Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mercilon 150 micrograms/20 micrograms tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 micrograms desogestrel and 20 micrograms ethinylestradiol.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet.
Product imported from Greece.
White, round biconvex tablets, coded 'TR4' on one side and 'ORGANON' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormonal contraception.

4.2 Posology and method of administration

Before starting Mercilon, a thorough general medical and gynaecological examination (including breasts and a cytological smear of the cervix) should be carried out and the family medical history carefully noted. Disturbances of the clotting mechanisms should be ruled out if any members of the family have suffered from thromboembolic diseases (e.g. deep vein thrombosis, stroke, myocardial infarction) at a young age.
Pregnancy must be excluded ideally by a pregnancy test.
As a precaution, thorough examinations should be conducted at approximately six month intervals during the use of the tablets.

First cycle
Tablet-taking from the first pack of Mercilon is started on the 1st day of the menstrual cycle, i.e. the first day of menstrual bleeding.
One tablet is to be taken at around the same time of day on each of 21 consecutive days followed by a tablet-free interval of 7 days during which a withdrawal bleeding occurs.

Subsequent cycles
Tablet taking from the next pack of Mercilon is continued after the 7-day interval, beginning on the same day of the week as the first pack.

Changing from another oral contraceptive
The first tablet of Mercilon should be taken on the first day of bleeding that occurs after the intake of the last active tablet of the patient's previous oral contraceptive.

Irregular tablet-taking
If the woman forgets to take a Mercilon tablet then it must be taken within 12 hours of the usual time of taking it. If a missed tablet is not taken within 12 hours then it should be taken when remembered and the remaining tablets taken as usual with extra non-hormonal contraceptive measures (except rhythm or temperature methods) used for the next 7 days. If these seven days extend beyond the end of the pack then the next pack of tablets should be commended at once with no tablet-free interval. 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 during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be excluded before resuming with the next pack.

Postpartum
Normally, after delivery, Mercilon should be started after the first normal menstrual cycle.
If immediate reliable contraception is required for medical reasons, medication with Mercilon should be initiated after day 7 and before day 12 postpartum.

Postmiscarriage
Following a miscarriage oral contraception can be started immediately (day 2 but no later than day 5) for immediate cover.
When oral contraceptives are administered in the immediate postpartum/postmiscarriage 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 Mercilon 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 Mercilon even if irregular bleeding occurs. Should breakthrough bleeding persist or recur, appropriate diagnostic measures to exclude an organic cause should be taken.
This also applies in the case of spotting which occurs at irregular intervals in several consecutive cycles or which occurs for the first time after long use of Mercilon.

Gastro-intestinal upset
Vomiting or diarrhoea may reduce the efficacy of oral contraceptives by preventing full absorption. Tablet-taking from the current pack should be continued. Additional non-hormonal methods of contraception (except rhythm or temperature methods) should be used during the gastro-intestinal upset and for seven days following the upset. If these seven days overrun the end of the pack, the next pack should be started without a break. 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 during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack. Other methods of contraception should be considered if the gastro-intestinal disorder is likely to be prolonged.

4.3 Contraindications

Confirmed or suspected pregnancy and patients breast feeding infants.

2. Acute or chronic liver disease, jaundice or persistent pruritis during a previous pregnancy, Dubin-Johnson syndrome, Rotor syndrome.
3. Existing or previous arterial or venous thrombotic or embolic processes or conditions which predispose to them e.g. disorders of the clotting processes, coronary artery disease, cerebrovascular disease, valvular heart disease and atrial fibrillation.
4. Sickle-cell anaemia.
5. Current or previous known or suspected steroid-dependent neoplasia e.g. previous or existing liver tumours, cancer of the breast or endometrium.
6. Severe diabetes mellitus with vascular changes.
7. Disorders of lipid metabolism. (See 4.4 Precautions and Warnings).
8. Pemphigoid gestationis.

9. Deterioration of otosclerosis during pregnancy.
10. Undiagnosed vaginal bleeding.
11. Hypersensitivity to any of the components of Mercilon.

