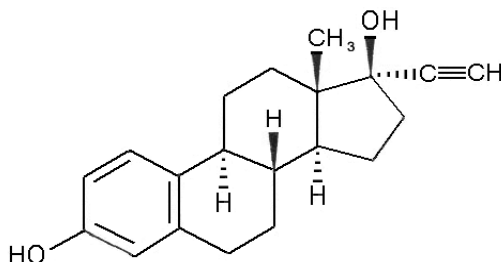


TRIPHASIL[®] TABLETS

(Ethinylloestradiol and Levonorgestrel)

DESCRIPTION

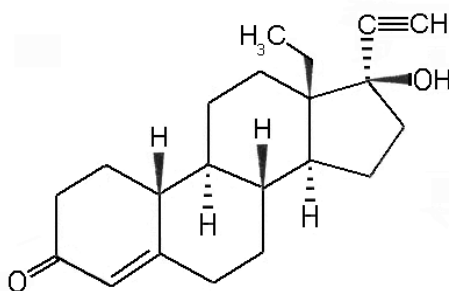
Ethinylloestradiol is a white to creamy white, odourless, crystalline powder. It is insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils, and aqueous solutions of alkali hydroxides. Chemically, ethinylloestradiol is 19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol and has the following structure:-



Chemical Formula: C₂₀H₂₄O₂
Melting Point: 181-185°C

Molecular Weight: 296.41
CAS No: [57-63-6]

Levonorgestrel is a white crystalline powder that is very slightly soluble in water, slightly soluble in alcohol and acetone, and soluble in chloroform. Chemically, levonorgestrel is (-)-13 β -Ethyl-17 β -hydroxy-18,19-dinor-17 α -pregn-4-en-20-yn-3-one and has the following structure:-



Chemical Formula: C₂₁H₂₈O₂
Melting Point: 232-239°C

Molecular Weight: 312.45
CAS No: [797-63-7]

Each TRIPHASIL package contains 28 tablets; 6 brown tablets each containing 30 microgram ethinylloestradiol and 50 microgram levonorgestrel, followed by 5 white tablets each containing 40 microgram of ethinylloestradiol and 75 microgram levonorgestrel, followed by 10 yellow tablets, each containing 30 microgram ethinylloestradiol and 125 microgram levonorgestrel, followed by 7 red inert tablets.

PHARMACOLOGY

The hormonal components of TRIPHASIL inhibit ovulation by suppressing gonadotropin release. Secondary mechanisms, which may contribute to the effectiveness of TRIPHASIL as a contraceptive, include changes in the cervical mucus (which increase the difficulty of sperm penetration) and changes in the endometrium (which reduce the likelihood of implantation).

Pharmacokinetics

Ethinylestradiol and levonorgestrel are rapidly and almost completely absorbed from the gastrointestinal tract. Ethinylestradiol is subject to considerable first-pass metabolism with a mean bioavailability of 40-45%. Levonorgestrel does not undergo first-pass metabolism and is therefore completely bioavailable.

Levonorgestrel is extensively plasma protein bound both to sex hormone binding globulin (SHBG) and albumin. Ethinylestradiol, however, is bound in plasma only to albumin and enhances the binding capacity of SHBG. Following oral administration, peak plasma levels of each drug occur within 1 to 4 hours.

The elimination half-life for ethinylestradiol is approximately 25 hours. It is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present both free and as conjugates with glucuronide and sulphate. Conjugated ethinylestradiol is excreted in bile and subject to enterohepatic recirculation. About 40% of the drug is excreted in the urine and 60% is eliminated in the faeces.

The elimination half-life for levonorgestrel is approximately 24 hours. The drug is primarily metabolised by reduction of the A ring followed by glucuronidation. About 60% of levonorgestrel is excreted in the urine and 40% is eliminated in the faeces.

INDICATIONS

TRIPHASIL is indicated for the prevention of pregnancy.

CONTRAINDICATIONS

TRIPHASIL should not be used in women with any of the following conditions:

1. A history of or current deep-vein thrombosis, thrombophlebitis, or thromboembolic disorders, thrombogenic valvulopathies, thrombogenic rhythm disorders.
2. Hereditary or acquired predisposition for venous or arterial thrombosis.
3. Cerebrovascular or coronary artery disease.
4. Known or suspected carcinoma of the breast.
5. Known or suspected oestrogen-dependent neoplasia.

