taking, or if you start to take, other medications. This applies to both prescription and non-prescription drugs.** These medications may change the effectiveness and/or cycle control of our birth control pills. **You may need to use a back-up method of birth control.**

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

HOW TO TAKE BIRTH CONTROL PILLS

1. **READ THESE DIRECTIONS**

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

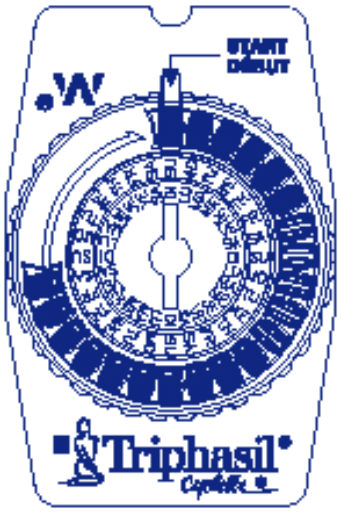
2. **LOOK AT YOUR PILL PACK** to see if it has 21 or 28 pills:

- **21-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then take no pills for one week

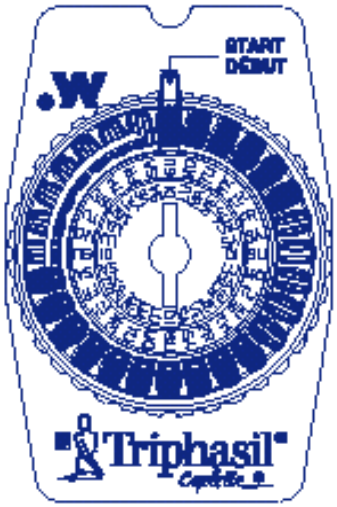
  or

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

ALSO CHECK:



Triphasil® 21



Triphasil® 28

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

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

5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL.** If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

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

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

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

8. **ALWAYS BE SURE YOU HAVE READY:**

- **ANOTHER KIND OF BIRTH CONTROL** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
- **AN EXTRA, FULL PACK OF PILLS.**

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

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

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

WHEN TO START THE *FIRST* PACK OF PILLS

BE SURE TO READ THESE INSTRUCTIONS:

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

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

Triphasil® 21

Triphasil® 28

A. 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. If Triphasil® tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on Triphasil® until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet-taking.

2. Take one pill at approximately the same time every day for 21 days; **THEN TAKE NO PILLS FOR SEVEN DAYS.** Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period.)

B. 28-DAY COMBINATION

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

1. THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE. 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. If Triphasil® tablets administration is initiated after Day 1 of the first menstrual cycle or postpartum, contraceptive reliance should not be placed on Triphasil® until after the first seven active tablets have been taken for seven consecutive days. Nonhormonal methods of contraception (such as latex condoms and spermicidal foam or gel) should be used for the first 7 days of tablet-taking.

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

WHAT TO DO DURING THE MONTH

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

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

2. WHEN YOU FINISH A PACK

- **21 PILLS**

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

- **28 PILLS**

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

WHAT TO DO IF YOU MISS PILLS

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

SUNDAY START	OTHER THAN SUNDAY START
Miss One Pill	**Miss One Pill**
Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.	Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.
Miss Two Pills in a Row	**Miss Two Pills in a Row**
First two weeks 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Keep taking one pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**First two weeks** 1. Take two pills the day you remember and two pills the next day. 2. Then take one pill a day until you finish the pack. 3. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. **Third week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**

Miss Three or More Pills in a Row	Miss Three or More Pills in a Row
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 nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 4. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**	**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 nonhormonal back-up method of birth control if you have sex in the seven days after you miss the pills. 3. You may not have a period this month. **If You Miss Two Periods in a Row, Call Your Doctor or Clinic.**

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

Always be sure you have on hand:

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

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

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CLINICAL TRIALS

The contraceptive efficacy and safety of Triphasil® (Levonorgestrel + Ethinyl Estradiol, Triphasic Regimen) has been evaluated in multi-centre studies.

A total of 3,546 patients, 46.2% of proven fertility, have completed 35,036 cycles over 37 months of use (Table 1).