4.4 Special warnings and precautions for use

Reasons for <u>immediate discontinuation</u> of medication with Mercilon:

1. Suspected or confirmed symptoms or signs of thrombophlebitis or thromboembolic events (e.g. unusual pains in or swelling of the legs).
2. Feeling of pain and tightness in the chest (stabbing pains on breathing or coughing for no apparent reason).
3. Occurrence for the first time, or exacerbation of migrainous headaches or an increased frequency of unusually severe headaches.
4. Sudden disturbances of vision or hearing or other perceptual disorders.
5. Six weeks before elective surgery and during immobilisation e.g. after accidents, surgery.
6. Onset of jaundice, hepatitis, itching of the whole body.
7. Increases in epileptic seizures.
8. Significant rise in blood pressure.
9. Onset of severe depression.
10. Severe upper abdominal pain or liver enlargement.
11. Pregnancy.

Patients with the following conditions should only use the oral contraceptive pill after detailed discussion with their General Practitioner. Patients with these conditions require strict medical supervision during medication.

1. Diabetes mellitus.
2. Hypertension.
3. Varicose veins.
4. Otosclerosis.
5. Multiple sclerosis.
6. Epilepsy.
7. Porphyria.
8. Tetany.
9. Sydenham's chorea.
10. Renal dysfunction.
11. Family history of breast cancer or past history of breast nodules.
12. Fibrocystic disease of the breast.
13. Asthma.
14. History of clinical depression.
15. Systemic lupus erythematosus.
16. Uterine myoma.
17. Migraine.
18. Endometriosis.

Deterioration in any of the above conditions may indicate that use of the oral contraceptive should be discontinued.

Epidemiological studies have suggested an association between the use of COCs 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 use of any COC is associated with an increased risk of venous thromboembolism (VTE) (manifesting as deep venous thrombosis and/or pulmonary embolism), compared with no use. VTE is fatal in 1-2% of cases. The incidence of VTE in users of low estrogen dose (< 50 mcg EE) OCs in general is considered to be up to 40 per 100,000 women years compared with 5-30 per 100,000 women years in non-OC users. The excess risk of VTE is highest during the first year a woman ever uses COC. This increased risk is less than the risk of VTE associated with pregnancy which is estimated as 60 cases per 100,000 pregnancies.

Some large epidemiological studies have suggested that women using COCs with ethinylestradiol, mostly with a dose of 30 mcg, and the progestin desogestrel have an increased risk of VTE compared with those using COCs containing less than 50 mcg ethinylestradiol and the progestogen levonorgestrel. The relative risk in these studies ranged between 1.5 and 2.0. Assuming an incidence of VTE of approximately 20 cases per 100,000 women-years of use for levenorgestrel-containing COCs with less than 50 mcg EE, these results would translate to approximately 30-40 cases per 100,000 women-years of use for desogestrel-containing COCs. These incidences are within the above-mentioned range for VTE. Data from other studies, that adjusted more closely for confounding factors, have not shown this increase in risk. Especially when corrections were made for duration of use and age, the differences were markedly reduced and odds ratios were around, and sometimes lower than 1.
All this information should be taken into account when prescribing this oral contraceptive. When counselling on the choice of contraceptive method(s), all the above information should be considered.

The physician should be alert to the earliest manifestations of these disorders. Should any of these occur or be suspected, Mercilon should be discontinued immediately.

The relative risk of arterial thromboses (e.g. stroke, myocardial infarction) is increased by the presence of other predisposing factors such as:

a) cigarette smoking
b) hypercholesterolaemia
c) obesity
d) diabetes
e) history of pre-eclamptic toxaemia
f) increasing age

After the age of 35 years, the physician and patient should carefully reassess the risk/benefit ratio of using combined oral contraceptives as opposed to alternative methods of contraception.
Changes in serum triglycerides, cholesterol and lipoprotein levels have been reported in users of oral contraceptives.
Oral contraceptives may cause a decrease in glucose tolerance.
An increase in blood pressure has been reported in women taking oral contraceptives. Elevated blood pressure usually returns to normal after discontinuation of oral contraceptives.
Some women may experience amenorrhoea or oligomenorrhoea after discontinuation of oral contraceptives, especially when these conditions existed prior to use. Women should be informed of this possibility.
In rare cases benign and, in even rarer cases, malignant liver tumours leading in isolated cases to life threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as those contained in Mercilon. If severe upper abdominal complaints, liver enlargement or signs of intra-abdominal haemorrhage occur, the possibility of a liver tumour should be included in the differential diagnosis.
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.
Six months should elapse after the regression of viral hepatitis before administration of the oral contraceptive pill.
Studies in animals have indicated that administration of very high doses of estrogens and/or progestogens will induce neoplastic tumours in some animal species.

