SCHEDULING STATUS:

S3

PROPRIETARY NAME (AND DOSAGE FORM):

MINULETTE® Tablets

COMPOSITION:

The 21 white active tablets contain:

Gestodene	75 μg
Ethinyl oestradiol	30 μg

The 7 red tablets are inactive.

PHARMACOLOGICAL CLASSIFICATION:

Category A18.8 Ovulation controlling agents.

PHARMACOLOGICAL ACTION:

The hormonal components of Minulette® inhibit ovulation by suppressing gonadotropin release. Secondary mechanisms include changes in the cervical mucous (which increases the difficulty of sperm penetration) and changes in the endometrium (which reduce the likelihood of implantation).

The pharmacological and biochemical profile of gestodene is very similar to that of progesterone. Due to the high binding affinity and biological activity of gestodene, there is an effective inhibition of ovulation at an exceptionally low dose.

Pharmacokinetics:

Ethinyl oestradiol and gestodene are rapidly and almost completely absorbed from the gastrointestinal tract. Peak plasma levels of each medicine 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 ethinyl oestradiol.

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

Gestodene is extensively plasma protein bound to sex hormone binding globulin (SHBG). Ethinyl oestradiol is bound in plasma to albumin and enhances the binding capacity of SHBG. The elimination half-life for ethinyl oestradiol 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 ethinyl oestradiol is excreted in bile and is subject to enterohepatic recirculation. About 40% of the medicine is excreted in the urine and 60% is eliminated in the faeces.

The elimination half-life for gestodene is approximately 16 - 18 hours after multiple oral doses. The medicine 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.

INDICATIONS:

MINULETTE® is indicated for prevention of pregnancy.

CONTRA-INDICATIONS:

Minulette is contra-indicated in patients with:

- Deep vein thrombosis (current or history)
- Thromboembolism (current or history)
- Cerebrovascular or coronary artery disease
- Thrombogenic valvulopathies
- Thrombogenic rhythm disorders
- Hereditary or acquired thrombophilias
- Headache with focal neurological symptoms, such as aura
- Diabetes with vascular involvement
- Uncontrolled hypertension
- Known or suspected carcinoma of breast, or other known or suspected oestrogen-dependent neoplasias
- Hepatic adenomas or carcinomas, or active liver disease as long as liver function has not returned to normal.
- Undiagnosed vaginal bleeding

- Known or suspected pregnancy (See PREGNANCY AND LACTATION)
- Hypersensitivity to any of the components of Minulette.

WARNINGS

- Cigarette smoking increases the risk of serious cardiovascular adverse reactions from oral contraceptive use. This risk increases with age and the extent of smoking (15 or more cigarettes per day was associated with a significantly increased risk) and is quite marked in women over 35 years of age. Women who use Minulette should be strongly advised not to smoke.

VENOUS AND ARTERIAL THROMBOSIS AND THROMBOEMBOLISM

Use of Minulette is associated with an increased risk of venous and arterial thrombotic and thromboembolic events.

Minimizing exposure to oestrogens and progestins is in keeping with good principles of therapeutics. For any particular oestrogen/progestin combination, the dosage regimen prescribed should be one that contains the least amount of oestrogen and progestin that is compatible with a low failure rate and the needs of the individual patient.

New acceptors of combination oral contraceptives (COCs) should be started on preparations containing less that 50 µg of oestrogen.

- Venous thrombosis and thromboembolism

Use of Minulette increases the risk of venous thrombotic and thromboembolic events. Reported events include deep venous thrombosis and pulmonary embolism. For information on retinal vascular thrombosis see “OCULAR LESIONS” below.

The use of Minulette carries an increased risk of venous thrombotic and thromboembolic events compared with no use. The excess risk is highest during the first year a women ever uses a combined oral contraceptive. This increased risk is less than the risk of venous thrombotic and thromboembolic events associated with pregnancy which is estimated as 60 cases per 100 000 women-years. Venous thromboembolism is fatal in 1-2% of cases.

In several epidemiological studies it has been found that women using COCs with ethinylestradiol, mostly with a dose of 30 µg, and a progestin such as gestodene have an increased risk of venous thrombotic

and thromboembolic events compared with those using COCs containing less than 50 µg of ethinylestradiol and the progestin levonorgestrel. Data from some additional studies have not shown this increase in risk.

