SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

MIRELLE® 0,015 mg/0,06 mg film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The 28-day pack (Every-Day pack) contains:
24 hormone-containing pale yellow coated tablets:
Each coated tablet contains ethinylestradiol 0,015 mg and gestodene 0,06 mg
Contains sugar (lactose – 38 mg)

4 hormone-free white coated tablets.
Contains sugar (lactose – 38 mg)

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The hormone-containing tablet is pale yellow, round with convex faces.
The hormone-free tablet is white, round with convex faces.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Oral contraception.

4.2. Posology and method of administration

Posology

How to take MIRELLE

Tablets must be taken every day at about the same time in the order directed on the package, and with some liquid as needed. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started on the day after taking the last tablet from the previous pack. A withdrawal bleed usually starts on days 2 to 3 after the last hormone-containing tablet and may not have finished before the next pack is started.

How to start MIRELLE

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

Tablet-taking should start on day 1 of the natural cycle (i.e. the first day of menstrual bleeding). Starting on days 2 to 5 is allowed, but during the first cycle a back-up method of birth control (such as condoms and spermicide) is recommended in addition for the first 7 days of tablet-taking.

- Changing from a combined hormonal contraceptive (combined oral contraceptive), vaginal ring, or transdermal patch

The woman should start with MIRELLE preferably on the day after the last hormone-containing tablet of her

previous combined oral contraceptive, but at the latest on the day following the usual tablet-free or hormone-free tablet interval of her previous combined oral contraceptive. In case a vaginal ring or transdermal patch has been used, the woman should start using MIRELLE preferably on the day of removal of the last ring or patch of a cycle pack, but at the latest when the next application would have been due.

- Changing from a progestogen-only method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)

The woman may switch any day from the minipill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- Following first trimester abortion

The woman may start immediately. When doing so, she does not need additional contraceptive measures.

- Following delivery or second trimester abortion

For breastfeeding women, see section 4.6.
Women should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of MIRELLE or the woman has to wait for her first menstrual period.

Management of missed tablets

Missed hormone-free white coated tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the hormone-free white tablet phase. The following advice only refers to missed hormone-containing pale yellow coated tablet.

If the user is ***less than 12 hours*** late in taking any hormone-containing pale yellow tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

If she is ***more than 12 hours*** late in taking any hormone-containing tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:
1. tablet-taking must never be discontinued for longer than 4 days.
2. 7 days of uninterrupted hormone-containing tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly, the following advice can be given in daily practice:

- Days 1 to 7

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets that are missed and the closer they are to the hormone-free white tablet phase, the higher the risk of a pregnancy.

- Days 8 to 14

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- Days 15 to 24

The risk of reduced reliability is imminent because of the forthcoming hormone-free white tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to use extra precautions for the next 7 days as well.

- The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the pale yellow tablets are used up. The 4 white hormone-free tablets must be discarded. The next pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the hormone-containing pale yellow tablets section of the second pack, but she may experience spotting or breakthrough bleeding.
- The woman may also be advised to discontinue taking the pale yellow tablets from the current pack. She should then have a tablet-free interval of up to 4 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the hormone-free white tablet phase, the possibility of a pregnancy should be considered.

Advice in case of gastrointestinal disturbances

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.
If vomiting occurs within 3 to 4 hours after taking a pale yellow hormone-containing tablet the advice concerning missed tablets as given in section “Management of missed tablets” is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

How to delay a period

To delay a period the woman should continue with another pack of MIRELLE without the hormone-free white tablets from her current pack. The extension can be carried on for as long as wished until the end of the pale yellow tablets in the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of MIRELLE is then resumed after the usual 4 day hormone-free white tablet interval.

How to shift a period

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming hormone-free white tablet phase by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the second pack (just as when delaying a period).

Special populations

Paediatric patients
MIRELLE is only indicated after menarche.

Geriatric patients
MIRELLE is not indicated after menopause.

Patients with hepatic impairment
MIRELLE is contraindicated in women with severe hepatic diseases. See also section 4.3.

Patients with renal impairment
MIRELLE has not been specifically studied in renally impaired patients.

Method of administration

Oral use

4.3. Contraindications

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

- Hypersensitivity to the active substances or to any of the excipients of MIRELLE (see section 6.1).
- Presence or a history of venous or arterial thrombotic/thromboembolic events (e.g. deep venous thrombosis, pulmonary embolism, myocardial infarction) or of a cerebrovascular accident.
- Presence or history of prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- History of migraine with focal neurological symptoms.
- Diabetes mellitus with vascular involvement.
- A high risk of venous or arterial thrombosis (see section 4.4).
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Use of antiviral medicines containing ombitasvir, paritaprevir, ritonavir, or dasabuvir, and combinations of these (see section 4.5).
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.

4.4. Special warnings and precautions for use

If any of the conditions/risk factors mentioned below are present, the benefits of combined oral contraceptive use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether its use should be discontinued.

