SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Climanor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Medroxyprogesterone acetate BP 5mg

3 PHARMACEUTICAL FORM

Round, white, biconvex film coated tablets, 6 mm in diameter

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Dysfunctional uterine bleeding, secondary amenorrhoea, mild to moderate endometriosis.

In combination with an oestrogen product for hormone replacement therapy (HRT) for oestrogen deficiency symptoms in peri- and post-menopausal women.

4.2 Posology and method of administration

Administration: Oral

Dysfunctional uterine bleeding: 5 - 10 mg a day for 5 - 10 days commencing on the assumed or calculated sixteenth to twenty first day of the cycle, for two consecutive cycles.

When bleeding occurs from a poorly developed proliferative endometrium, oestrogen therapy in conjunction with medroxyprogesterone acetate in doses of 5 - 10 mg a day for 12 days can be administered.

Secondary amenorrhoea: 5 - 10 mg a day for 5 - 10 days, beginning on the assumed or calculated sixteenth to twenty first day of the cycle, for three consecutive cycles. In amenorrhoea associated with a poorly developed proliferative endometrium, oestrogen therapy in conjunction with medroxy-progesterone acetate in doses of 5 - 10 mg for 12 days can be administered.

Mild to moderate endometriosis: 10 mg three times a day for 90 consecutive days beginning on the first day of the menstrual cycle. Breakthrough bleeding, which is self-limiting, may occur. No additional hormonal therapy is recommended for the management of this bleeding.

Hormone replacement therapy: In women with an intact uterus, Climanor should be given in a cyclic regimen of 10 mg a day for the last 14 days of each 28 day cycle to reduce the risk to the endometrium (*see Section 4.4*).

Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestagen in hysterectomised women.

When oestrogen and progestogen therapy is used for initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose of HRT for the shortest duration (*see also Section 4.4)* should be used.

Missed doses
If any dose is forgotten the patient should be advised to take it as soon as they remember. However, if it is time for the next dose, patients should be advised not to take the missed dose but to continue to take the tablets as prescribed until the end of each course. A missed dose may increase the likelihood of break-through bleeding and spotting

4.3 Contraindications

Known, past or suspected breast cancer;

Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);

Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;

Known hypersensitivity to the active substance or to any of the excipients;

Porphyria;

When used as part of an oestrogen-containing HRT regimen, the following also apply:

Known or suspected oestrogen dependent malignant tumours (eg endometrial cancer);

Undiagnosed genital bleeding;

Untreated endometrial hyperplasia.

4.4 Special warnings and precautions for use

a) Medical examination/follow-up

Before initiating or reinstituting therapy, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications (section 4.3) and warnings (section 4.4) for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman.

Women should be advised what changes in their breasts should be reported to their doctor or nurse (*see 'Breast cancer' below)*. Women should be

encouraged to participate in the national breast cancer screening programme (mammography) and the national cervical screening programme (cervical cytology) as appropriate for their age. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

b) Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with oestrogen/progestogens, in particular:

- Leiomyoma (uterine fibroids) or endometriosis;
- A history of, or risk factors for, thromboembolic disorders (see below);
- Risk factors for oestrogen dependent tumours, eg 1st degree heredity for breast cancer;
- Hypertension;
- Liver disorders (eg liver adenoma);
- Diabetes mellitus with or without vascular involvement;
- Cholelithiasis;
- Migraine or severe headache;
- Systemic lupus erythematosus;
- A history of endometrial hyperplasia (see below);
- Epilepsy;
- Asthma;
- Otosclerosis.

c) Reasons for immediate withdrawal of therapy

Therapy should be discontinued when a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function;
- Significant increase in blood pressure;
- New onset of migraine-type headache;
- Pregnancy.

d) General considerations

Women of child bearing potential should be advised to adhere to non-hormonal contraceptive methods.

Whether administered alone or in conjunction with oestrogens, Climanor should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy eliminated.

Rare cases of venous thrombo-embolism have been reported with the use of Climanor. Causality has not been established. *(see also section 4.4.(e) Venous thromboembolism).*

e) Use as HRT

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Endometrial hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.

For oral doses of estradiol >2mg, conjugated equine oestrogens >1.25 mg and patches >50ug/day the endometrial safety of added progestagens have not been studied.

Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies including the Million Women Study (MWS) have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestogen combinations or tibolone for HRT for several years (see Section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

HRT, especially oestrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two to threefold higher risk for users compared with non-users. For non-users, it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5

years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contraindicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible. Treatment should not be started until the woman is completely mobilised.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxy-progesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore it is uncertain whether these findings also extend to other HRT products.