6. Undiagnosed abnormal genital bleeding.
7. Known or suspected pregnancy.
8. Benign or malignant liver tumour, which developed during the use of oestrogen-containing products or active liver disease, as long as liver function has not returned to normal.
9. Diabetes with vascular involvement.
10. Uncontrolled hypertension.
11. Headaches with focal neurological symptoms, (such as aura), including hemiplegic migraine
12. Hypersensitivity to any of the components of TRIPHASIL.

PRECAUTIONS

Cigarette Smoking

CIGARETTE SMOKING INCREASES THE RISK OF SERIOUS CARDIOVASCULAR SIDE EFFECTS FROM THE USE OF ORAL CONTRACEPTIVES. THE RISK INCREASES WITH AGE AND WITH HEAVY SMOKING (15 OR MORE CIGARETTES PER DAY) AND IS QUITE MARKED IN WOMEN OVER 35 YEARS OF AGE. WOMEN WHO USE ORAL CONTRACEPTIVES SHOULD BE STRONGLY ADVISED NOT TO SMOKE.

Thromboembolic Disorders

Use of combined oral contraceptives is associated with an increased risk of venous and arterial thrombotic and thromboembolic events.

For any particular oestrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of oestrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient.

New acceptors of combined oral contraceptives should be started on preparations containing less than 50 micrograms of oestrogen.

Venous Thrombosis and Thromboembolism

Use of combined oral contraceptives increases the risk of venous thrombotic and thromboembolic events. The physician should be alert to the earliest manifestations of those disorders (e.g. thrombophlebitis, pulmonary embolism, cerebrovascular insufficiency, cerebral haemorrhage, cerebral thrombosis, coronary occlusion, retinal thrombosis, mesenteric thrombosis). Should any of these occur or be suspected; the drug should be discontinued immediately.

The use of combined oral contraceptives carries an increased risk of venous thrombotic and thromboembolic events compared to no use. The excess risk is highest during the first year a

woman ever uses a combined oral contraceptive. The approximate incidence of VTE in users of low oestrogen dose (<50µg ethinyloestradiol) oral contraceptives is up to 4 per 10,000 woman years compared to 0.5-3 per 10,000 woman years in non-oral contraceptive users. This increased risk is less than the risk of venous thrombotic and thromboembolic events associated with pregnancy (i.e., 6 per 10,000 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. When prescribing oral contraceptives, bear in mind the following predisposing conditions: obesity, surgery or trauma with increased risk of thrombosis, recent delivery or second trimester abortion or prolonged immobilisation.

A four-to six-fold increased risk of thromboembolic complications following surgery has been reported in users of oral contraceptives. If feasible, oral contraceptives should be discontinued at least 4 weeks before and two weeks after surgery associated with an increased risk of thromboembolism and during prolonged immobilisation.

Since the immediate post-partum period is associated with an increased risk of thromboembolism, combined oral contraceptives should be started no earlier than day 28 after delivery or second-trimester abortion.

Arterial Thrombosis and Thromboembolism

The use of combined oral contraceptives increases the risk of arterial thrombotic and thromboembolic events. An increased risk of myocardial infarction and cerebrovascular events (ischaemic and haemorrhagic stroke, transient ischaemic attack) associated with the use of oral contraceptives has been reported. The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors or predisposing conditions

Caution must be exercised when prescribing combined oral contraceptives for women with risk factors and predisposing conditions for arterial thrombotic and thromboembolic events. Examples of risk factors and predisposing conditions for arterial thrombotic and thromboembolic events are: smoking, hypertension, hyperlipidaemias, obesity, diabetes, history of pre-eclamptic toxæmia and increasing age.

Ocular Lesions

With use of combined oral contraceptives, there have been reports of retinal vascular thrombosis, which may lead to partial or complete loss of vision. Discontinue oral contraceptive and institute appropriate diagnostic and therapeutic measures if there is unexplained, gradual or sudden, partial or complete loss of vision; proptosis or diplopia; papilloedema; or any evidence of retinal vascular lesions or optic neuritis.

Elevated Blood Pressure

An increase in blood pressure has been reported in patients receiving oral contraceptives.