Nine pregnancies, 7 resulting from subject failure and 2 from method failure, occurred during the cyclical use of Triphasil®. The overall pregnancy rate as calculated by the Life Table Method is 0.88 and the Pearl Index is 0.33 per 100 woman-years. The corrected pregnancy rate (excluding the pregnancies which were classified as subject failures) is 0.08 as calculated by the Life Table Method and the corrected Pearl Index is 0.07 per 100 woman-years. This rate was registered in spite of many cycles (7.7%) in which tablets were reportedly missed.

Cycle control was excellent with the mean length of the menstrual cycle being 28.0 days with a standard deviation of 4.5 days. The mean length of menses was 4.6 days with a standard deviation of 1.2 days, while menstrual flow was moderate in 70.9% and light in 24.7% of total cycles. Only 4.3% of the cycles were associated with a heavy menstrual flow. The mean latent period was 2.1 days with a standard deviation of 1.1 days.

Inappropriate bleeding during therapy was minimal. Breakthrough bleeding occurred in 13.0% of first cycles and 5.7% of total cycles. Spotting occurred in 18.3% of first cycles and 7.2% of total cycles. Intermenstrual bleeding of any type occurred in 24.2% of first cycles and 10.5% of total cycles. The incidence of missed withdrawal bleeding (termed amenorrhea pre-treatment) was low with the use of Triphasil®, 1.1% of total cycles.

Clinical side effects commonly associated with the use of oral contraceptives were reported in a very low incidence. Those reported with a total incidence of 1.0% or greater were: acne (1.5%), breast discomfort (1.8%), depression (3.2%), dysmenorrhea (1.8%), GI symptoms (1.5%), simple headache (10.0%), and nausea (1.5%), (Table 2).

No clinically significant weight or blood pressure changes occurred over 36 months use.

Long-term laboratory results over 30 months generally were within the normal range with no clinically significant differences from pretreatment values. Laboratory tests for safety revealed no deviations from normal indicative of drug toxicity, (Table 3).

Cervical cytology determinations were within normal limits except for 26 pretreatment (2.2%) and 12 during-treatment (1.4%) smears, which were all Class III, (Table 4).

Plasma progesterone determinations were conducted while on Triphasil®; 52 determinations were performed with 50 anovulatory values and 2 ovulatory values. Both ovulatory values were from the same subject. Overall, the plasma progesterone values indicate anovulation as the primary mechanism of action for Triphasil® in more than 96% of the cycles tested.

Medical conditions reported during therapy only included asthma (1), breast masses (4), cystitis (6), fibroids (1), kidney disease (1), liver disease (1), vaginal infections (62), varicosities (8) and venereal disease (5).

A total of 401 subjects (11.3%) dropped out of the study for medical reasons, of which 347 (9.8%) were for side effects commonly associated with the use of combination oral contraceptives. Another 26 medical reasons were not related to the use of the triphasic preparation.