For COCs containing 30 µg of ethinylestradiol combined with desogestrel or gestodene compared with those containing less than 50 µg of ethinylestradiol and levonorgestrel, the overall relative risk of venous thrombotic and thromboembolic events has been estimated to range between 1.5 and 2.0. The incidence of venous thrombotic and thromboembolic events for levonorgestrel containing COCs with less than 50 µg of ethinylestradiol is approximately 20 cases per 100 000 woman-years of use. For Minulette, the incidence is approximately 30-40 cases per 100 000 woman-years of use, i.e. additional 10-20 cases per 100 000 women-years of use.

The risk of venous thrombotic and thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism. Caution must be exercised when prescribing Minulette for such women.

Examples of predisposing conditions for venous thrombosis and thromboembolism are:

- Obesity
- Surgery or trauma with increased risk of thrombosis
- Recent delivery or second-trimester abortion
- Prolonged immobilization
- Increasing age

Further risk factors, which represent contraindications for the use of Minulette, are listed under “Contra-indications”.

The relative risk of postoperative thromboembolic complications has been reported to be increased two-to four-fold with the use of combination oral contraceptives, such as Minulette. The relative risk of venous thrombosis in women with predisposing conditions is twice that of women without such conditions. If feasible, Minulette should be discontinued:

- for four weeks prior to and for two weeks after elective surgery with increased risk of thrombosis, and during prolonged immobilisation.

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

- Arterial thrombosis and thromboembolism

The use of Minulette increases the risk of arterial thrombotic and thromboembolic events.

Reported events include myocardial infarction and cerebrovascular events (ischaemic and hemorrhagic stroke, transient ischaemic attack). For information on retinal vascular thrombosis see "OCULAR LESIONS" below.

The risk of arterial thrombotic and thromboembolic events is further increased in women with underlying risk factors.

Caution must be exercised when prescribing Minulette for women with risk factors for arterial thrombotic and thromboembolic events.

Examples of risk factors for arterial thrombotic and thromboembolic events are:

- smoking
- hypertension
- hyperlipidemias
- obesity
- increasing age.

Minulette users with migraine (particularly migraine with aura) may be at increased risk of stroke.

Further risk factors, which represent contraindications for the use of Minulette, are listed under "Contra-indications**".**

OCULAR LESIONS

With use of Minulette, there have been reports of retinal vascular thrombosis, which may lead to partial or complete loss of vision. If there are signs or symptoms such as visual changes, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, Minulette should be discontinued and the cause immediately evaluated.

BLOOD PRESSURE

Increases in blood pressure have been reported in women taking Minulette.

In women with hypertension, a history of hypertension or hypertension related diseases (including certain renal diseases); another method of contraception may be preferable. If Minulette is used in such cases, close monitoring is recommended and, if a significant increase in blood pressure occurs, Minulette should be discontinued.

Elevated blood pressure associated with Minulette use will generally return to baseline after stopping Minulette and there appears to be no difference in the occurrence of hypertension among ever- and never-users.

Minulette use is contra-indicated in women with uncontrolled hypertension (see "CONTRA-INDICATIONS").

CARCINOMA OF THE REPRODUCTIVE ORGANS

Some studies suggest that combination oral contraceptive use, such as Minulette may be associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women.

However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behaviour and other factors. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

A Meta analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed in women who are using combination oral contraceptives compared to never-users. The increased risk gradually disappears during the course of the 10 years after cessation of combination oral contraceptive use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to earlier detection of breast cancer in combination oral contraceptive users (due to more regular clinical monitoring), the biological effects of combination 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 combination 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 that the cancers diagnosed in never-users.

HEPATIC NEOPLASIA/ LIVER DISEASE

In very rare cases hepatic adenomas, and in extremely rare cases, hepatocellular carcinoma may be associated with combination oral contraceptive (COC) use, such as Minulette. The risk appears to increase with duration of oral contraceptive use. Rupture of hepatic adenomas may cause death through intra-abdominal haemorrhage. Women with a history of oral contraceptive related cholestasis or women with cholestasis during pregnancy are more likely to have this condition with Minulette use.
If these patients receive a Minulette they should be carefully monitored and, if the condition recurs, the Minulette should be discontinued.

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 Minulette and evaluation of the cause.
Women with migraine (particularly migraine with aura) who take Minulette may be at increased risk of stroke.