In women with hypertension, a history of hypertension or hypertension related diseases; another method of contraception may be preferable. If combined oral contraceptives are used

in such cases, close monitoring is recommended and, if a significant increase in blood pressure occurs, the drug should be discontinued. Combined oral contraceptives are contraindicated in women with uncontrolled hypertension.

In some women, hypertension may occur within a few months of beginning use. In the first year of use, the prevalence of women with hypertension is low but the incidence increases with increasing exposure. Age is also strongly correlated with the development of hypertension in oral contraceptive users. Women who previously have had hypertension during pregnancy may be more likely to develop an elevation of blood pressure when given oral contraceptives. If blood pressure rises markedly, the drug should be discontinued. Hypertension that develops as a result of taking oral contraceptives usually returns to normal after discontinuing the drug.

Carcinoma of the Reproductive Organs

Several epidemiological studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer. The studies suggest that there is an “ever used” effect in addition to duration of use. These findings must be balanced against evidence of effects attributable to sexual behaviour, smoking and other factors.

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

Long-term continuous administration of either natural or synthetic oestrogen in certain animal species increases the frequency of carcinoma of the breast, cervix, vagina and liver.

In all cases of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate diagnostic measures should be taken to eliminate the possibility of malignancy. Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care.

Hepatic Neoplasia/Liver Disease

In very rare cases hepatic adenomas, and extremely rare cases, hepatic hepatocellular carcinoma may be associated with combined oral contraceptive use. Hepatic adenomas may rupture and cause death through intra-abdominal haemorrhage. The risk appears to increase with duration of combined oral contraceptive use. Such lesions may present as an abdominal mass or with the signs and symptoms of an acute abdomen and should be considered if the patient has abdominal pain and tenderness or evidence of intra-abdominal bleeding.

Cholestatic jaundice has been reported in users of oral contraceptives. If this occurs, the drug should be discontinued. Women with a history of cholestasis during pregnancy or combined oral contraceptive-related cholestasis are more likely to have this condition with combined oral contraceptive use. If these patients receive a combined oral contraceptive they should be carefully monitored and, if the condition recurs, the combined oral contraceptive should be discontinued.

Hepatocellular injury has been reported with combined oral contraceptive use. Early identification of drug-related hepatocellular injury can decrease the severity of hepatotoxicity when the drug is discontinued. If hepatocellular injury is diagnosed, patients should stop their combined oral contraceptive use, use a non-hormonal form of contraception and consult their doctor.

Steroid hormones may be poorly metabolised in patients with impaired liver function and should be administered with caution to such patients.

Gallbladder Disease

Studies report an increased risk of surgically confirmed gallbladder disease in users of oestrogens and oral contraceptives. Combined oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

Headache

The onset or exacerbation of migraine or development of headache of a new pattern that is recurrent, persistent, or severe, requires discontinuation of the drug and evaluation of the cause.

Women with migraine (particularly migraine with aura) who take combined oral contraceptives may be at increased risk of stroke.

Medical Examinations

A thorough personal and family medical history and physical examination should be performed before prescribing oral contraceptives and periodically during their administration. Special attention should be given to blood pressure, breasts, abdomen, and pelvic organs. As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed. Papanicolaou smears should be performed before prescribing these drugs and periodically during their administration. Baseline and periodic blood glucose determinations should be performed in patients predisposed to diabetes mellitus.

Carbohydrate and Lipid Metabolic Effects

Glucose intolerance has been reported in combined oral contraceptive users. Women with impaired glucose tolerance or diabetes mellitus who use combined oral contraceptives should be carefully monitored.

A small proportion of women will have adverse lipid changes while taking oral contraceptives. Non-hormonal contraception should be considered in women with uncontrolled dyslipidaemias.

Persistent hypertriglyceridaemia may occur in a small proportion of combined oral contraceptive users. Elevations of plasma triglycerides may lead to pancreatitis and other complications.

Women who are being treated for hyperlipidaemias should be followed closely if they elect to use combined oral contraceptives.

Genital Bleeding

In some women withdrawal bleeding may not occur during the inactive-tablet interval. If TRIPHASIL 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 non-hormonal back-up method of contraception should be used until the possibility of pregnancy is excluded.

