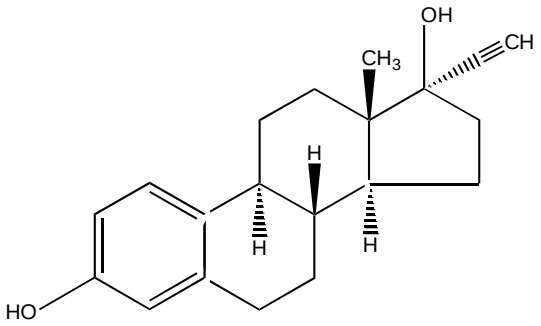
PRODUCT INFORMATION

MINULET®

NAME OF THE MEDICINE

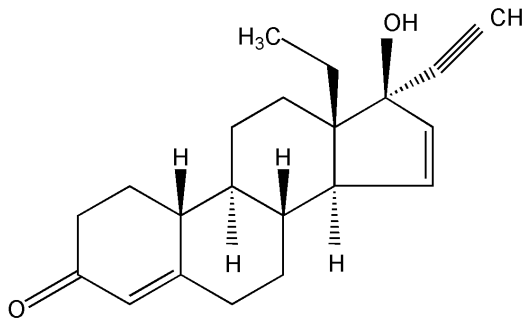
Gestodene and Ethinylestradiol

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



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

The chemical name for gestodene is 17α ethinyl-13-ethyl-17β-hydroxy-4, 15-gonadiene-3-one and has the following structural formula:



Chemical Formula: $C_{21}H_{26}O_2$
Molecular Weight: 310.44
Melting Point: 196-202°C
CAS No.: [60282-87-3]

DESCRIPTION

Each MINULET® calendar blister pack consists of 28 tablets: 21 white tablets, each containing ethinylestradiol 30 µg and gestodene 75 µg and 7 red inert tablets.

Ethinylestradiol is an estrogen. Ethinylestradiol 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.

Gestodene is a progestogen, which is a gonane derivative. Gestodene is a white to off-white crystalline powder that is easily soluble in chloroform and dioxane and soluble in acetone and methanol.

Each white active tablet contains 75 µg gestodene and 30 µg ethinylestradiol and the excipients lactose monohydrate, maize starch, povidone, sodium calcium edetate, magnesium stearate, sucrose, calcium carbonate, purified talc, macrogol 6000 and glycol montanate.

Each red inactive tablet contains the excipients lactose monohydrate, maize starch, povidone, sodium calcium edetate, magnesium stearate, sucrose, calcium carbonate, purified talc, macrogol 6000, glycol montanate and the colouring agents brilliant scarlet 4R and erythrosine. Minulet does not contain gluten, tartrazine or any other azo dyes.

PHARMACOLOGY

The hormonal components of MINULET inhibit ovulation by suppressing gonadotrophin release. Secondary mechanisms, which may contribute to the effectiveness of MINULET 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). The pearl index for MINULET is 0.06.

Non-contraceptive Benefits

In addition to providing protection against pregnancy, oral contraceptives have been reported to be associated with the following beneficial effects: a reduction in the incidence of benign breast disease; a reduction in iron-deficiency anaemia; a reduction in the risk of endometrial carcinoma; a reduction in the incidence of ectopic pregnancy; a reduction in the incidence of pelvic inflammatory disease; a reduction in the incidence of ovarian cysts; a reduction in the incidence of dysmenorrhoea; a reduction in the severity of acne; a possible reduction in the incidence of ovarian carcinoma.

Pharmacokinetics

Ethinylestradiol and gestodene are rapidly and almost completely absorbed from the gastrointestinal tract.

Peak plasma levels of each drug are reached within 1-2 hours. Post maximum concentration curves show two phases with half-lives of 1 and 15 hours in the case of gestodene, and 1-3 and approximately 24 hours in the case of ethinylestradiol.

After oral administration, gestodene, unlike ethinylestradiol, is not subject to first-pass metabolism. Following oral administration, gestodene is completely bioavailable, ethinylestradiol about 40%.

