SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

**MELODENE**

Tablets

COMPOSITION

The 28-day pack (Every-Day pack) contains 21 hormonal tablets each with gestodene (17α-ethiny1-13-ethyl-17β-hydroxy-4,15-gonadiene-3-one) 0,075 mg and ethinylestradiol (17α-ethinyl-estra-1,3,5(10)-triene-3,17β-diol) 0,02 mg, plus 7 non-hormonal tablets.

PHARMACOLOGICAL CLASSIFICATION

A.18.8 Ovulation controlling agents.

PHARMACOLOGICAL ACTION

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

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

**Pharmacokinetics**

**Gestodene**

Orally administered gestodene is rapidly and completely absorbed. Following single ingestion of Melodene, maximum drug serum levels of about 3,5 ng/ml are reached at about 1 hour. Thereafter, gestodene serum levels decreased in two phases. The terminal disposition phase is characterised by a half-life of about 12 hours. For gestodene, an apparent volume of distribution of 0,7 l/kg and a metabolic clearance rate from serum of about 0,8 ml/min/kg were determined. Gestodene is not excreted in unchanged form but as metabolites, which are eliminated with a half-life of about 1 day. Gestodene metabolites are excreted at an urinary to biliary ratio of about 6:4. The biotransformation follows the known pathways of steroid metabolism. No pharmacologically active metabolites are known.

Gestodene is bound to serum albumin and to SHBG. Only about 1,3% of the total serum drug levels are present as free steroid, but about 69% are specifically bound to SHBG. The relative distribution (free, albumin-bound, SHBG-bound) depends on the SHBG concentrations in the serum. Following induction of the binding protein, the SHBG - gestodene bound fraction increases to about 80% while the unbound and the albumin-bound fraction decrease.

Following daily repeated administration of Melodene, gestodene concentrations in the serum increase by a factor of 23. Mean serum levels are fourfold higher at steady-state conditions which are generally
reached during the second half of a treatment cycle. The pharmacokinetics of gestodene is influenced by SHBG serum levels. Under treatment with Melodene a twofold increase in the serum SHBG levels has been observed for the first treatment cycle. Due to the specific binding of gestodene to SHBG, the increase in SHBG levels is accompanied by an almost parallel increase in gestodene serum levels. After three treatment cycles the extent of SHBG induction per cycle does not change anymore. The absolute bioavailability of gestodene was determined to be 99% of the dose administered.

Ethinylestradiol

Orally administered ethinylestradiol is rapidly and completely absorbed. Following ingestion of Melodene, maximum drug serum levels of about 65 pg/ml are reached at 1.7 hours. Thereafter ethinylestradiol serum levels decrease in two phases characterised by half-lives of 1 to 2 hours and about 20 hours. Because of analytical reasons, these parameters can only be calculated following the administration of higher doses. For ethinylestradiol, an apparent volume of distribution of about 5 l/kg and a metabolic clearance rate from serum of about 5 ml/min/kg were determined. Ethinylestradiol is highly but non-specifically bound to serum albumin. About 2% of drug levels are present unbound. During absorption and first-liver passage, ethinylestradiol is metabolised resulting in a reduced absolute and variable oral bioavailability. Unchanged drug is not excreted. Ethinylestradiol metabolites are excreted at an urinary to biliary ratio of 4:6 with a half-life of about 1 day.

According to the half-life of the terminal disposition phase from serum and the daily ingestion, steady-state serum levels are reached after 3 to 4 days and are higher by 30 to 40% as compared to a single dose.

During established lactation, 0.02% of the daily maternal dose could be transferred to the new-born via milk.

The systemic availability of ethinylestradiol might be influenced in both directions by other drugs. There is, however, no interaction with high doses of Vitamin C. Ethinylestradiol induces the hepatic synthesis of SHBG and CBG during continuous use. The extent of SHBG induction, however, depends on the chemical structure and the dose of the co-administered progestogen. During treatment with Melodene, SHBG concentrations in the serum increased from 107 nmol/l to 217 nmol/l in the first cycle and to 223 nmol/l in the third cycle. Serum concentrations of CBG were increased from 42 µg/ml to 77 µg/ml in the first cycle and remained constant thereafter.

Clinical trials have not been performed in patients younger than 18 years.