TABLE 1: HISTOGRAM OF NUMBER OF WOMEN
BY NUMBER OF CYCLES COMPLETED

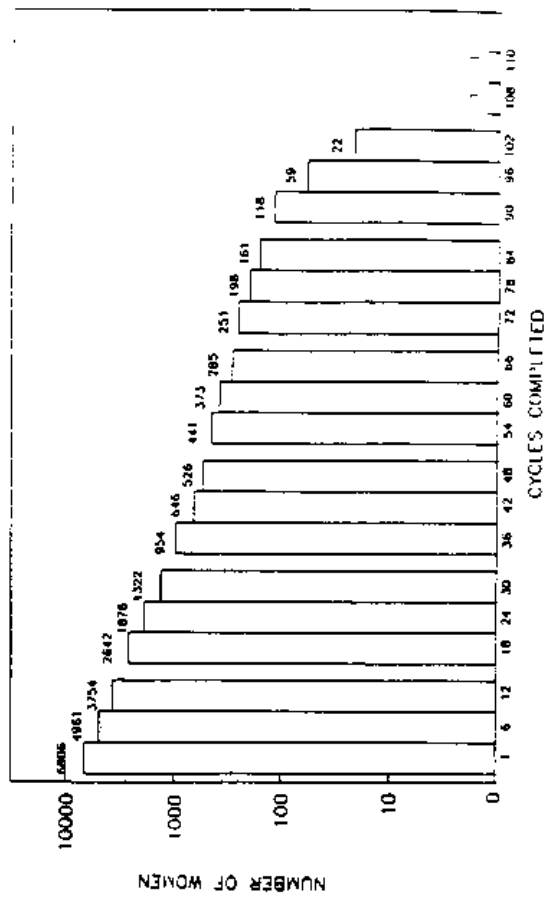

TABLE 2: Side Effects by Percentage in Triphasil® Treated Patients

NO. ENROLLED 3546	CYCLE 1	CYCLE 2	CYCLE 3	CYCLE 6	CYCLE 12	CYCLE 18	CYCLE 24	CYCLE 1 - 37 TOTAL INCIDENCE
Acne	2.7	2.8	2.2	1.2	0.6	0.4		1.5
Allergic Rash	0.1		0.1	0.2				0.1
Appetite Decrease	0.2	0.3	0.2	0.1				0.1
Appetite Increase	1.7	0.6	0.8	1.0	0.4			0.6
Backache	1.6	0.6	0.7	0.8	0.4	0.9		0.7
Breakthrough Bleeding	13.0	8.3	6.6	5.1	4.1	4.1	2.8	5.7
Breast Discomfort	4.4	2.8	2.9	1.9	1.5	0.4		1.8
Breast Enlargement	2.0	0.8	0.8	0.5	0.4			0.6
Breast Secretion			0.1	0.1				0.0
Chloasma or Melasma		0.1	0.1			0.4	0.9	0.0
Depression	1.9	4.4	3.4	3.7	2.7	5.7	5.2	3.2
Dizziness	0.9	0.3	0.5	0.5			0.9	0.4
Dysmenorrhea	3.0	2.5	2.7	2.1	1.1	0.9	1.7	1.8
Dyspareunia	0.1	0.1	0.2	0.2		0.4		0.1
Edema	0.9	0.3	0.4	0.6	0.2			0.3
Fatigue	0.6	0.8	0.7	0.3	0.8		0.9	0.6
G.I. Symptoms	3.8	2.1	1.7	1.5	0.6	1.3		1.5
Headache - Migraine	0.6	0.4	0.4	0.2	0.2	0.4		0.4
Headache - Simple	9.5	10.4	10.1	9.4	11.6	11.0	7.0	10.0
Hirsutism								0.0
Itching	0.3	0.1	0.1		0.2			0.1
Leg Cramps	0.7	0.6	0.3	0.3	0.4	0.4	0.9	0.4
Libido Decrease	0.3	0.1	0.2	0.3				0.1
Libido Increase	0.1	0.6	0.1	0.4	0.2			0.3
Loss of Scalp Hair	0.1	0.1	0.2					0.1
Missed Withdrawal Bleeding	0.3	1.6	1.6	1.2	1.0	1.1	1.4	1.1
Nausea	5.6	2.6	2.2	1.2	0.2	0.4		1.5
Nervousness	1.2	0.7	0.7	0.6	0.4	1.3	1.7	0.7
Spotting	18.3	10.4	8.2	6.5	5.1	4.1	4.4	7.2
Vaginal Discharge	0.9	0.4	0.5	0.8	0.8	1.8		0.6
Vomiting	0.6	0.4	0.3	0.2				0.3