Gestodene is extensively plasma protein bound to sex hormone binding globulin (SHBG). Ethinylestradiol is bound in plasma to albumin and enhances the binding capacity of SHBG.

The elimination half-life for gestodene is approximately 16-18 hours after multiple oral doses. The drug is primarily metabolised by reduction of the A ring followed by glucuronidation. About 50% of gestodene is excreted in the urine and 33% is eliminated in the faeces.

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.

INDICATIONS

MINULET is indicated for the prevention of pregnancy.

CONTRAINDICATIONS

MINULET should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during MINULET use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see **PRECAUTIONS**).
  - A history of, or current thromboembolic disorders, deep vein thrombosis and conditions that predispose to such diseases (e.g. disturbance of the clotting system with a tendency towards thrombosis).
  - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
  - Major surgery with prolonged immobilisation.
  - A high risk of venous thromboembolism due to the presence of multiple risk factors.
  - Sickle cell anaemia.
- Presence or risk of arterial thromboembolism (ATE) (see **PRECAUTIONS**).
  - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA]) and conditions that predispose to such diseases (e.g. disturbance of the clotting system with a tendency towards thrombosis and certain heart diseases e.g. valvular heart disease, thrombogenic valvulopathies and thrombogenic rhythm disorders).
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (e.g. anticardiolipin-antibodies and lupus anticoagulant).
  - Headaches with focal neurological symptoms (such as aura) including hemiplegic migraine.
  - A high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk factor such as:
    - Diabetes mellitus with vascular symptoms.
    - Uncontrolled hypertension.
    - Abnormal lipid metabolism.
- Pancreatitis or a history thereof if associated with severe hypertriglyceridaemia.
- Severe hepatic dysfunction or active liver disease, a history of cholestatic jaundice or pruritus of pregnancy or previous or existing liver tumours (adenomas or carcinomas), Dubin-Johnson syndrome or Rotor syndrome.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g. of the genital organs or the breasts).

- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- History of herpes gestationis, a history of otosclerosis with exacerbation in pregnancy.
- Combined oral contraceptives (COCs) are contraindicated for concomitant use with certain anti-viral hepatitis C virus (HCV) medicinal products such as ombitasvir, paritaprevir, ritonavir and dasabuvir (see **PRECAUTIONS - Hepatic Neoplasia/Liver Disease/Hepatitis C** and **INTERACTIONS WITH OTHER MEDICINES**).
- Hypersensitivity to any of the ingredients contained in MINULET.

Due to the vague symptomatology of many venous thromboembolic events, discontinuation of oral contraceptives and the provision of alternative contraception should be considered in cases of suspected thrombosis in patients on oral contraceptives, while diagnostic tests are being conducted.

In cases of an uncertain diagnosis of venous thromboembolic events, alternative contraceptive strategies should be discussed with the patient, as the event may represent a first signal of a thrombotic tendency associated with the use of the oral contraceptive.

PRECAUTIONS

In the absence of the above contraindications, if any of the conditions/risk factors mentioned below are present, the benefits of MINULET should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide whether MINULET should be discontinued.

Reasons for Immediate Discontinuation of MINULET

1. The occurrence for the first time of migrainous headaches or the more frequent occurrence of unusually severe headaches.
2. Acute disturbances of vision, hearing or other perceptual disorders.
3. First symptoms of thromboembolism.
4. Development of jaundice (cholestasis), anicteric hepatitis or generalised pruritus.
5. Increase in epileptic seizures.
6. Significant rise in blood pressure.
7. Pregnancy (known or suspected).

Circulatory Disorders

Epidemiological studies have suggested an association between the use of combined oral contraceptives (COCs) containing ethinylestradiol and an increased risk of venous and arterial thrombotic and thromboembolic events, such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely in average-risk women.

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

Venous Thrombosis and Thromboembolism

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

Risk of venous thromboembolism (VTE)

The use of any COC increases the risk of VTE compared with no use. The women considering using MINULET should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a COC is re-started after a break in use of 4 weeks or more.

The risk of VTE with the COC is greatest for products containing over 50 µg of ethinylestradiol. There is less risk for products such as MINULET containing less than 35 µg ethinylestradiol.

