

DATA SHEET

MINULET[®]

Ethinylestradiol 30 µg and gestodene 75 µg

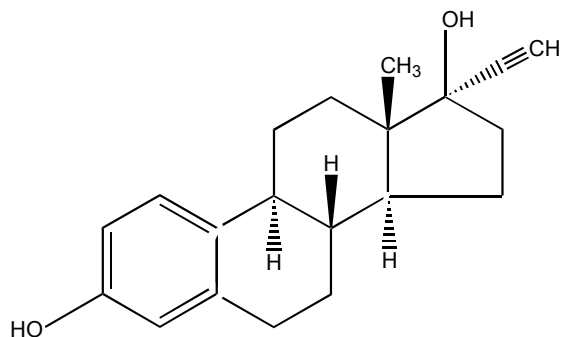
DESCRIPTION

Each MINULET[®] calendar blister pack consists of 28 tablets:

21 white tablets, each containing ethinylestradiol 30 µg and gestodene 75 µg

7 red inert tablets

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



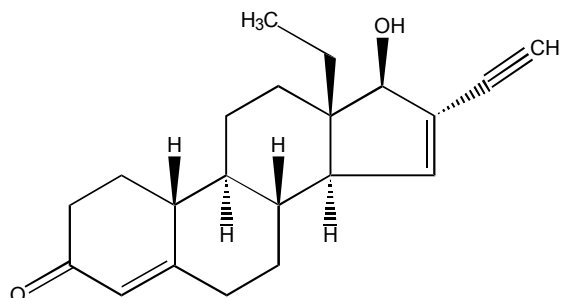
Chemical Formula: C₂₀H₂₄O₂

Molecular Weight: 296.41

Melting Point: 181-185°C

CAS No [57-63-6]

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



Chemical Formula: C₂₁H₂₆O₂

Molecular Weight: 310.44

Melting Point: 196-202°C

CAS No.: [60282-87-3]

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

Each red inactive tablet contains the excipients lactose, maize starch, povidone, sodium calcium edetate, magnesium stearate, sucrose, calcium carbonate, talc, Macrogol 6000, glycol montanate and the colouring agents brilliant scarlet 4R CI 16255, erythrosine CI 45430.

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

1. A history of, or current thrombophlebitis, thromboembolic disorders, deep vein thrombosis 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).

2. Hereditary or acquired predisposition for venous or arterial thrombosis
3. History of, or existing cerebrovascular or coronary artery disease
4. Known or suspected carcinoma of the breast or the endometrium or other oestrogen-dependent neoplasia
5. Undiagnosed vaginal bleeding
6. 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
7. Known or suspected pregnancy, a history of herpes in pregnancy, a history of otosclerosis with exacerbation in pregnancy
8. Diabetes with vascular involvement
9. Headaches with focal neurological symptoms (such as aura) including hemiplegic migraine
10. Abnormal lipid metabolism
11. Sickle cell anaemia
12. Uncontrolled hypertension
13. Hypersensitivity to any of the components of 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

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 thrombophlebitis or 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).

Cigarette Smoking

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 who use oral contraceptives should be strongly advised not to smoke.

Venous and Arterial Thrombosis and Thromboembolism

Use of combined oral contraceptives is associated with an increased risk of venous and arterial thrombotic and thromboembolic events, including thromboembolism, strokes, myocardial infarction, pulmonary embolism and deep vein thrombosis.

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.

Disturbances of the clotting system must be considered if any members of the woman's immediate family have suffered from thromboembolic diseases (e.g. deep vein thrombosis, stroke, myocardial infarction). The physician and the woman should be alert to the earliest manifestations of thrombotic disorders. These may include occurrence for the first time of migrainous headaches or more frequent occurrence of unusually severe headaches, sudden perceptual disorders (e.g. disturbances of vision or hearing), first signs of thrombophlebitis or thromboembolic symptoms (for example, unusual pains in or swelling of the legs, stabbing pains on breathing or coughing for no apparent reason), a feeling of pain and tightness in the chest. Should any of these occur or be suspected treatment should be discontinued immediately.