TABLE 3: LABORATORY VALUES

INDEX	Pretreatment (Percentage)			Treatment (Percentage)		
	Low	Normal	High	Low	Normal	High
	HEMATOLOGY			HEMATOLOGY		
Hemoglobin	2.1	93.8	4.2	2.5	95.7	1.7
Hematocrit	7.9	90.9	1.3	7.9	91.1	1.0
RBC	12.1	86.4	1.5	9.9	89.0	1.0
WBC	4.1	90.6	5.3	3.7	91.7	4.6
Seg. Neutro.	13.0	80.2	6.8	13.3	80.4	6.3
Band Neutro.	-	98.7	1.3	0.1	98.2	1.6
Lymphocytes	4.6	79.0	16.4	4.1	80.1	15.8
Monocytes	1.5	93.6	4.9	1.1	93.7	5.3
Eosinophils	0.7	94.6	4.6	0.7	95.3	4.0
Basophils	-	98.4	1.6	-	97.8	2.2
Platelets	-	92.2	7.8	-	97.0	3.0
	BIOCHEMISTRY			BIOCHEMISTRY		
BUN	15.1	84.2	0.6	15.3	84.3	0.4
FBS	7.5	89.2	3.3	4.8	94.3	0.9
PPBS	-	100.0	-	-	100.0	-
Tot. Protein	-	100.0	-	2.9	97.1	-
Albumin	0.7	98.6	0.7	1.0	98.1	1.0
Globulin	-	100.0	-	-	100.0	-
Calcium	-	100.0	-	-	100.0	-
Uric Acid	-	100.0	-	3.0	97.0	-
Creatinine	-	100.0	-	-	100.0	-
Cholesterol	11.1	86.8	2.0	7.3	90.1	2.6
T_3	-	-	-	-	100.0	-
T_4	-	-	-	-	25.0	75.0
	LIVER PROFILE			LIVER PROFILE		
Tot. Bilirubin	1.0	94.5	4.5	0.3	98.4	1.3
SGOT	-	97.7	2.3	1.2	98.8	-
SGPT	0.7	94.2	5.1	6.2	91.9	1.9
LDH	12.8	87.2	-	7.4	91.2	1.5
Alk. Phosphatase	2.6	92.7	4.6	4.5	93.4	2.1
	URINALYSIS			URINALYSIS		
Spec. Gravity	3.5	90.7	5.8	1.7	95.0	3.4
pH	0.6	95.7	3.7	0.5	96.4	3.1
Urine Albumin	-	99.6	0.4	-	99.8	0.2
Urine Glucose	-	99.8	0.2	-	99.7	0.3

TABLE 4: PAP SMEAR BY CLASS

	Pretreatment				During Treatment			
Class	I	II	III	IV-V	I	II	III	IV-V
No.	1029	122	26	-	758	70	12	-
Percentage	(87.4%)	(10.4%)	(2.2%)	-	(90.2%)	(8.3%)	(1.4%)	-

PHARMACOLOGY

Animal

NORGESTREL IS A RACEMATE CONTAINING EQUAL PARTS OF D- AND L-ENANTIOMERS. THE L-ENANTIOMER HAS BEEN TESTED IN A BROAD RANGE OF BIOLOGICAL ASSAYS AND ITS INACTIVITY HAS BEEN CONFIRMED. THE D-ENANTIOMER (NAMED LEVONORGESTREL) ACCOUNTS FOR ALL THE BIOLOGICAL ACTIVITY FOUND IN NORGESTREL, AS LEVONORGESTREL WAS TWICE AS POTENT AS THE RACEMATE IN EXPERIMENTS IN WHICH NORGESTREL WAS EFFECTIVE.

Intensive biological investigations have been carried out with norgestrel alone and in combination with ethinyl estradiol in rats, mice, rabbits, dogs and monkeys.

In tests for progestational alteration of the endometrium of rabbits, norgestrel by the subcutaneous route proved to be about nine times more active than progesterone and about one hundred times more active than norethisterone by oral and subcutaneous routes. In contrast to norethisterone, which is inactive, norgestrel will maintain pregnancy in spayed laboratory rats and produce endometrial gland development in rabbits when administered directly into the uterine lumen. In a broad series of biological tests, its activities are similar to those of progesterone. Although certain androgenic effects typical of many relatives of 19-nortestosterone are evident at high doses, norgestrel is devoid of such effects at usual clinical doses, and the separation of progestational from androgenic effects for norgestrel is greater than for related compounds. Norgestrel is not estrogenic, nor is it apparently converted in vivo to estrogen; it is an exceedingly potent estrogen antagonist. When combined with ethinyl estradiol, norgestrel tends to ameliorate the effects of the estrogen, while the estrogen will modify the effects of the progestogen. In rats, suppression of fertility with norgestrel/ethinyl estradiol combinations is followed by recovery of normal fertility and fecundity.