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with COCs, and how her current risk factors influence this risk.

Risk[1] of developing a blood clot (VTE) in a year

Women not using a combined hormonal contraceptive and not pregnant	About 2 out of 10,000 women[1]
Women using a COC containing levonorgestrel, norethisterone or norgestimate	About 5-7 out of 10,000 women
Women using a COC containing etonogestrel or norelgestromin	About 6-12 out of 10,000 women
Women using a COC containing drospirenone, gestodene, desogestrel or cyproterone[2]	About 9-12 out of 10,000 women
Women using a COC containing chlormadinone, dienogest or nomegestrol	Not yet known[3]

[1] In any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

[2] While cyproterone is indicated for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism, it is known to have efficacy as a contraceptive. The risk of VTE associated with cyproterone use is considered to be 1.5 to 2 times higher than for COCs containing levonorgestrel and may be similar to the risk with contraceptives containing gestodene, desogestrel or drospirenone.

[3] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products. Where the risk for a particular progestogen is uncertain, the risk of the class should be used in determining the risk for the individual patient.

It is important that women understand that VTE associated with COC use is rare in average-risk women. The risk in pregnancy (5 - 20 per 10,000 women over 9 months) and the risk in

the post-partum period (45 - 65 per 10,000 women over 12 weeks) is higher than that associated with COC use.

However VTE is a serious condition and may be fatal in 1 - 2% of cases. Extremely rarely, thrombosis has been reported to occur in COC users in other blood vessels, e.g. hepatic, cerebral, mesenteric, renal or retinal veins and arteries.

The risk for venous thromboembolic complications in COC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

MINULET is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a COC should not be prescribed.

Risk factors for VTE

The risk of venous thrombotic and thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism. Examples of predisposing conditions for venous thrombosis and thromboembolism are:

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises.
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma.
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.
- Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).
- Biochemical factors Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency.
- Other medical conditions associated with VTE:
  - Cancer.
  - Systemic lupus erythematosus.
  - Haemolytic uraemic syndrome.
  - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis).
  - Sickle cell disease.
- Increasing age, particularly above 35 years.
- Smoking.
- Recent delivery or second trimester abortion.

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of MINULET (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid

unintentional pregnancy. Antithrombotic treatment should be considered if MINULET has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

The increased risk of VTE during the postpartum period should be considered if re-starting MINULET. 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 a non-lactating woman, or second-trimester abortion.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a COC.

Symptoms of deep vein thrombosis (DVT) can include:

- Unilateral swelling of the leg and/or foot or along a vein in the leg.
- Pain or tenderness in the leg which may be felt only when standing or walking.
- Increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- Sudden onset of unexplained shortness of breath or rapid breathing.
- Sudden coughing which may be associated with haemoptysis.
- Sharp chest pain.
- Severe light headedness or dizziness.
- Rapid or irregular heartbeat.

Some of these symptoms (e.g. “shortness of breath”, “coughing”) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Arterial Thrombosis and Thromboembolism

Risk of arterial thromboembolism (ATE)

Epidemiological studies have associated the use of COCs with an increased risk for arterial thrombotic and thromboembolic events (e.g. myocardial infarction, angina pectoris, and cerebrovascular events, such as ischaemic and haemorrhagic stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thrombotic and thromboembolic complications in COC users further increases in women with risk factors. MINULET is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a COC should not be prescribed.

Risk factors for ATE

Caution must be exercised when prescribing COCs for women with risk factors for arterial thrombotic and thromboembolic events, such as:

- Increasing age, particularly above 35 years.
- Smoking.
- Hypertension.
- Hyperlipidaemias.
- Obesity.
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).
- Biochemical factors: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant).
- Migraine.
- Other medical conditions associated with adverse vascular events:
  - Diabetes mellitus.
  - Hyperhomocysteinaemia.
  - Valvular heart disease.
  - Atrial fibrillation.
  - Dyslipoproteinaemia.
  - Systemic lupus erythematosus.
  - History of pre-eclamptic toxaemia.

