PRODUCT INFORMATION
TRIPHASIL® TABLETS

NAME OF MEDICINE

Levonorgestrel and Ethinyloestradiol

Chemically, ethinyloestradiol is 19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17-diol and has the following structure:

Chemical Formula: C_{20}H_{24}O_{2}
Molecular Weight: 296.41
Melting Point: 181-185°C
CAS No: [57-63-6]

Chemically, levonorgestrel is (-)-13β-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one and has the following structure:

Chemical Formula: C_{21}H_{28}O_{2}
Molecular Weight: 312.45
Melting Point: 232-239°C
CAS No: [797-63-7]

DESCRIPTION

Ethinyloestradiol 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.

Levonorgestrel is a white crystalline powder that is very slightly soluble in water, slightly soluble in alcohol and acetone, and soluble in chloroform.

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

Each tablet contains the following excipients; calcium carbonate, glycol montanate, macrogol 6000, magnesium stearate, sucrose, maize starch, povidone, glycerol, purified talc and...
lactose. The brown tablets contain the colourants iron oxide yellow CI 77492, iron oxide red CI 77491 and titanium dioxide. The yellow tablets contain the colourants iron oxide red CI 77491 and titanium dioxide. The red inactive tablets contain the colourants erythrosine CI45430 and brilliant scarlet 4R CI16255.

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

Ethinyloestradiol and levonorgestrel are rapidly and almost completely absorbed from the gastrointestinal tract. Ethinyloestradiol 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. Ethinyloestradiol, 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 ethinyloestradiol 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 ethinyloestradiol 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:

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

• Undiagnosed genital bleeding.

• Known or suspected pregnancy.

• 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.

• Diabetes with vascular involvement.

• Uncontrolled hypertension.

• Headaches with focal neurological symptoms, (such as aura), including hemiplegic migraine.

• Pancreatitis associated with severe hypertriglyceridaemia (current or history).

• 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 toxoaemia 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, or 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**

**Cervical Cancer**

The most important risk factor for cervical cancer is persistent human papillomavirus infection.

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.

**Breast Cancer**

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.

Established risk factors for the development of breast cancer include increasing age, family history, obesity, nulliparity, and late age for first full-term pregnancy.
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, 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.

Acute or chronic disturbances of liver function require the discontinuation of combined oral contraceptive use until liver function has returned to normal (see **CONTRAINDICATIONS**).

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.

**Migraine/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 (see **Arterial Thrombosis and Thromboembolism**).
**Angioedema**

Exogenous oestrogens may induce or exacerbate symptoms of angioedema, particularly in women with hereditary angioedema.

**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 while receiving the drug.

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 in combined oral contraceptive users 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 alternative method of contraception in an attempt to determine whether the symptom is drug-related.

**Vomiting and/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 in 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.

**Paediatric Use**

Safety and efficacy of combined oral contraceptives have been established in women of reproductive age. Use of these products before menarche is not indicated.

**Use in the Elderly**

Combined oral contraceptives are not indicated for use in postmenopausal women.

**Interactions with Other Medicines**

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

Decreased ethinyloestradiol 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 ethinyloestradiol concentrations include any substance that reduces gastrointestinal transit time and, therefore, ethinyloestradiol 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 ethinyloestradiol 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 ethinyloestradiol 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 lead 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.

Examples of substances that may increase ethinyloestradiol 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.

Increased intermenstrual bleeding and occasional pregnancies have been reported during concomitant administration of oral contraceptives and ampicillin, phenoxy methyl penicillin, and other penicillins, sulphamethoxy pyridazine, 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.

Ethinyloestradiol 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 ethinyloestradiol 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 EFFECTS**

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: $\geq 10\%$
- Common: $\geq 1\%$ and $<10\%$
- Uncommon: $\geq 0.1\%$ and $<1\%$
- Rare: $\geq 0.01\%$ and $<0.1\%$
- Very rare: $<0.01\%$
Use of combined oral contraceptives has been associated with an increased risk of the following:
* 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
* Breast cancer diagnosis
* Benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenomas).

