

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

MONOFEME[®] 150 µg and 30 µg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 µg Levonorgestrel and 30 µg Ethinylestradiol

Excipients with known effects:

- Lactose monohydrate
- Sucrose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Each MONOFEME calendar blister pack contains 28 tablets; 21 active (white) tablets of which each contain 30 micrograms ethinylestradiol and 150 micrograms levonorgestrel, and 7 inert (red) tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MONOFEME is indicated for prevention of pregnancy.

4.2 Dose and method of administration

How to Take MONOFEME

Each package of MONOFEME contains 21 white active tablets and 7 red inactive tablets. To achieve maximum contraceptive effectiveness, MONOFEME must be taken in the order directed on the package and at intervals not exceeding 24 hours. Women should be instructed to take the tablets at about the same time every day, preferably after the evening meal or at bedtime. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started on the day after the current pack is completed. A withdrawal bleed usually starts on Day 2-3 after the last active tablet and may not have finished before the next pack is started.

How to Start MONOFEME

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 takes the first white active tablet corresponding to that day of the week from the green shaded section of the MONOFEME package. Thereafter, one white active tablet is taken daily, following the arrows on the package, until all 21 white active tablets have been taken. The woman should then be instructed to take one red tablet from the light shaded section of the MONOFEME pack daily for the next seven days following the arrows marked. Withdrawal bleeding should usually occur

within 3 days after the last active tablet is taken.

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

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

Subsequent cycles

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

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

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

Changing from another Combined Oral Contraceptive

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

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

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

The woman may switch any day from the progestogen-only pill and should begin MONOFEME the next day. She should start MONOFEME on the day of an implant removal or, if using an injection, the day the next injection would be due. In all these situations, the woman should be advised to use a non-hormonal back-up method (other than the rhythm or temperature methods) for the first 7 days of active tablet taking.

Following First-Trimester Abortion

Women may start MONOFEME immediately. Additional contraceptive measures are not needed.

Following Delivery or Second-Trimester Abortion

Since the immediate post-partum period is associated with an increased risk of thromboembolism, COCs should be started no earlier than day 28 after delivery in the non-lactating mother or after second trimester abortion. Women should be advised to also use a non-hormonal back-up method (other than the rhythm or temperature methods) for the first 7 days of active tablet taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of MONOFEME use or the woman has to wait for her first menstrual period (see section 4.4, Thromboembolism and section 4.6).

Management of Missed Tablets

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

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

If one active tablet is missed and is **more than 12 hours late** or if more than one active tablet is missed, contraceptive protection may be reduced. The last missed tablet should be taken as soon as it is remembered, even if this means taking two tablets in one day. Subsequent tablets should be taken at the usual time. In addition, a non-hormonal back-up method of birth control (other than the rhythm or temperature methods) should be used for the next 7 days.

If the 7 days where back-up is required run beyond the last active tablet in the current pack, the next pack must be started on the day following the intake of the last active tablet in the current pack. Discard all red inactive tablets. This prevents an extended break in tablet taking of active tablets that may increase the risk of escape ovulation. The user is unlikely to have a withdrawal bleed until the red inactive tablet interval of the second pack, but she may experience spotting or breakthrough bleeding on days when active tablets are taken.

If the user does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming tablet taking.

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

How to Delay a Period

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

Concomitant Medication

During concomitant use of MONOFEME and substances that may lead to decreased

ethinylestradiol serum concentrations, it is recommended that a non-hormonal back-up method of birth control (other than the rhythm or temperature methods) be used in addition to the regular intake of MONOFEME. In the case of prolonged use of such substances COCs should not be considered the primary contraceptive (see section 4.5).

Vomiting and Diarrhoea

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

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.

4.3 Contraindications

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

A history of or current deep-vein thrombosis, thrombophlebitis or thromboembolic disorders, thrombogenic valvulopathies, thrombogenic rhythm disorders.

Hereditary or acquired predisposition for venous or arterial thrombosis.

Cerebrovascular or coronary artery disease.

Hereditary or acquired thrombophilias.

Known or suspected carcinoma of the breast.

Known or suspected estrogen-dependent neoplasia.

Undiagnosed genital bleeding.

Known or suspected pregnancy.

Benign or malignant liver tumour, which developed during the use of estrogen-containing products or active liver disease, as long as liver function has not returned to normal.

Diabetes with vascular involvement.

Uncontrolled hypertension.

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

Pancreatitis associated with severe hypertriglyceridaemia (current or history).

COCs are contraindicated for concomitant use with certain anti-viral hepatitis C virus (HCV) medicinal products such as ombitasvir, paritaprevir, ritonavir and dasabuvir (see section 4.4, Hepatitis C).

Hypersensitivity to any of the components of MONOFEME.

4.4 Special warnings and precautions for use

Cigarette Smoking

Cigarette smoking increases the risk of serious cardiovascular side effects from the use of oral contraceptives. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

Thromboembolic Disorders

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

For any particular 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.