Oral contraceptive use by cigarette smokers increases the risk of cardiovascular disease. This risk increases with heavy smoking and advancing age and is quite marked in women over the age of 35 years. Women should be advised not to smoke if they wish to use a COC. Women over 35 years of age who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.

Symptoms of ATE

Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a COC.

Symptoms of a stroke can include:

- Sudden numbness or weakness of the face, arm or leg, especially on one side of the body.
- Sudden trouble walking, dizziness, loss of balance or coordination.
- Sudden confusion, trouble speaking or understanding.
- Sudden trouble seeing in one or both eyes.
- Sudden, severe or prolonged headache with no known cause.
- Loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

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

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

Symptoms of myocardial infarction (MI) can include:

- Pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone.
- Discomfort radiating to the back, jaw, throat, arm, stomach.
- Feeling of being full, having indigestion or choking.
- Sweating, nausea, vomiting or dizziness.
- Extreme weakness, anxiety, or shortness of breath.
- Rapid or irregular heartbeats.

Medical Examination/Consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the contraindications and precautions, and should be repeated at least annually during the use of COCs. A Papanicolaou (Pap) smear should be performed if the patient has been sexually active or if it is otherwise indicated. Pregnancy should be ruled out before the start of therapy. Baseline and periodic blood glucose determinations should be performed in patients predisposed to diabetes mellitus. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests such as urinalysis.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given.

Elevated Blood Pressure

An increase in blood pressure has been reported in women receiving oral contraceptives. In some women, hypertension may be evident within a few months of beginning use and the incidence increases with the duration of use and the age of the woman. A significant rise in blood pressure is a reason for immediate discontinuation of use of 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, they should be monitored closely and if a significant elevation of blood pressure occurs, the medicine should be discontinued.

For most women, elevated blood pressure will generally return to baseline after stopping combined oral contraceptives, and there appears to be no difference in the occurrence of hypertension among ever- and never- users.

Combined oral contraceptive use is contraindicated in women with uncontrolled hypertension (see **CONTRAINDICATIONS**).

Angioedema

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

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. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

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. 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. 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. 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.

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 (see **CONTRAINDICATIONS**). The requirement for insulin or oral anti-diabetics can either increase or decrease. In general, the urine should be checked for sugar before the prescription of and at six-month intervals during the use of oral contraceptives in pre-diabetic and diabetic patients.

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 oral contraceptive users. Elevations of plasma triglycerides in combined oral contraceptive users may lead to pancreatitis and other complications.

Estrogens increase serum high-density lipoproteins (HDL cholesterol), whereas a decline in serum HDL cholesterol has been reported with many progestational agents. Some progestogens may elevate low-density lipoprotein (LDL) levels and may render the control of hyperlipidaemias more difficult. The net effect of a COC depends on the balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogens used in the contraceptive. The amount of both hormones should be considered in the choice of a COC.

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 MINULET 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 used until the possibility of pregnancy is excluded.

Breakthrough bleeding or spotting may occur in women taking combined oral contraceptives, especially during the first three months of use. If this bleeding persists or recurs, non-hormonal causes should be considered and adequate diagnostic measures may be indicated to rule out pregnancy, infection, malignancy, or other conditions. If pathology has been excluded, continuation of MINULET or a change to another formulation may solve the problem. Changing to a regimen with a higher estrogen content may be useful in minimising menstrual irregularity.

Some women may encounter post-pill amenorrhoea (possibly with anovulation) or oligomenorrhoea, especially when such a condition was pre-existent.

Ocular Lesions

Optic neuritis and retinal vascular thrombosis, which may lead to partial or complete loss of vision, have been reported in association with oral contraceptive use. Oral contraceptives should be discontinued and the cause immediately evaluated if there are signs or symptoms such as visual changes; onset of proptosis, diplopia; papilloedema or retinal vascular lesions.

Temporary Impairment of Fertility

The first spontaneous ovulation after stopping oral contraceptives is sometimes delayed; and there is evidence of temporary impairment of fertility in some women who discontinue oral contraception, which appears to be independent of the duration of use. This has been observed more often in women with a history of oligomenorrhoea or secondary amenorrhoea. Impairment diminishes with time, but may be evident up to 30 months after cessation of oral contraception in nulliparous women. It should be suggested to women who decide to become pregnant that alternative methods of contraception be used until they have their first spontaneous period, so that the estimated date of delivery may be made with more certainty.

