SELECT THE REQUIRED INFORMATION

PROFESSIONAL INFORMATION

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE

MELODENE® 0,02 mg/0,075 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

21 hormone-containing white coated tablets:
Each coated tablet contains ethinylestradiol-0,02 mg and gestodene 0,075 mg.
Excipient: lactose 35 mg and sucrose 20 mg

7 hormone-free pink coated tablets.
Excipient: lactose 45 mg and sucrose 34 mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablets

The hormone-containing tablet is small, white round with convex faces.
The hormone-free tablet is large, pink round with convex faces.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MELODENE is indicated for the prevention of pregnancy (oral contraception).

4.2. Posology and method of administration

Posology

How to take MELODENE

MELODENE, when taken correctly, has a failure rate of approximately 1 % per year. The failure rate may increase when tablets are missed or taken incorrectly.

Tablets must be taken in the order directed by the arrows on the pack, every day at about the same time with some liquid as needed. One tablet is to be taken daily for 28 consecutive days. The first tablet should be taken from the silver section of the calendar pack by selecting the appropriate tablet for that day of the week (e.g. “MO” for Monday). Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts 2 to 3 days after starting the hormone-free pink tablets and may not have finished before the next pack is started. If a patient starts MELODENE during the latter part of the week, the very first cycle may be slightly shortened.

How to start MELODENE

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

Tablet taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2 to 5 is allowed, but during the first cycle an additional barrier method is recommended in addition for the first 7 days of tablet-taking.

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

The woman should start with MELODENE 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 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 MELODENE 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

The woman may switch on any day from the minipill (from an implant or the intrauterine system 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 21 to 28 days 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 MELODENE use, or the woman must wait for her first menstrual period.

Management of missed tablets

The pink tablets are hormone-free tablets and missing these can be disregarded. However, they should be discarded to avoid unintentionally prolonging the hormone-free tablet phase. The following advice only refers to missed hormone-containing white coated tablets:

If the user is ***less than 12 hours*** late in taking any hormone-containing 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 7 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:

- First 7 days of hormone-containing tablet-taking

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

- Second 7 days of hormone-containing tablet-taking

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.

- Third 7 days of hormone-containing tablet-taking

The risk of reduced reliability is imminent because of the forthcoming hormone-free pink tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. If either of the following two options is adhered to, 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 also to use extra precautions for the next 7 days as well.

1. 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 hormone-containing white tablets are used up. The 7 pink 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 white tablets section of the second pack, but she may experience spotting or breakthrough bleeding.
2. The woman may also be advised to discontinue taking the hormone-containing white tablets from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack, starting in the silver section with the tablet for the appropriate day of the week.

If the woman missed hormone-containing white tablets and subsequently has no withdrawal bleed in the hormone-free pink 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 white hormone-containing tablet, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she must 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 MELODENE without taking the hormone-free pink tablets from her current pack. The extension can be carried on for as long as wished until the end of the white hormone-containing tablets in the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of MELODENE is then resumed after the hormone-free pink tablet phase.

Special population

Paediatric patients

MELODENE is only indicated after menarche.

Geriatric patients

Not applicable. MELODENE is not indicated after menopause.

Patients with hepatic impairment

MELODENE is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal. See also section 4.3

Patients with renal impairment

MELODENE has not been specifically studied in renally impaired patients. Available data do not suggest a change in treatment in this patient population.

Method of administration

Oral use

4.3. Contraindications

MELODENE 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 MELODENE use, MELODENE should be stopped immediately.

- Hypersensitivity to the active substances or to any of the excipients of MELODENE (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 prodromata 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)
- Severe hepatic disease, as long as liver function values have not returned to normal.
- Use of direct-acting antiviral (DAA) medicines containing ombitasvir, paritaprevir, 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 (see section 4.6).

4.4. Special warnings and precautions for use

If any of the conditions/risk factors mentioned below are present, the benefits of MELODENE 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 medical practitioner. The medical practitioner 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, such as MELODENE, and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism.

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 MELODENE, 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 MELODENE, is higher than for non-users of combined oral contraceptives.

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

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

Thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in combined oral contraceptive users, such as MELODENE.

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. MELODENE 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 MELODENE (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

The increased risk of thromboembolism in the puerperium must be considered (see section 4.6).

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

The onset of, or increase in frequency or severity of migraine during MELODENE use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of MELODENE.

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

When considering risk/benefit, the medical practitioner 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 low-dose oral contraceptive use, such as MELODENE, (< 0,05 mg ethinylestradiol).

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 MELODENE. The excess risk gradually disappears during the course of the 10 years after cessation of MELODENE use.

Benign liver tumours, and 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 MELODENE.

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 MELODENE.

Small increases in blood pressure have been reported in many women taking combined oral contraceptives, such as MELODENE; clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of MELODENE, then it is prudent for the medical practitioner to withdraw MELODENE and treat the hypertension. Where considered appropriate, MELODENE use may be resumed if normotensive values can be achieved with antihypertensive

therapy.