The results of recent studies in human beings suggest that there is a small but statistically increased incidence of breast cancer in women who have been treated with estrogens. All women, in particular those over 35 years should have regular breast examinations while on the pill.
Herbal preparations containing St. John's wort (Hypericum perforatum) should not be used while taking Mercilon due to the risk of decreased plasma concentrations and reduced clinical effects of Mercilon (see Section 4.5 “Interactions”).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-glactose malabsorption should not take this medication.

4.5 Interaction with other medicinal products and other forms of interaction

Hepatic enzyme inducers such as barbiturates, primidone, hydantoins, phenylbutazone, rifampicin, carbamazepine and griseofulvin can impair the efficacy of Mercilon. For women receiving long-term therapy with hepatic enzyme inducers another method of contraception should be used. The use of ampicillin and other antibiotics may also reduce the efficacy of Mercilon, possibly by altering the intestinal flora and individual pregnancies have been reported.
Women receiving short courses of enzyme inducers or broad spectrum antibiotics should take additional, non-hormonal (except rhythm or temperature method) contraceptive precautions during the time of concurrent medication and for 7 days afterwards. If these 7 days overrun the end of the pack, the next pack should be started without a break. 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 during the tablet-free interval following the end of the second pack, the possibility of pregnancy must be ruled out before resuming with the next pack. With rifampicin, additional contraceptive precautions should be continued for 4 weeks after treatment stops, even if only a short course was administered.
Herbal preparations containing St. John's wort (Hypericum perforatum) should not be taken concomitantly with oral contraceptives as this could potentially lead to a loss of contraceptive effect. Breakthrough bleeding and unintended pregnancies have been reported. This is due to induction of drug metabolising enzymes by St. John's wort. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort.
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.

4.6 Pregnancy and lactation

If pregnancy occurs during medication with Mercilon, the preparation should be withdrawn immediately.
An increased risk of congenital abnormalities, including heart defects and limb defects, has been reported following the use of sex hormones, including oral contraceptives in pregnancy.
The use of Mercilon during lactation may lead to a reduction in the volume of milk produced and to a change in its composition. Minute amounts of the active substances are excreted with the milk.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

There is an increased risk of venous thromboembolism for all women using a combined contraceptive. For information on differences in risk between combined oral contraceptives, see Section 4.4.
Cases of headaches, gastric upsets, nausea, breast tenderness, changes in body weight, fluid retention, thrombophlebitis, changes in libido, breakthrough bleeding, depressive moods, candidiasis, rash, urticaria, pruritis, erythema nodosum, erythema multiforme and alopecia can occur.
In predisposed women, use of Mercilon can sometimes cause chloasma which is exacerbated by 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.
Refer to Section 4.4 “Special Warnings and Precautions for Use” for additional information.

4.9 Overdose

Overdosage may cause nausea, vomiting and withdrawal bleeding in females. Serious ill effects have not been reported following large doses of oral contraceptives in children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mercilon is an oral contraceptive combination containing 150 micrograms desogestrel and 20 micrograms ethinylestradiol.
Ethinylestradiol is a well known synthetic estrogen.
Desogestrel is a synthetic progestogen. After oral administration it has a strong ovulation-inhibiting activity, a strong progestational and anti-estrogenic activity, no estrogenic activity, very weak androgenic/anabolic activity.
Both estrogenic and progestational components inhibit the release of gonadotrophins from the pituitary and thus inhibit ovulation.

5.2 Pharmacokinetic properties

After oral administration, desogestrel shows rapid absorption, followed by distribution throughout the body, and subsequent excretion, not resulting in retention of the drug and/or its metabolites. The freely extractable fraction in serum of volunteers contains desogestrel 3-keto-desogestrel and polar metabolites. The level of the unchanged drug decreases rapidly and the level of the biologically active 3-keto-metabolite is still measurable 24 hours after dosing.

5.3 Preclinical safety data

The toxicology studies did not reveal any effects other than those which can be explained from the hormonal profile of Mercilon.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

dl-alpha-tocopherol
Potato starch
Povidone
Stearic acid
Colloidal anhydrous silica
Lactose Monohydrate
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

- Do not store above 25^{o} C
- Store in the original package.

6.5 Nature and contents of container

Blister strip containing 21 tablets, overwrapped with a sealed aluminium laminated sachet, contained in an outer cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 Parallel Product Authorisation Holder

PCO Manufacturing Limited
Unit 10, Ashbourne Business Park
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8 Parallel Product Authorisation Number

PPA 0465/154/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 12 August 2005

10 DATE OF REVISION OF THE TEXT

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