Gallbladder Disease

Earlier epidemiological studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. However, the results of more recent studies indicate the risk of gallbladder disease may be minimal.

Hepatic Neoplasia/Liver Disease/Hepatitis C

In rare cases hepatic adenomas and in extremely rare cases, hepatocellular carcinoma may be associated with combined oral contraceptive use. The risk appears to increase with duration of combined oral contraceptive use. Rupture of hepatic adenomas may cause death through intra-abdominal haemorrhage.

If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occurs, differential diagnostic consideration should be given to the presence of a liver tumour.

Women with a history of combined oral contraceptive-related cholestasis or women with cholestasis during pregnancy 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**).

Hepatitis C

During clinical trials with patients treated for HCV infections with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as COCs (see **CONTRAINDICATIONS** and **INTERACTIONS WITH OTHER MEDICINES)**.

Depression

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

Sexually Transmissible Diseases

Patients should be counselled that MINULET does not protect against HIV infection (AIDS) and other sexually transmissible diseases. The woman should be advised that additional measures are needed to prevent the transmission of STDs.

Vomiting and/or Diarrhoea

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

Other

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

Serum folate levels may be depressed by oral contraceptive use. Women who became pregnant shortly after discontinuing these medicines may have a greater chance of developing folate deficiency and its complications. Folate supplementation may be required if a woman becomes pregnant shortly after ceasing tablet taking.

Moniliasis: Women should be warned that vulvo-vaginal monilial infection may occur or recur, and of the need for appropriate treatment.

Adolescent women: Estrogens may accelerate epiphyseal closure. Preferably they should not be prescribed before regular menstruation is established, and with discretion until bone growth is complete.

Use in Pregnancy

Category B3

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

Oral contraceptives have not been shown to have any deleterious effects on the fetus 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.

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

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

The increased risk of VTE during the postpartum period (recent delivery or second trimester abortion) should be considered when re-starting MINULET.

Use in Lactation

Small amounts of contraceptive steroids and/or metabolites have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and breast enlargement. Lactation may be influenced by combined oral contraceptives as they may reduce the quantity and change the composition of breast milk. The use of combined oral contraceptives is generally not recommended until the nursing mother has completely weaned her child.

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.

Carcinogenicity

Pre-clinical studies revealed an increased incidence of mammary and hepatic tumours in gestodene-treated rats. The reason for such increases in tumour incidence is unknown. The relationship of this finding to the development of similar tumours in women using gestodene has not been established.

Laboratory Test Interactions

Estrogen-containing preparations can affect many laboratory tests. Some examples are:-

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 radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

3. Reduced response to metyrapone test.

The results of these tests should not be regarded as reliable until oral contraceptive 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.

INTERACTIONS WITH OTHER MEDICINES

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

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

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see **CONTRAINDICATIONS** and **PRECAUTIONS - Hepatic Neoplasia/Liver Disease/Hepatitis C**). Therefore, COC users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with anti-viral HCV medicinal products such as ombitasvir, paritaprevir, ritonavir, dasabuvir. COCs can be restarted 2 weeks following completion of treatment with an anti-viral HCV medicinal product.

Drugs that May Decrease Ethinylestradiol Concentrations

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 anti-convulsants (phenytoin, primidone, barbiturates), rifampicin, rifabutin, griseofulvin, topiramate, modafinil, ritonavir, dexamethasone and some protease inhibitors, certain antibiotics (e.g. ampicillin and other penicillins, tetracyclines, chloramphenicol) and phenylbutazone.

Breakthrough bleeding has been reported in patients taking oral contraceptives and St. John's wort (*Hypericum perforatum*). St. John's wort may induce hepatic microsomal enzymes, which theoretically may result in reduced efficacy of oral contraceptives. If oral contraceptives and St. John's wort are used concomitantly, a non-hormonal back-up method of birth control is recommended.