Additional experiments in laboratory animals were directed toward evaluating the endocrine effects and safety of the norgestrel and ethinyl estradiol formulation at dose levels approximating those employed clinically (on a milligram per kilogram basis). Metrotropic effects (uterine glandular development and growth) were most clearly demonstrated. Blockade of pituitary gonadotrophins can be produced by the estrogenic component alone at the clinical dose range; this pituitary effect does not appear to be modified by addition of the progestogen.

The following properties, observed with high doses of norgestrel or norgestrel/ethinyl estradiol combinations, were absent at doses approximating the clinical range: pregnancy maintenance in spayed female rats; parturition delay in pregnant rats; estrogenic changes in mouse vaginal cytology; anti-estrogenic effect in mouse uterine growth or vaginal smear tests; androgenic, myotrophic or fetal masculinizing effects in rats; claudogenic (anti-nidatory) effects in rats; thymolymphatic involution in mice; mineralocorticoid effects in rats and dogs and anti-mineralocorticoid effects in rats. No glucocorticoid (rat liver glycogen) or anti-inflammatory (Selye pouch, TBR-arthritis or granuloma pellet tests) effects have been seen at any dose.

Human

Progestogens can have, in addition to progestational activity, estrogenic, anti-estrogenic and androgenic activity. When combined with estrogen, the progestogen will markedly affect the overall biological activity by producing a synergistic, summative or diminutional effect on activity. Comparisons of progestogen potency are not considered scientifically valid because the effects of one progestogen cannot be directly compared with those of another.[22]

A study of serum luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone and 17β-estradiol in patients taking other low-dose oral contraceptives indicated reduction or abolition of the

mid-cycle ovulatory peak and post-ovulatory levels commonly associated with these hormones and gonadotrophins respectively. (For plasma progesterone determinations, see Clinical Trials). Also, administering Triphasil®, Spona et al[26] showed that serum LH levels were suppressed. That FSH was not suppressed is borne out by the levels of 17β–estradiol which also remained at the follicular level throughout the cycle indicating that ovarian steroidogenesis was not completely arrested. However, it is obvious from the absence of the pre-ovulatory surge of estrogen and LH that ovulation is blocked with this triphasic formulation.[36] (The weaker suppression with Triphasil®, especially in the first six days of treatment, is compensated by the step-wise increase in the doses of both hormones in the next two phases where timing is important.)[36]

The increasing doses of levonorgestrel increase the viscosity of the cervical mucus (cervical barrier), and the degree of spinnbarkeit and ferning remain low, thereby increasing contraceptive protection by inhibiting the penetration and migration of sperm.[36] Spona et al also recorded the cervical score and karyopyknotic index of vaginal smear samples.

The conclusion was drawn that Triphasil® acts by inhibiting ovulation and providing a backup mechanism by reducing the cervical score.[26]

With this triphasic regimen, studies done by Robertson[10] and Brosens[10] indicate that a moderate degree of endometrial proliferation occurs 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 normal cycles.[35]

The results of studies on endogenous hormone levels while on Triphasil® indicate that the mid-cycle surge of 17β-estradiol and LH is inhibited; at the same time, basal endogenous hormone levels are maintained at follicular level concentrations and not eliminated. The endometrial developmental changes continue, but they do so at a reduced level with a shortened proliferative phase and a prolonged secretory phase.[35] This triphasic contraceptive readjusts the hormonal balance to a lower but functioning level.[34,35]

A human study of the metabolism of ^{14}C-labelled norgestrel, revealed that most of the urinary excretion of norgestrel occurred on the first day. There was no difference in the rate of excretion of norgestrel whether administered orally or intravenously. The amount of radioactivity in plasma fell rapidly within the first few hours and at the end of two days only small amounts were present. The foregoing and other studies with ^{14}C-labelled and unlabelled norgestrel have shown that saturation of the 4,5-double bond with and without concomitant reduction of the 3-carbonyl to a 3-hydroxyl group are important reactions during metabolism.

In a pharmacokinetic study using the tablet (75 μg levonorgestrel + 40 μg ethinyl estradiol), the mean pharmacokinetic parameter estimates for levonorgestrel were: C_{max} 4.1 ng/mL, t_{max} 1.5 hr, and $t_{½}$ 15 hr; and for ethinyl estradiol were: C_{max} 0.358 ng/mL, t_{max} 1.6 hr, and $t_{½}$ 14 hr.

