SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

MIRELLE

Tablets

COMPOSITION

The 28-day pack (Every-Day pack) contains 24 hormonal tablets each with gestodene (17α-ethinyl-13-ethyl-17β-hydroxy-4,15-gonadiene-3-one) 0,06 mg and ethinylestradiol (17α-ethinyl-estra-1,3,5(10)-triene-3,17β-diol) 0,015 mg, plus 4 inactive tablets.

PHARMACOLOGICAL CLASSIFICATION

A. 18.8 Ovulation controlling agents.

PHARMACOLOGICAL ACTION

Pharmacodynamics

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.

Pharmacokinetics

- 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 drug 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, drug serum levels increase about fourfold 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 drug levels are higher by 30 to 40% as compared to single dose.

INDICATIONS

Oral contraception.

CONTRA-INDICATIONS

Combined oral contraceptives 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 combined oral contraceptive use, the product should be stopped immediately.

- Thrombosis (venous or arterial) present or in history (eg deep venous thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident).
- Presence or history of prodromi of a thrombosis (eg transient ischaemic attack, angina pectoris).
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contra-indication (see “Warnings”).
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected malignant conditions of the genital organs or the breasts, if sex steroid-influenced.

- Undiagnosed vaginal bleeding.
- Known or suspected pregnancy.
- Hypersensitivity to any of the components of Mirelle.

WARNINGS

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.

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all combined oral contraceptives. The approximate incidence of venous thromboembolism in users of low estrogen dose (< 50 μg ethinylestradiol) oral contraceptives is up to 4 per 10 000 woman years compared to 0,5 to 3 per 10 000 woman years in non-oral contraceptive users. However, the incidence of venous thromboembolism occurring during combined oral contraceptive use is substantially less than the incidence associated with pregnancy (ie 6 per 10 000 pregnant woman years).

Extremely rarely, thrombosis has been reported to occur in other blood vessels, eg hepatic, mesenteric, renal or retinal veins and arteries, in combined oral contraceptive users. There is no consensus as to whether the occurrence of these events is associated with the use of combined oral contraceptives.

Symptoms of venous or arterial thrombosis can include: unilateral leg pain and/or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; diplopia; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen.

The risk of thromboembolism (venous and/or arterial) 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 (ie 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.
- 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 combined oral contraceptive 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, hemolytic 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 combined oral contraceptive use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the combined oral contraceptive.

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

An increased risk of cervical cancer in long-term users of combined oral contraceptives has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus.

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. 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. 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.

Other conditions

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

Although small increases in blood pressure have been reported in many women taking combined oral contraceptives, 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 a combined oral contraceptive then it is prudent for the physician to withdraw the combined oral contraceptive and treat the hypertension. Where considered appropriate, combined oral contraceptive 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 combined oral contraceptive 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 combined oral contraceptives.

Although combined oral contraceptives may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using combined oral contraceptives.

However, diabetic women should be carefully observed while taking combined oral contraceptives.

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

Chloasma may occasionally 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 combined oral contraceptives.

DOSAGE AND DIRECTIONS FOR USE

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of combined oral contraceptive use, guided by the "Contra-indications" and "Warnings" and should be repeated at least annually during the use of combined oral contraceptives. Periodic medical assessment is also of importance because contra-indications (eg a transient ischaemic attack, etc) or risk factors (eg a family history of venous or arterial thrombosis) may appear for the first time during the use of a combined oral contraceptive. 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 oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmissible diseases.

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 active 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 (ie 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 another combined oral contraceptive
Mirelle should be started preferably on the day after the last active tablet of her previous combined oral contraceptive, but at the latest on the day following the usual tablet-free or inactive tablet interval of her previous combined oral contraceptive.

Changing from a progestogen-only method (minipill, injection, implant)
Switch from the minipill can take place on any day and Mirelle can be started on the following day. Mirelle should be started on the day of implant removal, or if using an injectable, the day the next injection would be due. In all of these situations, the woman should 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, no additional contraceptive measures need to be taken.

Following delivery or second trimester abortion
Since the immediate post-partum period is associated with an increased risk of thromboembolism, oral contraceptives should be started no earlier than days 21 to 28 after delivery or second trimester abortion. 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 a combined oral contraceptive or the woman has to wait for her first menstrual period.