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td>Vaginitis, including candidiasis</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, and unspecified</td>
<td>Hepatic adenomas; hepatocellular carcinomas</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Anaphylactic/anaphylactoid reactions, including very rare cases of urticaria, angioedema and severe reactions with respiratory and circulatory symptoms.</td>
</tr>
<tr>
<td>Very Rare</td>
<td>Exacerbation of systemic lupus erythematosus</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Changes in appetite (increase or decrease)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Glucose intolerance</td>
</tr>
<tr>
<td>Rare</td>
<td>Exacerbation of porphyria</td>
</tr>
<tr>
<td>Very Rare</td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Mood changes, including depression; changes in libido</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache, including migraines</td>
</tr>
<tr>
<td>Very Common</td>
<td>Nervousness; dizziness</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Very Rare</td>
<td>Exacerbation of chorea</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Intolerance to contact lenses</td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Very Rare</td>
<td>Optic neuritis*; retinal vascular thrombosis</td>
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<td></td>
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<tr>
<td><strong>System Organ Class</strong></td>
<td><strong>Adverse Reaction</strong></td>
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<tr>
<td><strong>Vascular Disorders</strong></td>
<td>Aggravation of varicose veins</td>
</tr>
<tr>
<td>Very Rare</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Nausea; vomiting; abdominal pain</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Abdominal cramps; bloating</td>
</tr>
<tr>
<td>Very Rare</td>
<td>Pancreatitis; ischaemic colitis</td>
</tr>
<tr>
<td>Unknown</td>
<td>Inflammatory bowel disease (Crohn’s disease, ulcerative colitis)</td>
</tr>
<tr>
<td><strong>Hepato-biliary Disorders</strong></td>
<td>Cholestatic jaundice</td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Very Rare</td>
<td>Gallbladder disease, including gallstones**</td>
</tr>
<tr>
<td>Unknown</td>
<td>Hepatocellular injury (e.g. hepatitis, hepatic function abnormal)</td>
</tr>
<tr>
<td><strong>Skin and Subcutaneous Tissue Disorders</strong></td>
<td>Acne</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Uncommon</td>
<td>Rash (allergic); chloasma (melasma), which may persist; hirsutism; alopecia</td>
</tr>
<tr>
<td>Rare</td>
<td>Erythema nodosum</td>
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<tr>
<td>Very Rare</td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td>Haemolytic uraemic syndrome</td>
</tr>
<tr>
<td>Very Rare</td>
<td></td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td>Metrorrhagia (Breakthrough bleeding/spotting)</td>
</tr>
<tr>
<td>Very Common</td>
<td>Breast pain, tenderness, enlargement, secretion; dysmenorrhoea; change in menstrual flow; change in cervical ectropion and secretion; amenorrhoea</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td>Fluid retention/oedema</td>
</tr>
<tr>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Adverse Reaction</td>
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<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Changes in weight (increase or decrease)</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Increase in blood pressure; changes in serum lipid levels, including hypertriglyceridaemia</td>
</tr>
<tr>
<td>Rare</td>
<td>Decrease in serum folate levels***</td>
</tr>
<tr>
<td>* Optic neuritis may lead to partial or complete loss of vision</td>
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<tr>
<td>** Combined oral contraceptives may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.</td>
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<tr>
<td>*** 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.</td>
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</table>

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**

Each package of TRIPHASIL contains 6 brown active tablets, 5 white active tablets, 10 yellow active tablets and 7 red inactive tablets. To achieve maximum contraceptive effectiveness, TRIPHASIL must be taken as directed and at intervals not exceeding 24 hours. Women should be instructed to take the tablets at the same time every day, preferably after the evening meal or at bedtime.