INDICATIONS

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

CONTRA-INDICATIONS

Melodene is contra-indicated in patients with:

- Pregnancy, known or suspected.
- Acute or chronic disturbances of liver function (including Dubin-Johnson syndrome, Rotor syndrome), current or previous history of liver tumours, recurrent cholestatic jaundice or severe pruritus during a previous pregnancy.
- Current or previous history of known or suspected sex steroid dependent neoplasias, (eg existing or treated cancer of the breast or endometrium).
- Current or previous history of arterial or venous thrombotic or embolic processes and conditions which predispose to them (eg defects of the coagulation system, valvular heart disease, atrial fibrillation), severe migraine or cerebrovascular insufficiency.
- Undiagnosed vaginal bleeding.
- Disorders of lipometabolism.
- Sickle-cell anaemia.
- Severe diabetes with vascular changes.
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- History of herpes gestationis.
- Otosclerosis with deterioration during pregnancy.
- Hypersensitivity to any of the components of Melodene.

**DOSAGE AND DIRECTIONS FOR USE**

Before starting Melodene, a thorough general medical and gynaecological examination (including the breasts and a cytological smear of the cervix) should be carried out and the family case history carefully noted. In addition, disturbances of the clotting system must be ruled out if any members of the family have suffered from thromboembolic diseases (eg deep vein thrombosis, stroke, myocardial infarction) at a young age. Pregnancy must be excluded.

Periodic medical examinations are advisable during long-term treatment.

**Initial course**

The first course of Melodene is started on the first day of the menstrual period (day 1 of the cycle) from the silver section of the pack by selecting the appropriate tablet for that day of the week (eg “Mo” for Monday). The tablet is swallowed whole with some liquid. Thereafter one tablet must be taken on each of the 28 consecutive days following the direction shown by the arrows. It does not matter at what time of the day the tablet is taken, but once the patient has selected a particular time, the tablet should be taken at the same time each day.

During the first cycle of use, additional non-hormonal methods of contraception (with the exception of the rhythm or temperature methods) must be used to ensure protection against pregnancy until a white active tablet has been taken for 7 consecutive days.

A withdrawal bleed should begin 2 to 4 days after the last white active tablet.

**Subsequent cycles**

Tablet-taking is continuous, which means that the next pack of Melodene follows immediately without a break, starting with a tablet from the silver section corresponding to the appropriate day. This will be the same day of the week as the start day of the previous pack. A withdrawal bleed usually occurs when the pink non-hormonal tablets are being taken.

**Changing from another oral contraceptive to Melodene**

The patient is instructed to take the first Melodene tablet on the first day of her withdrawal bleed that occurs after the last active tablet of her previous oral contraceptive pack.

A tablet is taken from the silver section corresponding to the appropriate day. To ensure protection against pregnancy, additional non-hormonal methods of contraception (with the exception of the rhythm and temperature methods) must be used until a white active tablet has been taken daily for 7 consecutive days. If the patient was taking a 28 day formulation, she will begin her Melodene on the first day of her withdrawal bleed even though she has not finished her current 28 day pack. Also in this case, additional non-hormonal methods of contraception (with the exception of rhythm and temperature methods) must be used until a white active tablet has been taken for 7 consecutive days.

**Missed tablets (instead of irregular tablet taking)**

If you are less than 12 hours late in taking your Melodene tablet, you are still protected against pregnancy. Take the tablet as soon as you remember and take the next one at your usual time. This may mean that you are taking 2 tablets in one day.

If you are more than 12 hours late in taking your Melodene tablet you will not be protected. Take the tablet as soon as you remember and take the next one at your normal time. This may mean taking 2 tablets in one day. You must take extra contraceptive precautions and you must follow the 7 day rule. Read the sections on “Extra contraceptive precautions” and “The 7 day rule” carefully.
If you have forgotten to take your Melodene tablets for a few days, consult your doctor to be sure you are not pregnant, then discard the missed tablets and follow the 7 day rule.

**Extra contraceptive precautions**

When you need extra contraceptive precautions, either:
- don’t have sex; or
- use a cap plus spermicide, or a condom.

Don’t use the rhythm or temperature methods as extra contraceptive precautions. This is because oral contraceptives disrupt the usual menstrual cycle changes such as changes in temperature and cervical mucus.

**The 7 day rule**

If:
- you are more than 12 hours late in taking a tablet; or
- you have vomiting or diarrhoea; or
- your doctor advises you to follow the 7 day rule because you are taking certain medicines;
continue to take your tablets as usual.

However, take extra contraceptive precautions during the next 7 days, BUT - if these days run beyond the end of the white active tablets in your pack - the 7 pink non-hormonal tablets must NOT be taken. Start the next pack on the white active tablets on the corresponding day in the silver section (following the direction of the arrows), as soon as you have finished the white active tablets of the present pack. Read the section “Extra contraceptive precautions” carefully.

Do not leave a gap between packs. Your menstrual period will occur after you have completed the second pack. If the period does not occur, consult your doctor before resuming the next pack.