Breakthrough bleeding, spotting and amenorrhoea are frequent reasons for patients discontinuing oral contraceptives. Breakthrough bleeding/spotting may occur in women taking TRIPHASIL, especially during the first three months of use. If this bleeding persists or recurs, as in all cases of irregular bleeding from the vagina, nonfunctional causes should be borne in mind. In undiagnosed persistent or recurrent abnormal bleeding from the vagina, appropriate diagnostic measures are indicated to rule out pregnancy, infection, malignancy or other conditions. If pathology has been excluded, continuation of TRIPHASIL or a change to another formulation may solve the problem. Changing to a regimen with a higher oestrogen content, while potentially useful in minimising menstrual irregularity should be done only if necessary, since this may increase the risk of thromboembolic disease.

Women with a history of oligomenorrhoea or secondary amenorrhoea or young women without regular cycles may have a tendency to remain anovulatory or to become amenorrhoeic after discontinuation of oral contraceptives. Women with these pre-existing problems should be advised of this possibility and encouraged to use other methods of contraception. Post-use anovulation, possibly prolonged, may also occur in women without previous irregularities.

Depression

Oral contraceptives may cause depression. Patients with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related.

Vomiting or Diarrhoea

Diarrhoea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations (see **DOSAGE AND ADMINISTRATION**).

Other

Under the influence of oestrogen-containing oral contraceptives, pre-existing uterine leiomyomata may increase in size.

These agents may cause some degree of fluid retention. Women with cardiac or renal dysfunction, convulsive disorders, migraine, or asthma require careful observation since these conditions may be exacerbated by the fluid retention which may occur in users of oral contraceptives.

Users of oral contraceptives may have disturbances in normal tryptophan metabolism, which may result in a relative pyridoxine deficiency. The clinical significance of this is yet to be determined.

Serum folate levels may be depressed by oral contraceptive use. Women who became pregnant shortly after discontinuing these drugs may have a greater chance of developing folate deficiency and its complications.

Patients should be counselled that this product does not protect against HIV infection (AIDS) or other sexually transmitted diseases.

Use During or Immediately Preceding Pregnancy

Category B3

Pregnancy must be excluded before starting TRIPHASIL. If pregnancy occurs during use of TRIPHASIL, the preparation must be withdrawn immediately.

Oral contraceptives have not been shown to have any deleterious effects on the foetus or to increase the incidence of miscarriage in women who discontinue their use PRIOR to conception. However, in women who discontinue oral contraceptives with the intent of becoming pregnant, a non-hormonal method of contraception is recommended for three months before attempting to conceive.

Animal studies have shown that high doses of progestogens can cause masculinisation of the female foetus. The results of these experiments in animals do not seem to be relevant to humans because of the low doses used in oral contraceptives

Studies do not suggest a teratogenic effect when oral contraceptives are taken inadvertently during early pregnancy.

Female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that oestrogens are ineffective for these indications, and there is no evidence from well-controlled studies that progestogens are effective for these uses.

The administration of progestogen-only or oestrogen-progestogen combinations to induce withdrawal bleeding should not be used as a test for pregnancy.

Ectopic as well as intrauterine pregnancy may occur in contraceptive failures.

Use during Lactation

Oestrogen-containing oral contraceptives given in the postpartum period may interfere with lactation. There may be a decrease in the quantity and a change in the composition of the breast milk. Furthermore, small amounts of contraceptive steroids and/or metabolites of such oral contraceptives have been identified in the milk of mothers receiving them. A few adverse effects on the child have been reported, including jaundice and breast enlargement. The use of oestrogen-containing oral contraceptives should be deferred until the infant has been completely weaned.

Drug Interactions

Interactions between ethinylestradiol and other substances may lead to decreased or increased ethinylestradiol concentrations, respectively.

Decreased ethinylestradiol serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the oral contraceptive.

Examples of substances that may decrease serum ethinylestradiol concentrations include any substance that reduces gastrointestinal transit time and, therefore, ethinylestradiol absorption, and substances that induce hepatic microsomal enzymes, such as rifampicin, phenytoin, primidone, rifabutin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, modafinil, ritonavir and barbiturates.

St. John's wort (*Hypericum perforatum*) may induce hepatic microsomal enzymes, which theoretically may result in reduced efficacy of oral contraceptives. This may also result in breakthrough bleeding.