Circulatory disorders

Epidemiological studies have suggested an association between the use of combined oral contraceptives and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely.

The risk of venous thromboembolism (VTE) is highest during the first year of use. This increased risk is present after initially starting combined oral contraceptives, such as MIRELLE, or restarting (following a 4 week or greater pill free interval) the same or different combined oral contraceptives. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose (< 50 µg ethinylestradiol) combined oral contraceptives, such as MIRELLE, is higher than for non-users of combined oral contraceptives.

VTE may be life-threatening or may have a fatal outcome (in 1-2 % of the cases).

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all combined oral contraceptives, such as MIRELLE.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries, in combined oral contraceptive users.

Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a

combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. MIRELLE should not be prescribed in case of a negative risk benefit assessment. (see section 4.3).

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- Age.
- Smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age).
- A positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any combined oral contraceptive use.
- Obesity (body mass index over 30 kg/m^2).
- Dyslipoproteinaemia.
- Hypertension.
- Migraine
- Valvular heart disease.
- Atrial fibrillation.
- Prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue MIRELLE use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

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

The increased risk of thromboembolism in the puerperium must be considered.

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

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

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis, and that the risk associated with pregnancy is higher than that associated with combined oral contraceptive use.

Tumours

The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of combined oral contraceptives may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour including use of barrier contraceptives.

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 currently using combined oral contraceptives, such as MIRELLE. The excess 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 overall 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, the biological effects of combined oral contraceptives, or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced

clinically than the cancers diagnosed in never-users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of combined oral contraceptives, such as MIRELLE. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking combined oral contraceptives.

Malignancies may be life-threatening or may have a fatal outcome.

Other conditions

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using MIRELLE.

Although small increases in blood pressure have been reported in many women taking combined oral contraceptives such as MIRELLE, clinically relevant increases are rare. A relationship between combined oral contraceptive use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of MIRELLE then it is prudent for the physician to withdraw MIRELLE and treat the hypertension. Where considered appropriate, MIRELLE use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and combined oral contraceptive use, but the evidence of an association with combined oral contraceptive use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

Acute or chronic disturbances of liver function may necessitate the discontinuation of MIRELLE use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of MIRELLE.

MIRELLE may have an effect on peripheral insulin resistance and glucose tolerance. Hence, diabetic women should be carefully observed while taking MIRELLE.

Crohn's disease and ulcerative colitis have been associated with combined oral contraceptive use, such as MIRELLE.

Chloasma may occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking MIRELLE.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of MIRELLE, guided by the contraindications and warnings (see sections 4.3 and 4.4) and should be repeated at least annually during the use of MIRELLE. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of MIRELLE. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts,

abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

Women should be advised that MIRELLE do not protect against HIV infections (AIDS) and other sexually transmissible diseases.

Reduced efficacy

The efficacy of MIRELLE may be reduced in the event of e.g. missed hormone-containing pale yellow tablets, gastrointestinal disturbances during hormone-containing white tablet taking or concomitant medication (see sections 4.2 and 4.5).

Reduced cycle control

With all combined oral contraceptives, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, the non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the hormone-free white tablet phase. If MIRELLE has been taken according to the directions described, it is unlikely that the woman is pregnant. However, if MIRELLE has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before MIRELLE use is continued.

4.5. Interaction with other medicines and other forms of interaction

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

Effects of other medicines on MIRELLE

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and oral contraceptive failure.

Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of medicine therapy enzyme induction may be sustained for about 4 weeks.

Women on treatment with any of these medicines should temporarily use a barrier method in addition to MIRELLE or choose another method of contraception. The barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing pale yellow tablets in the current pack, the hormone-free white tablets must be discarded and the next pack started right away.

Substances increasing the clearance of MIRELLE (diminished efficacy by enzyme-induction), e.g.:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort

Substances with variable effects on the clearance of MIRELLE, e.g.:

When co-administered with MIRELLE, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of MIRELLE (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen or the progestin or both.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1,4 to 1,6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0,035 mg ethinylestradiol.

Effects of MIRELLE on other medicines

Oral contraceptives may affect the metabolism of certain other medicine. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism-based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

Pharmacodynamic interactions

Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increases in ALT levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see section 4.3).

Other forms of interactions

Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins, e.g. corticosteroid binding globulin and lipid-lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

4.6. Pregnancy and lactation

Pregnancy

MIRELLE is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during treatment with MIRELLE, further intake must be stopped. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used combined oral contraceptives prior to pregnancy, nor a teratogenic effect when combined oral contraceptives were taken inadvertently during early pregnancy.

Lactation

Lactation may be influenced by MIRELLE as it may reduce the quantity and change the composition of breast milk, therefore, the use of MIRELLE should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk but there is no evidence that this adversely affects infant health.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of MIRELLE.