Errors in taking the non-hormonal pink tablets can be ignored.

**Post-partum or post-abortum use**

Normally, after a delivery or an abortion, Melodene should be prescribed no earlier than after the first normal menstrual cycle.

If immediate reliable contraception is required for medical reasons, medication with Melodene may be initiated by the 12th (but not before the 7th) day post-partum, or by the 5th day post-abortum at the latest.

When oral contraceptives are administered in the immediate post-partum/post-abortum period, the increased risk of thromboembolic disease must be considered.

**Absence of withdrawal bleeding**

If, in exceptional cases, withdrawal bleeding fails to occur, pregnancy must be ruled out before the use of Melodene is continued.

**Procedure in the event of irregular bleeding**

Breakthrough bleeding and spotting are sometimes encountered, primarily during the first three months of use, and usually cease spontaneously. The woman, therefore, should continue to use Melodene even if irregular bleeding occurs. Should breakthrough bleeding persist or recur, appropriate diagnostic measures to exclude an organic cause are indicated, and may include curettage.

**Gastrointestinal upset**

If vomiting or diarrhoea occurs within 3 to 4 hours of taking a white active tablet, the efficacy of oral contraceptives may be reduced. Nevertheless, tablet-taking from current pack should be continued in order to avoid premature withdrawal bleeding. Also, an additional, non-hormonal method of contraception (with the exception of the rhythm and temperature methods) should be used for the duration of the gastrointestinal disturbance and for 7 days following the upset. If these 7 days overrun the last white active tablet of a pack, the pink non-hormonal tablets are not taken, and a new pack of Melodene should be commenced the day after the last white active tablet was taken. Start the new pack with a white active
tablet on the corresponding day (in the silver section, following the direction of the arrows). In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming the next pack. Other methods of contraception should be considered if the gastrointestinal disorder is likely to be prolonged.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects

In rare cases, headaches, gastric upsets, nausea, breast tenderness, changes in body weight, changes in libido, depressive moods can occur.

In predisposed women, use of Melodene can sometimes cause chloasma which is exacerbated by exposure to sunlight. Such women should avoid prolonged exposure to sunlight.

Individual cases of poor tolerance of contact lenses have been reported with use of oral contraceptives. Contact lens wearers who develop changes in lens tolerance should be assessed by an ophthalmologist.

Special precautions

1. *Thromboembolic disorders and other vascular problems:* There is evidence of an association between the use of combined oral contraceptives and an increased risk of venous and arterial thromboembolic diseases such as myocardial infarction, stroke, pulmonary embolism, thrombophlebitis, and retinal thrombosis. Full recovery from these disorders does not always occur, and it should be realised that in a few cases they are fatal. *The physician should therefore be alert to the earliest manifestations of these disorders. Should any of these occur or be suspected, oral contraceptives should be discontinued immediately.*

   *The risk of arterial thrombosis (e.g., stroke, myocardial infarction) associated with combined oral contraceptives increases with age and with heavy smoking. For this reason, women over 35 years of age who use oral contraceptives should be strongly advised not to smoke.*

   Certain disease states such as hypertension, hyperlipidemia, obesity, and diabetes mellitus may increase the observed risk of thromboembolic events associated with oral contraceptive use. The suitability of using oral contraceptives in these disease states should be weighed against the risk associated with the condition, and should be discussed with the patient before she decides to take an oral contraceptive.

2. *Carcinoma of the breasts:* The evidence linking combined oral contraceptives and breast cancer remains inconclusive. The results of epidemiological studies have revealed that overall there is no increased risk of breast cancer in women who had ever used oral contraceptives. The results of some studies suggesting a possible increased risk in certain subgroups of women remain conflicting.

3. *Hepatic neoplasia:* In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of 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 oral contraceptives.

4. *Gallbladder disease:* Earlier studies reported an increased risk of surgically confirmed gallbladder disease in users of estrogens and oral contraceptives. However, more recent studies have shown that the relative risk of developing gallbladder disease may be minimal.

5. *Lipid and carbohydrate metabolism:*
Changes in serum triglyceride, cholesterol and lipoprotein levels have been reported in users of oral contraceptives. Oral contraceptives may also cause a decrease in glucose tolerance.

6. **Elevated blood pressure:**
   An increase in blood pressure has been reported in women taking oral contraceptives. Elevated blood pressure usually returns to normal after discontinuing oral contraceptives.