The following conditions have been reported to occur or deteriorate with combined oral contraceptive use: 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.

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

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

Although MELODENE 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 MELODENE. However, diabetic women should be carefully observed while taking MELODENE.

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

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 MELODENE.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose-free diet should take this amount into consideration.

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 MELODENE use, guided by the contraindications and warnings (see sections 4.3 and 4.4), and should be repeated periodically. 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 MELODENE. 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 MELODENE does not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

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

Reduced cycle control

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, then 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 pink tablet phase. If MELODENE has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if MELODENE 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 MELODENE use is continued.

4.5. Interactions 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 MELODENE

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/or 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 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 MELODENE, 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 white tablets in the MELODENE pack, the hormone-free pink tablets should be omitted and the next MELODENE pack should be started.

Substances increasing the clearance of MELODENE (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 MELODENE, e.g.:

When co-administered with MELODENE, 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 MELODENE (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 MELODENE on other medicines

MELODENE may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin and benzodiazepines) 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 CYP2J. 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 medicines with direct-acting antiviral (DAA) medicines 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 MELODENE 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

MELODENE is contraindicated in pregnancy. If pregnancy occurs during treatment with MELODENE, further intake should be stopped.

Lactation

Lactation may be influenced by MELODENE as it may reduce the quantity and change the composition of breast milk. Therefore, the use of MELODENE should generally not be recommended until the breast-feeding mother has completely weaned her child. Small amounts of the active ingredients of MELODENE and/or their metabolites may be excreted with the milk.

4.7. Effects on ability to drive and use machines

No observed effects.

4.8. Undesirable effects

a) Summary of safety profile

The most commonly reported adverse reactions with MELODENE 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 summary of adverse reactions

System Organ Class (MedDRA)	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1000 to < 1/100)**	**Rare (≥ 1/10,000 to ≤ 1/1000)**
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 case of taking an overdose of white hormone-containing tablets are: nausea; vomiting; and withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidently 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

MELODENE is a combined low-dose monophasic oral contraceptive with estrogenic (ethinylestradiol) and progestogenic (gestodene) peripheral effects.

The contraceptive effect of MELODENE is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion.

5.2. Pharmacokinetic properties

Gestodene

Absorption

Orally administered gestodene is rapidly and completely absorbed. Peak serum concentrations of 3,5 ng/ml are reached at about 1 hour after single dose ingestion. Bioavailability is about 99 %.

Distribution

Gestodene is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 1 to 2 % of the total serum gestodene concentrations are present as free steroid, 50 to 70 % are 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 l/kg.

Metabolism

Gestodene is completely metabolised by the known pathways of steroid metabolism. The clearance rate from serum is 0,8 ml/min/kg. No interaction was found with the co-administered ethinylestradiol.

Elimination

Gestodene serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 12 hours. Gestodene is not excreted in its unchanged form. Its metabolites are excreted at a urinary to biliary ratio of about 6:4. The half-life of metabolite excretion is about 24 hours.

Steady-state conditions

Gestodene pharmacokinetics are influenced by SHBG levels, which are increased about two-fold when co-administered with ethinylestradiol. Following daily ingestion, gestodene serum 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 65 pg/ml are reached at 1,7 hours. During absorption and first liver passage, ethinylestradiol is metabolised extensively, resulting in a mean oral bioavailability of about 45 % with a large interindividual variation of about 20 to 65 %.

Distribution

Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2,8 to 8,6 l/kg was reported.

Metabolism

Ethinylestradiol is subject to presystemic conjugation in both the 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 clearance rate was reported to be 2,3 to 7 ml/min/kg.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases characterised by half-lives of about 1 hour and 10 to 20 hours, respectively. Unchanged ethinylestradiol is not excreted; ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 24 hours.

Steady-state conditions

According to the variable half-life of the terminal disposition phase from serum and the daily ingestion, steady-state serum levels of ethinylestradiol will be reached after about 1 week.

5.3. Preclinical safety data

None

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

calcium carbonate
ferric oxide pigment, red
ferric oxide, yellow
glycerol 85 % (w/w)
lactose monohydrate
macrogol 6 000
magnesium stearate
maize starch
montanglycol wax (wax E)
povidone 25 000
povidone 700 000
sucrose
talc
titanium dioxide

6.2. Incompatibilities

Not applicable

6.3. Shelf life

3 years

6.4. Special precautions for storage

Store at or below 30 °C.
Protect from light.

6.5. Nature and contents of container

MELODENE is packed in colourless transparent PVC/aluminium blisters containing 21 white hormone-containing tablets plus 7 pink hormone-free tablets per blister strip. The blister strip is packed into an outer cardboard carton.
Pack sizes: 28 tablets and 84 tablets.
Not all pack sizes are marketed.

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

31/18.8/0462

9. DATE OF FIRST AUTHORISATION

6 April 1998

10. DATE OF REVISION OF TEXT

20 May 2022