(a) Venous thrombosis and Thromboembolism

The use of any combined oral contraceptive carries an increased risk of venous thrombotic and thromboembolic events. 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. Some epidemiological studies have suggested that low-dose oral contraceptives containing desogestrel or gestodene may be associated with a higher relative risk of venous thromboembolism than other low-dose combined oral contraceptives, which would translate into an excess risk of approximately one to two cases per 10,000 woman years of use. Data from some additional studies have not shown this increase in risk. The incidence of VTE during any combined oral contraceptive use is less than the incidence 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, prolonged immobilisation and increasing age.

A two- to four-fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of combined oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, combined oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery with an increased in risk of thrombosis, 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.

(b) Arterial Thrombosis and Thromboembolism

The use of combined oral contraceptives increases the risk of arterial thrombotic and thromboembolic events. Reported events include myocardial infarction and cerebrovascular events (ischaemic and haemorrhagic stroke, transient ischaemic attack). The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors. Caution must be exercised when prescribing combined oral contraceptives for women with the following risk factors or predisposing conditions: smoking, hypertension, hyperlipidaemias, obesity and increasing age.

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, 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 drug 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.

Migraine/Headache

The onset or exacerbation of migraine or development of headache with a new pattern that is recurrent, persistent or severe requires discontinuation of oral contraceptive treatment and evaluation of the cause. Women with migraine (particularly migraine with aura) who take combined oral contraceptives may be at increased risk of stroke.

Carcinoma of the Reproductive Organs

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

A meta-analysis from 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using combined oral contraceptives compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of combined oral contraceptive use. 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.

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. 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 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 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 oestrogen 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 oestrogens. However, the results of more recent studies indicate the risk of gallbladder disease may be minimal.

Hepatic Neoplasia/Liver Disease

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.

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 alternate method of contraception in an attempt to determine whether the symptom is drug-related.

Medical Examinations

Before prescribing oral contraceptives a complete history including the family case history and physical examination is desirable, with particular reference to blood pressure, breasts, abdomen and pelvic organs. A Papanicolaou smear and urinalysis should be carried out. In general, oral contraceptives should not be prescribed for longer than one year without further physical examinations.

Sexually Transmissible Diseases

Patients should be counseled 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 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: Oestrogens 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 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.

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 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.

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.

Carcinogenesis/Mutagenesis

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.

Interactions with Other Drugs

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

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

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

During concomitant use of MINULET and substances that may lead to decreased ethinylloestradiol 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 ethinylloestradiol 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 ethinylloestradiol 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 result in a failure of contraception

Examples of substances that may decrease serum ethinylloestradiol concentrations include any substance that reduces gastrointestinal transit time and, therefore, ethinylloestradiol 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.

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.

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.

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).

Oestrogens may possibly inhibit the metabolism of tricyclic antidepressants such as imipramine and desmethyl imipramine 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.

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

Oestrogens may enhance the effects of glucocorticoids.

Drugs that may increase ethinylloestradiol concentrations

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

Laboratory Test Interactions

Oestrogen-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.

ADVERSE REACTIONS

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

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

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

Use of Combined Oral Contraceptives has been associated with an increased risk of:

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

System Organ Class

Adverse Reaction

Infections and Infestations

Common

Vaginitis, including candidiasis

Neoplasms benign, malignant, and unspecified

Very rare

Hepatic adenomas, hepatocellular carcinomas

Immune system disorders

Rare

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

Very rare

Exacerbation of systemic lupus erythematosus

Metabolism 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

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 ectropion 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

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

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

No Preceding Hormonal Contraceptive Use (in the Past Month)

First Cycle

On the first day of the menstrual cycle, i.e. the first day of bleeding, the woman 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 **Advice in Case of Vomiting or Diarrhoea** and **Interactions with other Drugs**) 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.

Subsequent Cycles

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.

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 white active tablet is missed, but is less than 12 hours late, it should be taken as soon as it is remembered. Subsequent tablets should be taken at the usual time.

If one white active tablet is missed and is more than 12 hours late or if more than one active tablet is missed, contraceptive protection may be reduced. The last missed tablet should be taken as soon as it is remembered, even if this means taking two 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.

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.

Advice in Case of 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.

MEDICINE CLASSIFICATION

Prescription Medicine.

PRESENTATION

Three month pack containing 3 blisters.

Each blister containing 21 white tablets, each containing ethinylloestradiol 30 microgram and gestodene 75 microgram and 7 red inert tablets.

Store below 25°C.

NAME AND ADDRESS

Pfizer New Zealand Ltd
P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363

DATE OF PREPARATION

1 November 2010

® Registered Trade Mark