During concomitant use of TRIPHASIL and substances that may lead to decreased ethinylestradiol serum concentrations, it is recommended that a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) be used in addition to the regular intake of TRIPHASIL. In the case of prolonged use of such substances combined oral contraceptives should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased ethinylestradiol serum concentrations, use of a non-hormonal back-up method of contraception is recommended for at least 7 days.

Longer use of a non-hormonal back-up method, a minimum of 4 weeks, is advisable after discontinuation of substances such as rifampicin that have led to induction of hepatic microsomal enzymes. 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.

Increased intermenstrual bleeding and occasional pregnancies have been reported during concomitant administration of oral contraceptives and ampicillin, phenoxymethyl penicillin, and other penicillins, sulphamethoxypyridazine, chloramphenicol, nitrofurantoin, tetracycline and neomycin. The mechanism appears to be reduced enterohepatic circulation

of sex steroids due to change in bowel flora. It may be prudent for women to use supplemental forms of contraception during therapy with these antibiotics.

Oral contraceptives have been reported to antagonise the effectiveness of antihypertensive agents, anticonvulsants, oral anticoagulants, and hypoglycaemic agents. Patients should be carefully monitored for a decreased response to these drugs.

Ethinylloestradiol may interfere with the metabolism of other drugs by inhibiting hepatic microsomal enzymes, or by inducing hepatic drug conjugation, particularly glucuronidation. Accordingly, plasma and tissue concentrations may either be increased (e.g. cyclosporin, theophylline, corticosteroids) or decreased (e.g., lamotrigine).

Oral contraceptives may alter the effectiveness of other drugs such as phenothiazines, beta-adrenergic antagonists, tricyclic antidepressants and caffeine by either potentiating/enhancing their pharmacological effects or by decreasing their clearance.

Oral contraceptives may interfere with the oxidative metabolism of diazepam and chlordiazepoxide, resulting in plasma accumulation of the parent compound. Patients receiving these benzodiazepines on a long-term basis should be monitored for increased sedative effects.

Examples of substances that may increase ethinylloestradiol concentrations include atorvastatin, competitive inhibitors for sulphation in the gastrointestinal wall, such as ascorbic acid and paracetamol and substances that inhibit cytochrome P4503A4 isoenzymes such as indinavir and fluconazole.

The effects of benzodiazepines on oral contraceptive metabolism have not been determined.

The prescribing information of concomitant medications should be consulted to identify potential interactions.

Laboratory Test Interactions

Oestrogen-containing preparations affect the following blood components, endocrine and liver function tests: -

1. Increased prothrombin and Factors VII, VIII, IX, and X; decreased antithrombin 3; increased noradrenaline-induced platelet aggregability;
2. Increased thyroid-binding globulin (TBG) leading to increased circulating total-thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered;
3. Decreased pregnanediol excretion;
4. Reduced response to metyrapone test;
5. Increased sulphobromophthalein retention.

The results of these tests should not be regarded as reliable until oral contraceptives use has been discontinued for 1-2 months. Abnormal tests should then be repeated.

Oral contraceptives may produce false positive results when neutrophil alkaline phosphatase activity is evaluated for the early diagnosis of pregnancy.

ADVERSE REACTIONS

The most serious adverse reactions associated with the use of oral contraceptives are indicated under **PRECAUTIONS**.

Adverse reactions are listed in the Table per CIOMS frequency categories:

Very common:	≥10%
Common:	≥1% and <10%
Uncommon:	≥0.1% and <1%
Rare:	≥0.01% and <0.1%
Very rare:	<0.01%

Use of combined oral contraceptives has been associated with an increased risk of:

- * Arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attack, venous thrombosis and pulmonary embolism.
- * Cervical intraepithelial neoplasia and cervical cancer.
- * Being diagnosed with breast cancer
- * An increased risk of benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenomas).