These have been reported to result in contraceptive failure, presumably by hepatic enzyme induction and/or reduced entero-hepatic circulation of sex steroids due to changes in bowel flora.

During concomitant use of MINULET and substances that may lead to decreased ethinylestradiol serum concentrations, it is recommended that a non-hormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of

MINULET. 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 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 ethinylestradiol 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.

Drugs that May Increase Ethinylestradiol Concentrations

Examples of substances that may increase ethinylestradiol 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.

Effect of Ethinylestradiol on the Metabolism of Other Drugs

Ethinylestradiol 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).

Increased intermenstrual bleeding has been reported during concomitant administration of nitrofurantoin, phenoxymethyl penicillin and neomycin.

Drugs That May be Affected by Oral Contraceptives

Anti-diabetic agents - Oral contraceptives may impair glucose tolerance, and there may occasionally be a small increase in insulin requirements or oral antidiabetic agents. Diabetic women should be watched closely.

Anticoagulants - The effectiveness of bishydroxycoumarin may be reduced (the use of oral contraceptives in patients with some form of clotting disorder would be contraindicated).

Estrogens may possibly inhibit the metabolism of tricyclic antidepressants such as imipramine and desmethylimipramine leading to increased plasma levels and accumulation.

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

Estrogens may enhance the effects of glucocorticoids.

ADVERSE EFFECTS

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

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 the following:

- Arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, venous thrombosis, transient ischaemic attack and pulmonary embolism
- Cervical intraepithelial neoplasia and cervical cancer
- Breast cancer diagnosis
- Benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenomas).

Adverse Reaction by System Organ Class

Infections and Infestations

Common	Vaginitis, including candidiasis

Neoplasms benign, malignant, and unspecified

Very Rare	Hepatic adenoma, 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 and 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

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
Unknown	Inflammatory bowel disease (Crohn's disease, ulcerative 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; 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	Breakthrough bleeding/spotting
Common	Breast pain, tenderness, enlargement, secretion; dysmenorrhoea; change in menstrual flow; change in cervical ectropian and secretion; amenorrhoea

General disorders and administration site conditions

Common	Fluid retention/oedema

Investigations

Common	Changes in weight (increase or decrease)
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.

DOSAGE AND ADMINISTRATION

How to Take MINULET

Each package of MINULET contains 21 active white tablets and 7 red inactive tablets.

To achieve maximum contraceptive effectiveness, MINULET must be taken as directed and at daily intervals not exceeding 24 hours. Women should be instructed to take the tablets at the same time every day, preferably at bedtime.

How to Start MINULET

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 is instructed to take a white active tablet corresponding to that day of the week from the purple section of the MINULET pack. Thereafter, one white active tablet is taken daily, following the arrows marked on the package, until all 21 white active tablets have been taken from the pink section. The woman should be instructed then to take one red inactive tablet daily for the next seven days following the arrows marked on the MINULET pack. Withdrawal bleeding should usually occur within 2 to 4 days after the last white active tablet is taken. The woman should be advised that her first cycle after taking MINULET is likely to be shorter than usual, i.e. approximately 23 to 24 days in length. Thereafter, cycles should be approximately 28 days in length.

If withdrawal bleeding does not occur and MINULET has been taken according to directions, and conditions possibly impairing contraceptive effectiveness (refer to **Vomiting and/or Diarrhoea** and **INTERACTIONS WITH OTHER MEDICINES**) can be ruled out, it is unlikely that the woman has conceived. She should be instructed to begin a second course of MINULET on the usual day. If bleeding does not occur at the end of this second cycle, MINULET should not be taken until diagnostic procedures to exclude the possibility of pregnancy have been performed.

The next and all subsequent courses of MINULET will begin on the day after the last package was completed, even if withdrawal bleeding is still in progress. Each course of MINULET is thus begun on the same day of the week as the first course, always beginning with a white tablet.