4.8. Undesirable effects

a) Summary of the safety profile

The most commonly reported adverse reactions with MIRELLE are nausea, abdominal pain, increased weight, headache, depressed mood, altered mood, breast pain, breast tenderness. They occur in ≥ 1 % of users.

Serious adverse reactions are arterial and venous thromboembolism.

b) Tabulated list of adverse reactions

System Organ Class (MedDRA)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1 000 to < 1/100)	Rare (≥ 1/10 000 to ≤ 1/1 000)
Eye disorders			contact lens intolerance
Gastrointestinal disorders	nausea abdominal pain	vomiting diarrhoea	
Immune system disorders			hypersensitivity
Investigations	increased weight		decreased weight
Metabolism and nutrition disorders		fluid retention	
Nervous system disorders	headache	migraine	
Psychiatric disorders	depressed mood altered mood	decreased libido	increased libido
Reproductive system and breast disorders	breast pain breast tenderness	breast hypertrophy	vaginal discharge breast discharge
Skin and subcutaneous tissue disorders		rash urticaria	erythema nodosum erythema multiforme
Vascular disorders			Venous and arterial thromboembolic events*

* - Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives. - 'Venous and arterial thromboembolic events' summarises the following Medical Entities: Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/Cerebral infarction and stroke not specified as haemorrhagic

c) Description of selected adverse reactions

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections 4.3 and 4.4):

Tumours

- The frequency of diagnosis of breast cancer is very slightly increased among oral contraceptive users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with combined oral contraceptive use is unknown.
- Liver tumours (benign and malignant)

Other conditions

- Women with hypertriglyceridemia (increased risk of pancreatitis when using combined oral contraceptives)

- Hypertension
- Occurrence or deterioration of conditions for which association with combined oral contraceptive use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema
- Liver function disturbances
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis.
- Chloasma

Interactions

Breakthrough bleeding and/or contraceptive failure may result from interactions of other medicines (enzyme inducers) with oral contraceptives (see section 4.5).

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9. Overdose

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in cases of taking an overdose of hormone-containing pale yellow tablets are nausea, vomiting and withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidentally taken the medicine. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group (ATC): Progestogens and estrogens, fixed combinations
ATC Code: G03AA

MIRELLE is a low-dose monophasic ovulation controlling agent with estrogenic and progestogenic peripheral effects.

The mode of action of gestodene in combination with ethinylestradiol includes:
- the inhibition of ovulation by suppression of the mid-cycle surge of luteinising hormone;
- the 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.

5.2. Pharmacokinetic properties

Gestodene

Absorption
Orally administered gestodene is rapidly and completely absorbed. Peak serum concentrations of 4 ng/ml is reached at about 1 hour after single ingestion. Bioavailability is approximately 99 %.

Distribution
Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1 to 2 % of the total

serum concentration is present as free steroid, 50 to 70 % is specifically bound to SHBG. The ethinylestradiol-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 to 1,4 l/kg.

Metabolism
Gestodene is completely metabolised by the known pathways of steroid metabolism. The metabolic clearance rate from the serum is 0,8 to 1,0 ml/min/kg. When gestodene was acutely coadministered with ethinylestradiol, 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 to 20 hours. Gestodene is not excreted in unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 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 threefold when coadministered with ethinylestradiol. Following daily ingestion, serum gestodene levels increase about four-fold reaching steady-state conditions during the second half of a treatment cycle.

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 80 pg/ml are reached within 1 to 2 hours. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60 %.

Distribution
Ethinylestradiol 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 to 18 l/kg was determined.

Metabolism
Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol 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 sulphate. The metabolic clearance rate is about 5 to 13 ml/min/kg.

Elimination
Ethinylestradiol serum levels decrease in two phases, the terminal disposition phase is characterised by a half-life of approximately 16 to 24 hours. Only metabolites of ethinylestradiol 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 to 4 days when serum ethinylestradiol levels are higher by 30 to 40 % as compared to single dose.

5.3. Preclinical safety data

None.

6. PHARMACETUICAL PARTICULARS

6.1. List of excipients

ferric oxide red
ferric oxide yellow
hydroxypropyl cellulose
hypromellose
lactose monohydrate
macrogol 1450
magnesium stearate
microcrystalline cellulose
polacrilin potassium
polyethylene glycol
titanium dioxide
wax E

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Store below 25 °C.
Protect from moisture and light

6.5. Nature and contents of container

MIRELLE is packed in colourless transparent PVC/aluminium blisters containing 24 pale yellow hormone-containing tablets plus 4 white hormone-free tablets per blister strip.
The blister strip is packed into an outer cardboard carton.
Pack sizes: 28 tablets

6.6. Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
Isando
1609

8. REGISTRATION NUMBER

33/18.8/0364

9. DATE OF FIRST AUTHORISATION

24 August 2000

10. DATE OF REVISION OF THE TEXT

3 August 2022

Namibia: NS2 04/18.8/1531