7. **Bleeding irregularities:**
   Breakthrough bleeding and spotting are sometimes encountered, primarily during the first three months of use, and usually cease spontaneously. The woman, therefore, should continue to take Melodene, even if irregular bleeding occurs. Should breakthrough bleeding persist or recur, appropriate diagnostic measures to exclude an organic cause are indicated and may include curettage. The same applies in the case of spotting which occurs at irregular intervals in several consecutive cycles or which occurs for the first time after long term use of Melodene.  After discontinuation of oral contraceptives, some women may experience amenorrhoea or oligomenorrhoea, especially when these conditions existed prior to use. Women with these pre-existing menstrual patterns should be informed of this possibility. Occasionally, withdrawal bleeding may not occur during the 7 day pink non-hormonal tablet taking period. Pregnancy must be ruled out before use of the preparation is continued.

8. **Use during pregnancy:**
   Pregnancy must be excluded before starting Melodene. If pregnancy occurs during use of Melodene, the preparation is to be withdrawn immediately.

9. **Use during lactation:**
   Minute amounts of the components of oral contraceptives have been identified in the milk of nursing mothers. Additionally, oral contraceptives given in the post-partum period may interfere with lactation by decreasing the volume of milk produced and by changing the composition of the breast milk.

**Reasons for immediate discontinuation of Melodene**

1. Occurrence for the first time of migrainous headaches or more frequent occurrence of unusually severe headaches.
2. Acute disturbances of vision, hearing or other perceptual disorders.
3. First symptoms of thrombophlebitis or thromboembolism (eg unusual pains in or swelling of the legs, stabbing pains on breathing or coughing for no apparent reason).
4. A feeling of pain or tightness in the chest.
5. Pending operations (six weeks beforehand), immobilisation (eg following accidents). In all these cases there may be an increased risk of thrombosis.
6. Onset of severe clinical depression.
7. Severe upper abdominal pain or liver enlargement.

Further reasons for discontinuation are: onset of jaundice, onset of hepatitis, itching of the whole body, increase in epileptic seizures, significant rise in blood pressure, pregnancy.

The following conditions require strict medical supervision during medication with oral contraceptives. Deterioration of some of these conditions may indicate that use of the oral contraceptive should be discontinued: asthma, diabetes mellitus or a tendency towards diabetes mellitus, hypertension, varicose veins, a history of phlebitis, otsclerosis, multiple sclerosis, epilepsy, porphyria, tetany, Sydenham’s chorea, renal dysfunction, family history of clotting disorders, obesity, family history of breast cancer and patient history of breast nodules, history of clinical depression, systemic lupus erythematosus, uterine myoma, migraine and conditions aggravated by fluid retention.

**Drug interactions**

Hepatic enzyme inducers such as barbiturates (eg phenobarbital), primidone, hydantoins (eg phenytoin), phenylbutazone, rifampicin, carbamazepine and griseofulvin, can impair the efficacy of Melodene and increase the incidence of menstrual irregularities. For women receiving long term therapy with hepatic enzyme inducers, another method of contraception should be used.
The use of ampicillin, tetracycline and other antibiotics may also reduce the efficacy of Melodene, possibly by altering the intestinal flora.

Women receiving short courses of enzyme inducers or broad spectrum antibiotics should take additional non-hormonal (except rhythm or temperature methods) contraceptive precautions during the time of concurrent medication and for 7 days after its discontinuation. If these 7 days overrun the last white active tablet of a pack, the pink non-hormonal tablets are disregarded, and a new pack of Melodene should be commenced the day after the last white active tablet was taken. In this situation, a withdrawal bleed should not be expected until the end of the second pack. If the patient does not have a withdrawal bleed at the end of the second pack, the possibility of pregnancy must be ruled out before resuming the next pack. With rifampicin, additional contraceptive precautions should be continued for 4 weeks after treatment discontinuation, even if only a short course was administered.

The requirement for oral antidiabetics or insulin can change as a result of the effect on glucose tolerance.

The use of oral contraceptives may influence the results of certain laboratory tests including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Laboratory staff should therefore be informed about oral contraceptive use when laboratory tests are requested.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

Overdosage may cause nausea, vomiting and withdrawal bleeding in females may occur.

In children, serious ill effects have not been reported following large doses of oral contraceptives.

Treatment is supportive and symptomatic.

**IDENTIFICATION**

21 small white round coated hormonal tablets and 7 large pink round coated non-hormonal tablets.

**PRESENTATION**

Cartons with one or three calendar packs each containing 28 tablets.

**STORAGE INSTRUCTIONS**

In original packs at room temperature (below 30°C). Protect from light. Keep out of reach of children. For shelf-life refer to the imprint on the pack.

**REGISTRATION NUMBER**

31/18.8/0462

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

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