The following have been reported and are believed to be drug related:

<i>System Organ Class</i>	<i>Adverse Reaction</i>
Infections and Infestations	
Common	Vaginitis, including candidiasis
Neoplasms benign, malignant, and unspecified	
Very Rare	Hepatic adenomas, hepatocellular carcinomas
Immune System Disorders	
Rare	Anaphylactic/anaphylactoid reactions, including very rare cases of urticaria, angioedema and severe reactions with respiratory and circulatory symptoms.
Very Rare	Exacerbation of systemic lupus erythematosus
Metabolism & Nutrition Disorders	
Uncommon	Changes in appetite (increase or decrease)
Rare	Glucose intolerance
Very Rare	Exacerbation of porphyria
Psychiatric Disorders	
Common	Mood changes, including depression, changes in libido

System Organ Class**Adverse Reaction****Nervous System Disorders**

Very Common

Headache, including migraines

Common

Nervousness; dizziness

Very Rare

Exacerbation of chorea

Eye Disorders

Rare

Intolerance to contact lenses

Very Rare

Optic neuritis*, retinal vascular thrombosis

Vascular Disorders

Very Rare

Aggravation of varicose veins

Gastrointestinal Disorders

Common

Nausea, vomiting, abdominal pain

Uncommon

Abdominal cramps, bloating

Very Rare

Pancreatitis, ischaemic colitis

Hepato-biliary Disorders

Rare

Cholestatic jaundice

Very Rare

Gallbladder disease, including gallstones**

Unknown

Hepatocellular injury (e.g. hepatitis, hepatic function abnormal)

Skin and Subcutaneous Tissue Disorders

Common

Acne

Uncommon

Rash (allergic), chloasma (melasma), which may persist, hirsutism, alopecia

Rare

Erythema nodosum

Very Rare

Erythema multiforme

Renal and Urinary Disorders

Very Rare

Haemolytic uraemic syndrome

Reproductive System and Breast Disorders

Very Common

Metrorrhagia (Breakthrough bleeding/spotting)

Common

Breast pain, tenderness, enlargement, secretion, dysmenorrhoea, change in menstrual flow, change in cervical ectropion and secretion, amenorrhoea

General Disorders and Administration Site Conditions

Common

Fluid retention/oedema

Investigations

Common

Changes in weight (increase or decrease)

System Organ Class

Adverse Reaction

Uncommon

Increase in blood pressure, changes in serum lipid levels, including hypertriglyceridaemia

Rare

Decrease in serum folate levels***

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

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

*** Serum folate levels may be depressed by combined oral contraceptive therapy. This may be of clinical significance if the woman becomes pregnant shortly after discontinuing combined oral contraceptives.

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

Change in corneal curvature (steepening), premenstrual-like syndrome, cataracts, cystitis-like syndrome, haemorrhagic eruption, Budd-Chiari Syndrome, megaloblastic anaemia.

DOSAGE AND ADMINISTRATION

How to Take TRIPHASIL

To achieve maximum contraceptive effectiveness, TRIPHASIL must be taken in the order directed on the package and at intervals not exceeding 24 hours. Women should be instructed to take the tablets at about the same time every day, preferably after the evening meal or at bedtime. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started on the day after the current pack is completed. A withdrawal bleed usually starts on day 2-3 after the last yellow active tablet and may not have finished before the next pack is started.

How to Start TRIPHASIL

Each package of TRIPHASIL contains 6 brown active tablets, 5 white active tablets, 10 yellow active tablets and 7 red inactive tablets.

No Preceding Hormonal Contraceptive Use (in the Past Month)

First Cycle

On the first day of the menstrual cycle, i.e. the first day of bleeding, the woman will take the tablet corresponding to that day of the week from the silver section of the TRIPHASIL package. Thereafter, one tablet is taken daily, following the arrows marked on the package, until all 28 tablets have been taken.

During this first cycle, a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) is recommended until 7 consecutive daily active tablets have been taken. If the tablets are begun after Day 5, it must be considered that ovulation and conception may have occurred before the tablets were started.

If withdrawal bleeding does not occur and TRIPHASIL has been taken according to directions, and conditions possibly impairing contraceptive effectiveness (refer to **Advice in Case of Vomiting** and **Concomitant Medication**) can be ruled out, it is unlikely that the woman has conceived. She should be instructed to begin a second course of TRIPHASIL on the usual day. If bleeding does not occur at the end of this second cycle, TRIPHASIL should not be taken until diagnostic procedures to exclude the possibility of pregnancy have been

performed.

