SCHEDULING STATUS: S3

PROPRIETARY NAME (and dosage form):

MINESSE® 28

COMPOSITION:

Each active yellow tablet contains 60 μg gestodene and 15 μg ethinylestradiol (24 tablets).

The 4 white tablets are placebo and do not contain any active ingredients.

PHARMACOLOGICAL CLASSIFICATION:

A 18.8 Ovulation controlling agents

PHARMACOLOGICAL ACTION:

Pharmacodynamics

MINESSE® is a low-dose monophasic ovulation-controlling agent with oestrogenic and progestogenic peripheral effects.

The mode of action of gestodene in combination with ethinyl estradiol includes the inhibition of ovulation by suppression of the mid-cycle surge of luteinising hormone, suppression of endometrial development thus rendering the endometrium unreceptive to implantation and the thickening of cervical mucus so as to constitute a barrier to sperm.

Pharmacokinetics

Gestodene

Absorption

Orally administered gestodene is rapidly and completely absorbed. Peak serum concentration of approximately 2-4 ng/mL is reached at about 1 hour after acute ingestion. Bioavailability is approximately 99 %.

Distribution

Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1 – 2 % of the total serum drug concentration is present as free steroid, 50 – 70 % is specifically bound to SHBG. The ethinyl estradiol - induced increase in SHBG influences the proportion of gestodene bound to the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of gestodene is 0.7 - 1.4 L/kg.

Metabolism

Gestodene is completely metabolised by the known pathways of steroid metabolism. The mean metabolic clearance rate from the serum is 0.8 - 1.0 mL/min/kg. When gestodene was acutely co administered with ethinyl estradiol, no direct interaction was found.

Elimination

Gestodene serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of 12 - 20 hours. Only metabolites of gestodene are excreted occurring at a urinary to biliary ratio of 6:4. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Gestodene pharmacokinetics are influenced by SHBG levels, which are increased about threefold when co-administered with ethinyl estradiol. Following daily

ingestion, drug serum levels increase about three to fourfold reaching steady-state conditions during the second half of a treatment cycle.

Ethinyl estradiol

Absorption

Orally administered ethinyl estradiol is rapidly and completely absorbed. Peak serum concentration of about 30 - 80 pg/mL is reached within 1 - 2 hours. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60 %.

Distribution

Ethinyl estradiol is highly but non-specifically bound to serum albumin (approximately 98.5 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 - 18 L/kg was determined.

Metabolism

Ethinyl estradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinyl estradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate is about 5 - 13 mL/min/kg.

Elimination

Ethinyl estradiol serum levels decrease in two phases, the terminal disposition phase is characterised by a half-life of approximately 16 - 24 hours. Only metabolites of Ethinyl estradiol are excreted occurring at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Steady-state conditions are reached after 3 - 4 days when serum drug levels are higher by 30 % to 40 % as compared to single dose.

INDICATIONS:

MINESSE® is indicated for the prevention of pregnancy.

CONTRA-INDICATIONS:

MINESSE® 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
- Hypersensitivity to any of the components of MINESSE®.
-

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 MINESSE® should be strongly advised not to smoke.

Venous and arterial thrombosis and thromboembolism

Use of MINESSE® 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 should be started on preparations containing less than 50 µg of oestrogen.

Venous thrombosis and thromboembolism

Use of MINESSE® 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”.

The use of MINESSE® 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 combined oral contraceptives 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 gestodene with 15 µg of ethinylestradiol (such as MINESSE®) there are no data on the comparative risk of venous thrombotic and thromboembolic events. 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 COCs containing 30 µg of ethinylestradiol combined with desogestrel or gestodene 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 or thromboembolic events is further increased in women with conditions predisposing for venous thrombosis and thromboembolism. Caution must be exercised when prescribing MINESSE® 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 MINESSE®, 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. The relative risk of venous thrombosis in women with predisposing conditions is twice that of women without such conditions. If feasible, MINESSE® 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, MINESSE® should be started no earlier than day 28 after delivery or second-trimester abortion.

Arterial thrombosis and thromboembolism

The use of MINESSE® 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”.

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

Caution must be exercised when prescribing MINESSE® 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.

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

Further risk factors, which represent contraindications for the use of MINESSE®, are listed under "CONTRA-INDICATIONS**".**

Ocular lesions

With use of MINESSE®, 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, MINESSE® should be discontinued and the cause immediately evaluated.

Blood pressure

Increases in blood pressure have been reported in women taking MINESSE®.

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

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

MINESSE® use is contra-indicated in women with uncontrolled hypertension (See CONTRA-INDICATIONS).

Carcinoma of the reproductive organs

Some studies suggest that combination oral contraceptive such as MINESSE® use 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 neoplasma / 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 MINESSE®. 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 combination oral contraceptive use.

If these patients receive MINESSE® they should be carefully monitored and, if the condition recurs, MINESSE® 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 MINESSE® and evaluation of the cause.

Women with migraine (particularly migraine with aura) who take MINESSE® 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 MINESSE®.

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 MINESSE®. In the case of prolonged use of such substances MINESSE® 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 MINESSE®.

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 concentration (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 MINESSE® may 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 MINESSE® 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 lip/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 CONTRA-INDICATIONS).

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 MINESSE® as it may reduce the quantity and change the composition of breast milk. The use of combination oral contraceptives is generally not recommended until the breast-feeding mother has completely weaned her child. See also “WARNINGS” regarding postpartum use.

DOSAGE AND DIRECTIONS FOR USE:

How to take MINESSE®

Tablets 1 - 24 contain active ingredients (active tablets).

In MINESSE® 28-day packs, tablets 25 - 28 do not contain any active ingredients (inactive tablets).

To achieve maximum contraceptive effectiveness, MINESSE® 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 24 consecutive days, then either followed by 4 days of inactive (placebo) tablets or a 4- 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. The tablets are taken daily and pack follows pack without interruption and without regard to bleeding.

How to start MINESSE®

- 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 MINESSE®

The woman should start MINESSE® 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 MINESSE® the next day. She should start MINESSE® 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 MINESSE® 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, MINESSE® 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 MINESSE® use or the woman must wait for her first menstrual period. (See WARNINGS and PRECAUTIONS).

Management of missed tablets

Contraceptive protection may be reduced if active (yellow) tablets are missed and particularly if the missed tablets extend the inactive (white) 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 MINESSE® 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 MINESSE® is then resumed after the usual 4 –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 combination oral contraceptives such as MINESSE® 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)

System Organ Class

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[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

System Organ Class

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 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 MINESSE® use.

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

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.

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

Carbohydrate and lipid effects

Glucose intolerance has been reported in combination oral contraceptive users. Women with impaired glucose tolerance or diabetes mellitus who use MINESSE® should be carefully monitored.

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

Persistent hypertriglyceridemia may occur in a small proportion of MINESSE® 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 a combination oral contraceptive.

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

Genital bleeding

In some women withdrawal bleeding may not occur during the inactive-tablet interval. If MINESSE® 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 MINESSE®, 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 MINESSE® 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 MINESSE® should be carefully observed and the medicine discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking MINESSE® 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).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of MINESSE® 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:

24 pale yellow round film-coated hormonal tablets with convex faces.

4 white round film-coated non-hormonal tablets with convex faces.

PRESENTATION:

A carton containing a calendar pack consisting of a PVC and aluminium blister strip with 24 pale yellow hormonal tablets and 4 white non-hormonal tablets.

STORAGE INSTRUCTIONS:

Store below 25 °C. Protect from moisture and light.

REGISTRATION NUMBER:

33/18.8/0341

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

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