**How to Start TRIPHASIL**

**No Preceding Hormonal Contraceptive Use (in the Past Month)**

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. The first active tablet taken will be brown. Thereafter, one tablet is taken daily, following the arrows marked on the package, until all 28 tablets have been taken.

Withdrawal bleeding should usually occur within 3 days after the last active tablet is taken and may not have finished before the next pack is started.

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

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. If withdrawal bleeding does not occur and
TRIPHASIL has been taken according to directions, 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.

If the woman has not adhered to the prescribed regimen (missed one or more active tablets or started taking them on a day later than recommended), the probability of pregnancy should be considered at the time of the first missed period before TRIPHASIL is resumed.

Changing from another Combined Oral Contraceptive
Women changing from another combined oral contraceptive product should start TRIPHASIL on the day after the last active tablet of her previous combined oral contraceptive by taking the first tablet corresponding to that day of the week from the silver section of the package. This will shorten the last cycle of the previous combined oral contraceptive, and may prevent or reduce withdrawal bleeding at the end of that cycle. The first cycle with TRIPHASIL may also be shorter.

During the first TRIPHASIL cycle, a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) should be used until one active tablet has been taken daily for 7 consecutive days.

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 woman is advised to consult her physician.

Changing from a Progestogen Only Method (Progestogen-Only Tablet, Injection, Implant)
Women may switch any day from the progestogen-only tablet 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, women should be advised to use a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) until one active tablet has been taken daily for 7 consecutive days.

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, combined oral contraceptives should be started no earlier than day 28 after delivery in the non-lactating mother or after second trimester abortion. The woman should be advised to use a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) until one active tablet has been taken daily for 7 consecutive days. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of combined oral contraceptive use or the woman must wait for her first menstrual period.
Management of Missed Tablets

Contraceptive efficacy may be reduced if active tablets are missed and particularly if the missed tablets extend the inactive tablet interval.

If one active tablet is missed, but 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 two active tablets are 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 contraception (other than the rhythm or temperature methods) should be used until one active tablet has been taken daily for 7 consecutive 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; all inactive (red) tablets should be discarded. This prevents an extended break in tablet taking of active tablets that may increase the risk of escape ovulation. The woman is unlikely to have a withdrawal bleed until the inactive-tablet interval of the second pack, but she may experience spotting or breakthrough bleeding on days when active tablets are taken. If the woman 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 inactive (red) tablets, she is still protected against pregnancy, provided she begins the active brown tablets on the proper day.

If three consecutive active tablets are missed, TRIPHASIL should be discontinued and the remainder of the package discarded. A new package should be started on the eighth day after the last tablet was taken. A non-hormonal back-up method of contraception (other than the rhythm or temperature methods) should be used until one active tablet has been taken daily for 7 consecutive days.

If withdrawal bleeding does not occur and TRIPHASIL has been taken according to directions, 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.

If the woman has not adhered to the prescribed regimen (missed one or more active tablets or started taking them on a day later than recommended), the probability of pregnancy should be considered at the time of the first missed period before TRIPHASIL is resumed.

Vomiting and Diarrhoea

If vomiting occurs within 4 hours after 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 appropriate colour active tablet(s) needed from a back-up pack. Diarrhoea may increase gastrointestinal motility and reduce hormone absorption.
OVERDOSAGE

Symptoms of oral contraceptive 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.

HOW SUPPLIED

One month pack containing one blister
Four month pack containing 4 blisters.

Each blister contains:
- 6 brown tablets each containing ethinyloestradiol 30 microgram and levonorgestrel 50 microgram, followed by
- 5 white tablets each containing ethinyloestradiol 40 microgram and levonorgestrel 75 microgram, followed by
- 10 yellow tablets each containing ethinyloestradiol 30 microgram and levonorgestrel 125 microgram, followed by
- 7 red inert tablets.

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

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
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WEST RYDE NSW 2114

TGA Approval Date: 22 July 2004

Date of most recent amendment: 22 June 2011

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