Subsequent Cycles

The next and all subsequent courses of TRIPHASIL will begin on the day after the last package was completed, even if withdrawal bleeding has not occurred or is still in progress. Each course of TRIPHASIL is thus begun on the same day of the week as the first course, with a tablet from the silver section of the package.

Any time a new cycle of TRIPHASIL is started later than the eighth day after discontinuance of the last yellow active tablet, the woman should use a back up non-hormonal method of contraception (other than the rhythm or temperature methods), until an active tablet has been taken for 7 consecutive days.

Changing from another Combined Oral Contraceptive

Women should start TRIPHASIL on the day after the last active tablet of her previous combined oral contraceptive (COC) During the first TRIPHASIL cycle; a non-hormonal method of contraception (other than the rhythm or temperature methods) should be used until 7 consecutive daily active tablets have been taken.

If transient spotting or breakthrough bleeding occurs, the woman is instructed to continue the regimen since such bleeding is usually without significance. If the bleeding is persistent or prolonged, the patient is advised to consult her physician.

Changing from a Progestogen Only Method (Progestogen-only Pill, Injection, Implant)

Women may switch any day from the progestogen-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 these situations, the woman should be advised to use a non-hormonal back up method of contraception (other than the rhythm or temperature methods) for the first 7 days of active tablet taking.

Following First-Trimester Abortion

Women 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 non-lactating mother or after second trimester abortion. Women should be advised to also use a non-hormonal back up method of contraception (other than the rhythm or temperature methods) for the first 7 days of active tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of TRIPHASIL use or the woman has to wait for her first menstrual period (see **PRECAUTIONS: Thromboembolism** and **Use During or Immediately Preceding Pregnancy** and **Use during Lactation**).

Management of Missed Tablets

Contraceptive efficacy may be reduced if active tablets are missed and particularly if the

missed tablets extend the red inactive tablet interval.

- If one active tablet is missed, but is **less than 12 hours late**, it should be taken as soon as it is remembered. Subsequent tablets should be taken at the usual time.
- If one active tablet is missed and is **more than 12 hours late** or if more than one active tablet is missed, contraceptive protection may be reduced. The last missed tablet should be taken as soon as it is remembered, even if this means taking two tablets in one day. Subsequent tablets should be taken at the usual time. In addition, a non-hormonal back up method of birth control (other than the rhythm or temperature methods) should be used for the next 7 days.
- If the 7 days where back up is required run beyond the last active tablet in the current pack, the next pack must be started on the day following the intake of the last active tablet in the current pack. Discard all red inactive tablets. This prevents an extended break in tablet taking of active tablets that may increase the risk of escape ovulation. The user is unlikely to have a withdrawal bleed until the red inactive tablet interval of the second pack, but she may experience spotting or breakthrough bleeding on days when active tablets are taken.
- If the user does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming tablet taking.
- If the woman misses one or more red inactive tablets, she will still be protected against pregnancy provided she begins the brown active tablets on the appropriate day.

How to Delay a Period

To delay a period the woman should continue with another pack of TRIPHASIL without the red inactive tablet interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of TRIPHASIL is then resumed after the usual 7 day red inactive tablet interval.

Advice in Case of Vomiting

If vomiting occurs within 4 hours after active tablet taking, absorption may not be complete. In such an event, the advice concerning ***Management of Missed Tablets*** is applicable. The woman must take the extra active tablet(s) needed from a back up pack.

Concomitant Medication

During concomitant use of TRIPHASIL and substances that may lead to decreased ethinyloestradiol serum concentrations, it is recommended that a non-hormonal back up method of birth control (with the exception of the rhythm or temperature methods) 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 (see ***Drug Interactions***).

OVERDOSAGE

Symptoms of oral contraceptive overdose 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.

HOW SUPPLIED

Three month pack containing 3 blisters.

Each blister contains: -

6 brown tablets each containing ethinylestradiol 30 microgram and levonorgestrel 50 microgram, followed by

5 white tablets each containing ethinylestradiol 40 microgram and levonorgestrel 75 microgram, followed by

10 yellow tablets each containing ethinylestradiol 30 microgram and levonorgestrel 125 microgram, followed by 7 red inert tablets.

Store below 25°C in a cool, dry place.

MEDICINE CLASSIFICATION

Prescription Medicine.

NAME AND ADDRESS

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