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

Venous Thrombosis and Thromboembolism

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

The use of combined oral contraceptives carries an increased risk of venous thrombotic and thromboembolic events compared to no use. The excess risk is highest during the first year a woman ever uses a combined oral contraceptive. The approximate incidence of VTE in users of low estrogen dose (<50µg ethinylestradiol) oral contraceptives is up to 4 per 10,000 woman years compared to 0.5-3 per 10,000 woman years in non-oral contraceptive users. This increased risk is less than the risk of venous thrombotic and thromboembolic events associated with pregnancy (which is estimated as 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. Examples of predisposing conditions are: 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 increased risk of thromboembolic complications following surgery has been reported in users of oral contraceptives. If feasible, oral contraceptives should be discontinued at least 4 weeks before and 2 weeks after surgery associated with an increased risk of

thromboembolism and during prolonged immobilisation.

Because the immediate post-partum period is associated with an increased risk of thromboembolism, combined oral contraceptives use should begin no sooner than the 28th postpartum day following either delivery in the non-lactating woman or second-trimester abortion.

Arterial Thrombosis and Thromboembolism

The use of combined oral contraceptives increases the risk of arterial thrombotic and thromboembolic events. An increased risk of myocardial infarction and cerebrovascular events (ischaemic and haemorrhagic stroke, transient ischaemic attack) associated with the use of oral contraceptives has been reported. The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors or predisposing conditions. Caution must be exercised when prescribing combined oral contraceptives for women with risk factors and predisposing conditions for arterial thrombotic and thromboembolic events. Examples of risk factors and predisposing conditions for arterial thrombotic and thromboembolic events are: smoking, hypertension, hyperlipidaemias, obesity, diabetes, history of pre-eclamptic toxæmia and increasing age. COC users with migraine (particularly migraine with aura) may be at increased risk of stroke.

Ocular Lesions

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

Elevated Blood Pressure

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

In women with hypertension, or a history of hypertension or hypertension related diseases; another method of contraception may be preferable. If combined oral contraceptives are used in such cases, close monitoring is recommended and, if a significant increase in blood pressure occurs, the drug should be discontinued. Combined oral contraceptives are contraindicated in women with uncontrolled hypertension.

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

Carcinoma of the Reproductive Organs

Cervical cancer

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

Several epidemiological studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer. The studies suggest that there is an “ever used” effect in addition to duration of use. These findings must be balanced against evidence of effects attributable to sexual behaviour, smoking and other factors. 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. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combined oral contraceptive users is small in relation to the lifetime risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in combined oral contraceptive users, (due to more regular clinical monitoring), the biological effects of combined oral contraceptives or a combination of both. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

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

Women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be monitored with particular care.

Hepatic Neoplasia/Liver Disease/Hepatitis C

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

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

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

Acute or chronic disturbances of liver function require the discontinuation of combined oral contraceptive use until liver function has returned to normal (see section 4.3).

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

Hepatitis C

During clinical trials with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, transient, asymptomatic elevations of alanine transaminase (ALT) greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medications such as combined oral contraceptives.

MONOFEME must be discontinued 2 weeks prior to starting therapy with the combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin. MONOFEME can be restarted approximately 2 weeks following completion of treatment with the combination drug regimen (See section 4.3).

Gallbladder Disease

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

Migraine/Headache

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

Women with migraine (particularly migraine with aura) who take combined oral contraceptives may be at increased risk of stroke (see section 4.4, Arterial Thrombosis and Thromboembolism).

Angioedema

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

Medical Examinations

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

Carbohydrate and Lipid Metabolic Effects

Glucose intolerance has been reported in combined oral contraceptive users. Women with impaired glucose tolerance or diabetes mellitus who use combined oral contraceptives should be carefully monitored. See section 4.3.

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

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

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 combined oral contraceptive depends on the balance achieved between doses of estrogen and progestogen and the nature and absolute amount of progestogen used in the contraceptive. The amount of both hormones should be considered in the choice of an oral contraceptive.

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 MONOFEME has not been taken according to directions prior to the first missed withdrawal bleed, or if two consecutive withdrawal bleeds are missed, tablet taking should be discontinued and a non-hormonal back-up method of contraception should be used until the possibility of pregnancy is excluded.

Breakthrough bleeding, spotting and amenorrhoea are frequent reasons for patients discontinuing oral contraceptives. Breakthrough bleeding/spotting may occur in women taking MONOFEME, especially during the first three months of use. If this bleeding persists or recurs, non-hormonal causes should be considered and adequate diagnostic measures should be taken to eliminate the possibility of pregnancy, infection, malignancy or other conditions. If pathology has been excluded, continuation of MONOFEME or a change to another formulation may solve the problem. Changing to a regimen with a higher estrogen content, while potentially useful in minimising menstrual irregularity should be done only if necessary, since this may increase the risk of thromboembolic disease.

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

Depression

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

Vomiting and/or Diarrhoea

Diarrhoea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations (see section 4.2).

Other

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

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

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

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

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

4.5 Interaction with other medicines and other forms of interaction

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 section 4.3 and section 4.4, 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.