INTERACTIONS:

Interactions between ethinyl estradiol (EE) and other substances may lead to decreased or increased serum EE concentrations, respectively.
Decreased EE serum concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possible reduce efficacy of Minulette.
During concomitant use of EE- containing products and substances that may lead to decreased EE serum concentrations, it is recommended that a nonhormonal back-up method of birth control such as condoms and spermicide) be used in addition to the regular intake of Minulette. In the case of prolonged use of such substances Minulette should not be considered the primary contraceptive.
After discontinuation of substances that may lead to decreased EE serum concentrations, use of a nonhormonal 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 EE 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 decrease serum EE concentrations:

- Any substance that reduces gastrointestinal transit time and, therefore, EE absorption.
- Substances that induce hepatic microsomal enzymes, such as rifampicin, rifabutin, barbiturates, primidone, phenylbutazone, phenytoin, dexamethasone, griseofulvin, topiramate, some protease inhibitors, modafinil.
- Hypericum perforatum, also known as St. John's wort, and ritonavir[1] (possibly by induction of hepatic microsomal enzymes).
- Certain antibiotics (e.g. ampicillin and other penicillins, tetracyclines), by a decrease of enterohepatic circulation of oestrogens.

Examples of substances that may increase serum EE concentrations:

- Atorvastatin
- Competitive inhibitors for sulphation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and paracetamol.
- Substances that inhibit cytochrome P450 3A4 isoenzyme such as indinavir, fluconazole and troleandomycin. [1]

Troleandomycin may increase the risk of intrahepatic cholestasis during co-administration with combination oral contraceptives

EE may interfere with the metabolism of other drugs by

- inhibiting hepatic microsomal enzymes, or by
- inducing hepatic drug conjugation, particularly glucuronidation.

[1] Although ritonavir is an inhibitor of cytochrome P450 3A4, treatment with ritonavir has been shown to decrease EE serum concentrations (see above).

Accordingly, plasma and tissue concentrations may either be increased (e.g., cyclosporine, theophylline, corticosteroids) or decreased (eg. lamotrigine). In patients treated with flunarizine, use of oral contraceptives has been reported to increase the risk of galactorrhoea.

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

INTERFERENCE WITH LABORATORY AND OTHER DIAGNOSTIC TESTS

Effects on Laboratory Parameters

The use of Minulette may cause certain physiologic changes, which may be reflected in the results of certain laboratory tests, including

- biochemical parameters of liver function (including a decrease in bilirubien and alkaline phosphatase), thyroid function (increased total T3 and T4 due to increased TBG, decreased free T3 resin uptake), adrenal function (increased plasma cortisol, increased cortisol binding globulin, decreased dehydroepiandrosterone sulphate (DHEAS), and renal function (increased plasma creatinine and creatinine clearance)**.**
- plasma levels of (carrier) proteins, such as corticosteroid-binding globulin and lipid/lipoprotein fractions
- parameters of carbohydrate metabolism
- parameters of coagulation and fibrinolysis
- decreased serum folate levels

PREGNANCY AND LACTATION:

Pregnancy

Extensive epidemiological studies have revealed no increased risk of birth defects in children born to women who used combination oral contraceptives prior to pregnancy.

Studies do not suggest a teratogenic effect; particularly insofar as cardiac anomalies and limb-reduction defects are concerned, when taken inadvertently during early pregnancy. (See also Contraindications).

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 Minulette as it may reduce the quantity and change the composition of breast milk.

The use of Minulette is generally not recommended until the nursing mother has completely weaned her child. See also “WARNINGS” regarding postpartum use.

DOSAGE AND DIRECTIONS FOR USE:

HOW TO TAKE MINULETTE

Tablets 1-21 contain active ingredients (active tablets).

In Minulette 28-day packs, tablets 22-28 do not contain any active ingredients (inactive tablets).

To achieve maximum contraceptive effectiveness, Minulette must be taken in the order as directed on the package and at the same time every day, preferably after the evening meal or at bedtime. One active tablet is to be taken daily for 21 consecutive days, then either followed by 7 days of inactive (placebo) tablets or a 7-day tablet-free interval.

Each subsequent pack is started on the day after the last inactive tablet. A withdrawal bleed usually starts on days 2-3, after the last active tablet, and may not have finished before the next pack is started.

HOW TO START MINULETTE

- No preceding hormonal contraceptive use (in the past month)

On the first day of the woman’s natural menstrual cycle, i.e. the first day of menstrual bleeding, the patient will take the first tablet marked with the appropriate day of the week from those in the red area of the package. Starting on days 2-7 (e.g. Sunday start) is allowed, but for the first 7 days of tablet-taking during the first cycle a nonhormonal back-up method of birth control (such as condoms and spermicide) is recommended. Thereafter, one tablet is taken daily, following the arrows on the package, until all 28 tablets have been taken.