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA (medroxyprogesterone acetate). For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per

1000 users aged 50-59 years and between 1 and 9 (best estimate 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer

Long-term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than oestrogen-only products.

Other conditions

There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

f) Use in all patients receiving oestrogens

Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy since rare cases of large increases in plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.

Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein bound iodine (PBI), T4 levels (by column or radio-immunoassay) or T3 levels (by radioimmunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, ie corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, cerulo-plasmin).

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed since it is expected that the level of circulating (oestrogens and) progestogens will be increased.

See also section (e) for HRT use.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of (oestrogens and) progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (eg phenobarbital, phenytoin, carbamazepine) and anti-infectives (eg rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Herbal preparations containing St John's wort (Hypericum Perforatum) may induce the metabolism of (oestrogens and) progestogens.

The metabolism of medroxprogesterone acetate (Climanor) may be increased by the administration of Aminoglutethimide resulting in a significant reduction in the bioavailability of Climanor.

Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

4.6 Pregnancy and lactation

Climanor is not indicated in pregnancy. If pregnancy occurs during medication with Climanor consideration should be given to withdrawing treatment immediately.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of progestogens indicate no teratogenic or foetotoxic effect.

Climanor is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive or use machinery are reported.

4.8 Undesirable effects

The following medical events are occasionally associated with the use of progestogens:

Breasts - Breast tenderness or galactorrhoea, breast cancer (see below).

Genito-urinary System - Patients with intact uteri taking progestogens for endometrial safety may also report vaginal bleeding.

CNS - nervousness, insomnia, somnolence, fatigue, dizziness, depression (including pre-menstrual like depression), and headache.

Skin - urticaria, pruritus, rash, acne, hirsutism and alopecia have been reported occasionally.

Anaphylactoid-like reactions are rare.

Gastrointestinal – Nausea and indigestion have been noted in some subjects.

Miscellaneous - weight gain has been noted in some subjects.

Other adverse reactions have been reported in association with oestrogen/ progestogen HRT treatment:

- Oestrogen dependent neoplasms benign and malignant, eg endometrial cancer
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among HRT users than

among non-users. For further information see sections “4.3 Contra-indications” and “4.4 Warnings and precautions for use”
- Myocardial infarction and stroke
- Gall bladder disease
- Probable dementia (see section 4.4)

Breast Cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women’s Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI 1.21 – 1.49) and 1.30 (95%CI 1.21 – 1.40), respectively.

For *oestrogen plus progestogen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of oestrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of oestrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

- *For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.*
    - For 1000 current or recent users of HRT, the number of *additional* cases during the corresponding period will be
    - For users of *oestrogen-only* replacement therapy
        - between 0 and 3 (best estimate = 1.5) for 5 years’ use
        - between 3 and 7 (best estimate = 5) for 10 years’ use.
    - For users of *oestrogen plus progestogen* combined HRT,
        - between 5 and 7 (best estimate = 6) for 5 years’ use
        - between 18 and 20 (best estimate = 19) for 10 years’ use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestogen combined* HRT (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:

- For 1000 women in the placebo group,
  - about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used oestrogen + progestogen combined HRT (CEE + MPA), the number of *additional* cases would be
  - between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestogen to oestrogen-only therapy greatly reduces this increased risk.

4.9 Overdose

No action required other than cessation of therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Medroxyprogesterone acetate is a synthetic progestogen with actions similar to progesterone. As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

5.2 Pharmacokinetic properties

Medroxyprogesterone acetate is absorbed rapidly after oral administration. It is hydroxylated in the liver and excreted largely in faeces. Serum levels are maximal within two hours of ingestion of Climanor and are still detectable 12 hours after administration.

5.3 Preclinical safety data

None stated

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose EP
Crospovidone EP
Povidone EP
Talc EP
Magnesium stearate EP
Opadry white Y-1-7000
Methocel E5 Premium EP
Titanium dioxide EP
Polyethylene glycol NF HSE

6.2 Incompatibilities

No chemical or physical incompatabilities are noted.

6.3 Shelf life

Three years from the date of manufacture.

6.4 Special precautions for storage

Store below 25°C in a dry, dark place.

6.5 Nature and contents of container

PVC and aluminium foil blister pack enclosed in a cardboard carton.

Pack sizes: 14, 28 tablets. A physician’s sample pack of 14 tablets.

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PL 21812/0003

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