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

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

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

During concomitant use of MONOFEME and substances that may lead to decreased ethinylestradiol serum concentrations, it is recommended that a non-hormonal back-up method of contraception (other than the rhythm or temperature methods) be used in addition to the regular

intake of MONOFEME. In the case of prolonged use of such substances combined oral contraceptives should not be considered the primary contraceptive.

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

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

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

Increased intermenstrual bleeding and occasional pregnancies have been reported during concomitant administration of oral contraceptives and certain antibiotics (e.g. ampicillin, phenoxymethyl penicillin, and other penicillins, sulphamethoxypyridazine, chloramphenicol, nitrofurantoin, tetracycline and neomycin). It may be prudent for women to use supplemental forms of contraception during therapy with these antibiotics.

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

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).

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

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

Examples of substances that may increase 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.

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

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

Laboratory Test Interactions

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

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy - Category B3

Pregnancy must be excluded before starting MONOFEME. If pregnancy occurs during use of MONOFEME, 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.

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

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

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

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

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

Use in Lactation

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

4.7 Effects on ability to drive and use machines

None stated.

4.8 Undesirable effects

The most serious adverse reactions associated with the use of oral contraceptives are indicated under section 4.4.

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, transient ischaemic attack, venous thrombosis and pulmonary embolism.

Cervical intraepithelial neoplasia and cervical cancer.

Breast cancer diagnosis.

Benign hepatic tumours (e.g. focal nodular hyperplasia, hepatic adenomas).

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

System Organ Class	Adverse Reaction
<i>Infections and infestations</i>	
Common	Vaginitis, including candidiasis
<i>Neoplasms benign, malignant, and unspecified</i>	
Very Rare	Hepatic adenomas, hepatocellular carcinomas
<i>Immune system disorders</i>	
Rare	Anaphylactic/anaphylactoid reactions, including very rare cases of urticaria, angioedema and severe reactions with

System Organ Class

Very Rare

Metabolism and nutrition disorders

Uncommon

Rare

Very Rare

Psychiatric disorders

Common

Nervous system disorders

Very Common

Common

Very Rare

Eye disorders

Rare

Very Rare

Vascular disorders

Very Rare

Gastrointestinal disorders

Common

Uncommon

Very Rare

Not known

Hepato-biliary disorders

Rare

Very Rare

Not known

Skin and subcutaneous tissue disorders

Common

Uncommon

Adverse Reaction

respiratory and circulatory symptoms

Exacerbation of systemic lupus erythematosus

Changes in appetite (increase or decrease)

Glucose intolerance

Exacerbation of porphyria

Mood changes, including depression, changes in libido

Headache, including migraines

Nervousness, dizziness

Exacerbation of chorea

Intolerance to contact lenses

Optic neuritis*, retinal vascular thrombosis

Aggravation of varicose veins

Nausea, vomiting, abdominal pain

Abdominal cramps, bloating

Pancreatitis, ischaemic colitis

Inflammatory bowel disease (Crohn's disease, ulcerative colitis)

Cholestatic jaundice

Gallbladder disease, including gallstones**

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

Acne

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

System Organ Class	Adverse Reaction
Rare	Erythema nodosum
Very Rare	Erythema multiforme
<i>Renal and urinary disorders</i>	
Very Rare	Haemolytic uraemic syndrome
<i>Reproductive system and breast disorders</i>	
Very Common	Metrorrhagia (Breakthrough bleeding/spotting)
Common	Breast pain, tenderness, enlargement, secretion, dysmenorrhoea, change in menstrual flow, change in cervical ectropion and secretion, amenorrhoea
<i>General disorders and administration site conditions</i>	
Common	Fluid retention/oedema
<i>Investigations</i>	
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. This may be of clinical significance if the woman becomes pregnant shortly after discontinuing combined oral contraceptives.

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

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

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms

Symptoms of oral contraceptive overdose in adults and children may include nausea, vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue; withdrawal bleeding may occur in females.

Treatment

There is no specific antidote and further treatment of overdose, if necessary, is directed to the symptoms.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

The hormonal components of MONOFEME suppress gonadotropins in a manner that inhibits ovulation, which leads to contraception.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

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

Biotransformation

Ethinylestradiol is subject to considerable first-pass metabolism with a mean bioavailability of 40-45%. Levonorgestrel does not undergo first-pass metabolism and is therefore completely bioavailable.

Elimination

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

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

5.3 Preclinical safety data

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each active white tablet contains the following excipients: calcium carbonate, macrogol 6000, magnesium stearate, sucrose, maize starch, povidone, white beeswax, carnauba wax, purified talc and lactose monohydrate.

Each inactive red tablet contains the following excipients: calcium carbonate, glycol montanate macrogol 6000, magnesium stearate, sucrose, maize starch, povidone, purified talc, lactose monohydrate, colourants erythrosine and brilliant scarlet 4R.

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Three month pack containing 3 blisters.

Each blister contains 21 white active tablets and 7 red inert tablets.

6.6 Special precautions for disposal and other handling

None stated.

7. MEDICINE SCHEDULE

Prescription Medicine.

8. SPONSOR

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

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

26 January 1998

10. DATE OF REVISION OF THE TEXT

19 November 2018

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
5.1	Clarification of the mode of action