Management of missed tablets

Contraceptive reliability may be reduced if active tablets are missed and particularly if the missed tablets extend the inactive tablet interval. If active tablets were missed in the first week of the cycle and intercourse took place in the week before the tablets were missed, the possibility of a pregnancy should be considered.

Provided that the user is ***less than 12 hours*** late in taking any active tablet, when she remembers she should take it as soon as possible, and further tablets should be taken at the usual time.

If she is ***more than 12 hours*** late in taking any tablet, contraceptive protection may be reduced.

The management of missed tablets can be guided by the following two basic rules:
- Active tablet-taking must never be discontinued for longer than 4 days.
- 7 days of uninterrupted 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 inclusive

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 inactive tablet phase, the higher the risk of a pregnancy.

- Days 8 to 14 inclusive

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 inclusive

The risk of reduced reliability is imminent because of the forthcoming inactive 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 active tablets are used up. The 4 tablets from the last row (inactive 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 active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
- The woman may also be advised to discontinue tablet-taking 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 inactive tablet phase, the possibility of a pregnancy should be considered.

Errors in taking the inactive tablets can be ignored, provided the first active tablet from the next pack is begun on the proper day.

Advice in case of vomiting and diarrhoea

If vomiting occurs within 3 to 4 hours after tablet-taking, absorption may not be complete. In such an event, the advice under the 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 a new backup pack.

How to delay a period

To delay a period the woman should continue with another pack of Mirelle without an 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 Mirelle is then resumed after the usual 4 day inactive 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 inactive tablet phase by as many days as she likes. The shorter her 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).

Procedure in the event of irregular bleeding

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 inactive tablet phase. If the combined oral contraceptive has been taken according to the directions described, it is unlikely that the woman is pregnant. However, if the combined oral contraceptive 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 combined oral contraceptive use is continued.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Serious undesirable effects

See "Warnings".

Other possible undesirable effects

The following undesirable effects have been reported in users of combined oral contraceptives and the association has been neither confirmed nor refuted: breast tenderness, pain, secretion; headache; migraine; changes in libido; depressive moods; contact lens intolerance; nausea; vomiting; changes in vaginal secretion; various skin disorders; fluid retention; change in body weight; hypersensitivity reaction.

Interactions

Drug interactions which result in an increased clearance of sex hormones can lead to breakthrough bleeding and oral contraceptive failure. This has been established with hydantoins, barbiturates, primidone, carbazepine and rifampicin; oxcarbazepine, topiramate, felbamate and griseolfulvin are also suspected. The mechanism of this interaction appears to be based on the hepatic enzyme-inducing properties of these drugs. Maximal enzyme induction is generally not seen for 2 to 3 weeks but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Contraceptive failures have also been reported with antibiotics such as ampicillins and tetracyclines. The

mechanism of this effect has not been elucidated.

Women on short-term treatment with any of the abovementioned classes of drugs or individual drugs should temporarily use a barrier method in addition to the combined oral contraceptive, ie during the time of concomitant drug administration and for 7 days after their discontinuation. For women on rifampicin a barrier method should be used in addition to the combined oral contraceptive during the time of rifampicin administration and for 28 days after its discontinuation. If concomitant drug administration runs beyond the end of the active tablets in the current combined oral contraceptive pack, the inactive tablets must be discarded and the next combined oral contraceptive pack started right away.

In women on long-term treatment with hepatic enzyme-inducing drugs, experts have recommended to increase the contraceptive steroid doses. If a high contraceptive dosage is not desirable or appears to be unsatisfactory or unreliable, eg in the case of irregular bleeding, another method of contraception should be advised.

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, eg 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.

Pregnancy and lactation

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. See also “Contra-indications”.

Lactation may be influenced by combined oral contraceptives as they may reduce the quantity and change the composition of breast milk, therefore, the use of combined oral contraceptives 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There have been no reports of serious deleterious effects from overdose. Symptoms that may occur in this case are nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

IDENTIFICATION

24 pale yellow, round, film-coated hormonal tablets with convex faces.
4 white, round, film-coated inactive 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 inactive tablets.

STORAGE INSTRUCTIONS

Store below 25 °C. Protect from moisture and light. KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

33/18.8/0364

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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

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