- Changing from another Combination Oral Contraceptive to Minulette

The woman should start **Minulette** preferably on the day after the last active tablet of her previous combination oral contraceptive, but at the latest, on the day following the usual inactive tablet interval of her previous combination oral contraceptive.

- Changing from a progestin only method (progestin-only pill, injection, implant)

The woman may switch any day from the progestin-only pill and should begin Minulette the next day. She should start Minulette on the day of an implant removal or, if using an injection, the day the next injection would be due. In all of these situations, the woman should be advised to use a nonhormonal back-up method for the first 7 days of tablet-taking.

- Following first-trimester abortion

The woman may start Minulette 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, Minulette should be started no earlier than day 28 after delivery in the nonlactating mother or after second-trimester abortion. The woman should be advised to use a nonhormonal 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 Minulette use or the woman must wait for her first menstrual period. See "WARNINGS" and "PRECAUTIONS" sections.

MANAGEMENT OF MISSED TABLETS

Contraceptive protection may be reduced if active (white) tablets are missed and particularly if the missed tablets extend the inactive (red) 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 nonhormonal back-up method of birth control should be used for the next seven days.
    - If the seven days where back up is required run beyond the last active tablet in the current pack, the next pack must be started on the day following the intake of the last active tablet in the current pack; all inactive tablets should be discarded. 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 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.

ADVICE IN CASE OF VOMITING

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 backup pack.

HOW TO DELAY A PERIOD

To delay a period the woman should continue with another pack of Minulette without the 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 Minulette is then resumed after the usual 7 –day inactive tablet interval.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

SIDE-EFFECTS:

Adverse reactions are listed per CIOMS frequency categories:

Incidence terminology:

Very common: $\geq$ 10 %

Common: $\geq$ 1% of patients

Uncommon: $\geq$ 0,1% and < 1%

Rare: $\geq$ 0,01 % and < 0,1 %

Very rare: < 0,01%

Use of Minulette has been associated with:

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

System Organ Class

Infections and Infestations

Common	Vaginitis, including candidiasis

Neoplasms benign, malignant, and unspecified.

Very Rare	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 Other reactions of possible immunologic origin may be listed under other organ system subheadings.

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

System Organ Class	
Common	Nervousness; dizziness
Very rare	Exacerbation of chorea
Eye disorders	
Rare	Intolerance to contact lenses
Very rare	Optic neuritis[2]; 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 disorder	
Rare	Cholestatic jaundice
Very Rare	Gallbladder disease, including gallstones[3]
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 uremic syndrome
Reproductive system and breast disorders	
Very common	Breakthrough bleeding/spotting
Common	Breast pain, tenderness, enlargement, secretion; dysmenorrhoea; change in menstrual flow; change in

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

[3] combination oral contraceptives **may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.**

System Organ Class	
	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[4]

SPECIAL PRECAUTIONS:

Medical examinations

A complete personal and family medical history and physical examination, including blood pressure, should be taken prior to the initiation of Minulette use.

Such medical examinations should be repeated periodically during the use of Minulette.

Carbohydrate and lipid effects

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

A small proportion of women will have adverse lipid changes while taking Minulette. Nonhormonal contraception should be considered in women with uncontrolled dyslipidemias.

Persistent hypertriglyceridemia may occur in a small proportion of Minulette users. Elevations of plasma triglycerides may lead to pancreatitis and other complications.

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

Women who are being treated for hyperlipidemias should be followed closely if they elect to use Minulette.

Genital bleeding

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

Breakthrough bleeding/spotting may occur in women taking Minulette, especially during the first three months of use. The type and dose of progestin may be important. If this bleeding persists or recurs, nonhormonal 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, continued use of the Minulette or a change to another formulation may solve the problem.

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

Depression

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

Other

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

Diarrhoea and/or vomiting may reduce hormone absorption resulting in decreased serum concentrations (see “DOSAGE AND DIRECTIONS FOR USE”).

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

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

IDENTIFICATION:

The Minulette® package contains 28 tablets (21 white and 7 red).

PRESENTATION:

Each course of Minulette® comprises of 21 white and 7 red tablets packed in a blister type package.

STORAGE DIRECTIONS:

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

Keep out of reach of children.

REGISTRATION NUMBER:

W/18.8/11

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

Pfizer Laboratories (Pty) Ltd.

85 Bute Lane

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2196

South Africa

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