TOXICOLOGY

ACUTE TOXICITY

Acute oral toxicity studies have been carried out with oral, intraperitoneal and subcutaneous doses of levonorgestrel alone, ethinyl estradiol alone and in a combination of 5:1 ratio respectively.

The following table represents the findings of these studies:

SPECIES	ROUTE OF ADMIN.	LD50 LEVONORGESTREL	LD50 ETHINYL ESTRADIOL	LD50 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

SPECIES	DRUGS DOSE AND ROUTE OF ADMINISTRATION	DURATION OF ADMINISTRATION	SYMPTOMS	HISTOPATHOLOGY
RAT 16/sex/group	Norgestrel Oral - mg/kg 0.0001%, 0.0005%, 0.0025%	26 weeks	No signs and symptoms of toxicity.	No histopathological changes.
	Levonorgestrel Oral - mg/kg 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 - mg/kg 0.05, 0.1, 0.5	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 - mg/kg 0.0 0.003, 0.015, 0.0375	continuous 7 years	Estrus inhibited in all but low dosage group. Uterine enlargement and endometrial hyperplasia at 0.015 and 0.0375 mg/kg.	Norgestrel 0.0375 mg group - many dogs with cysts and absence of luteal phase. 1 dog mammary carcinoma (0.0375)
	Levonorgestrel Oral - mg/kg 0.5	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.
DOG 16 females/dose	Levonorgestrel Oral - mg/kg 0.01, 0.05, 0.125	cyclic - 7 years	No unexpected findings. The only drug effects observed were at the higher dose levels, were endocrine related and were considered to be related to the desired pharmacological effects of a progestational agent.	No apparent drug-related changes during the post-mortem examination.
RHESUS MONKEY 16 females/dose	Norgestrel Oral - mg/kg 0.0, 0.003, 0.015, 0.075	continuous 10 years (120 months)	Red vaginal discharge less frequent in 0.015 and 0.075 mg/kg group.	Mammary nodules in 3 animals at 0.075 mg/kg. 1 animal at 0.003 and 0.015 mg/kg.
	Levonorgestrel Oral - mg/kg 1.0	cyclic - (21 days) 10 years (120 months)	Red vaginal discharge more frequent in withdrawal period. Fibrinogen levels increased.	Mammary nodule in 1 animal.

CHRONIC TOXICITY

SPECIES	DRUGS DOSE AND ROUTE OF ADMINISTRATION	DURATION OF ADMINISTRATION	SYMPTOMS	HISTOPATHOLOGY
MICE 40/sex/dose	I Norgestrel II Ethinyl Estradiol III Norgestrel + Ethinyl Estradiol (10+1) Oral - mg/kg 0.02 + 0.002 0.7 + 0.07 2.0 + 0.2 3.0 + 0.3	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 tumours. Lymphocarcinoma-males interstitial tumours-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 - mg/kg 0.02 + 0.002 0.5 + 0.05 2.0 + 0.2	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 tumours were significantly increased over controls in both male 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.

CHRONIC TOXICITY

SPECIES	DRUGS DOSE AND ROUTE OF ADMINISTRATION	DURATION OF ADMINISTRATION	SYMPTOMS	HISTOPATHOLOGY
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.

Reproduction and Teratology

At doses in the clinical range, norgestrel, ethinyl estradiol and their combinations have no demonstrable effects on pregnant rats, their pregnancies, their offspring or the reproductive potential of the young.

Also at doses approximating the clinical range, norgestrel and/or ethinyl estradiol have no observable effects on lactating rats, the lactation process or the nursing young.

At doses in the clinical range and above, a small dose-related increase in the number of abnormal fetuses is observed in mice treated during pregnancy with norgestrel/ethinyl estradiol combinations in a ratio of 5:1. Abnormalities include open eye, cleft palate, exencephaly and umbilical hernia. Rabbits treated during pregnancy with doses of norgestrel and ethinyl estradiol in the clinical raknge and above, failed to demonstrate any teratogenic potential for the drug.

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