If withdrawal bleeding does not occur and MINULET has been taken according to directions, and conditions possibly impairing contraceptive effectiveness (refer to **Vomiting and/or Diarrhoea** and **INTERACTIONS WITH OTHER MEDICINES**) can be ruled out, it is unlikely that the woman has conceived. She should be instructed to begin a second course of MINULET on the usual day. If bleeding does not occur at the end of this second cycle, MINULET should not be taken until diagnostic procedures to exclude the possibility of pregnancy have been performed.

MINULET is effective from the first day of therapy if the tablets are begun as described above.

Changing from another Combined Oral Contraceptive

If the woman is switching to MINULET from another 28-day oral contraceptive pack, then all tablets in the current 28-day pack should be finished and MINULET started on the next day by taking a white active tablet, which corresponds to that day of the week. During the first MINULET cycle, a non-hormonal contraceptive method (other than rhythm or temperature method) should be used until 7 consecutive daily white active tablets have been taken. During this changeover, a period of shortened duration or no period may occur.

If the woman is switching to MINULET from another 21-day oral contraceptive pack, then the woman should wait seven (7) days from when the last active tablet was taken from the old pack and start this new MINULET pack on the eighth day by taking a white active tablet which corresponds to this day of the week from the purple section of the pack. A non-hormonal contraceptive method (other than rhythm or temperature method) should be used during the tablet-free interval and during the first MINULET cycle until 7 consecutive daily active white 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 woman is advised to consult her physician.

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

The woman may switch any day from the progestogen-only tablet and should begin MINULET the next day. She should start MINULET on the day of 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 for the first 7 days of tablet taking.

Following First-Trimester Abortion

The woman may start MINULET 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 second trimester abortion. The woman should be advised to use a non-hormonal 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 MINULET 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 white 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 white tablet is missed and is more than 12 hours late or if more than one active white 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 active white tablets in one day. Any earlier missed tablets should be discarded. 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 for 7 consecutive days.

If these 7 days extend into the section containing the red inactive tablets, she should start a new pack on the next day after having taken the last active white tablet from the current pack (i.e. skip the 7 red inactive tablets). This will mean that the woman may not have a period until the end of two packs.

However, if the woman misses one or more red inactive tablets, she will still be protected against pregnancy provided she begins the active tablets on the appropriate day.

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 MINULET is resumed. In the case of the continuous intake of active tablets from two packs of MINULET (see before), a period should occur at the end of the second pack. If it does not, pregnancy should be ruled out before MINULET is resumed.

If these 7 days extend into the section containing the red inactive tablets, she should start a new pack on the next day after having taken the last active white tablet from the current pack (i.e. skip the 7 red inactive tablets). This will mean that the woman may not have a period until the end of two packs.

However, if the woman misses one or more red inactive tablets, she will still be protected against pregnancy provided she begins the active tablets on the appropriate day.

Concurrent Medication

If the woman is taking other drugs that may interact with MINULET, then she should continue to take her tablets as usual but also employ a non-hormonal method of contraception (except the rhythm or temperature method) during the time she is taking the interacting medication and continued for 7 days after the medication is stopped. If these 7 days extend into the section containing the red inactive tablets, the woman should start a new pack on the next day after having taken the last active tablet from the current pack (i.e. skip the inactive tablets). This will mean that the woman may not have a period until the end of two packs. If the woman is taking interacting medications on a chronic basis, another method of contraception should be considered.

Vomiting or Diarrhoea

If vomiting or diarrhoea occurs during or shortly after the intake of MINULET, contraceptive reliability may be jeopardised. 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 extra active tablet(s) needed from a back-up pack. Mild laxatives do not impair the effectiveness of MINULET. If the circumstance reducing the effectiveness of MINULET is protracted, other methods of contraception should be considered.

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, if necessary is directed to the symptoms.

PRESENTATION AND STORAGE CONDITIONS

Three month pack containing three blisters. Each blister contains 21 white tablets, each containing ethinylestradiol 30 µg and gestodene 75 µg, followed by 7 red inactive tablets.

One month pack containing 1 blister; two month pack containing 2 blisters; and four month pack containing 4 blisters are registered but not marketed.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
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WEST RYDE NSW 2114

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

3 August 1994.

DATE OF MOST RECENT AMENDMENT

11 January 2018

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