Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Estopause Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each white tablet contains 2 mg of Oestradiol. Each pale blue tablet contains 2 mg of Oestradiol and 5 mg of Medroxyprogesterone Acetate.

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Calendar pack consisting of 16 round, white, biconvex tablets and 12 round, pale-blue, biconvex tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone replacement therapy (HRT) for estrogen deficiency symptoms. In post menopausal women with an intact uterus.

Second line therapy for prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for , other medicinal products approved for the prevention of osteoporosis.

The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Adults and elderly

Estopause is a continuous sequential combined HRT regimen (Oestrogen and Medroxyprogesterone). The oestrogen phase (2mg oestrogen [17 β oestradol] is given for the first 16 days. This is followed by a combined oestrogen and progesterone acetate for 12 days.

The regimen is based on a 28 day cycle which one tablet is taken daily without interruption. One tablet of oestrogen 2mg is taken daily for the first 16 days. This is followed by one tablet daily for the following 12 days of combined tablet contains (oestrogen 2mg and medroxyprogesterone 5mg). In menstruating women or women already on HRT, the first tablet should be taken in the fifth day of menstrual bleeding. If menstruating has stopped or is infrequent or sporadic, the first tablet can be taken at any time.

Tablets should be taken approximately at the same time of the day. If the patient has forgotten to take one tablet, the forgotten tablet is to be discarded.

Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

Use in children

Not be used in children

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration *(see also Section 4.4)* should be used.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependant malignant tumours (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- 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 the liver function tests have failed to return to normal
- Known hypersensitivity to the active substances or to any of the excipients
- Porphyria

4.4 Special warnings and precautions for use

Medical examination/Follow up

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

Before initiating or reinstituting HRT, 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 and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised that changes in their breasts should be reported to their doctor or nurses (see Breast cancer below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practice, modified to the clinical needs of the individual.

A careful appraisal of the risks and benefits should be undertaken over time in women treated with hormone replacement therapy.

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 Estopause, in particular:

- Leiomyoma (uterine fibroid) or endometriosis
- A history of, or risk factors for thromboembolic disorders
- Risk factors for oestrogen dependant tumours, e.g. 1st degree hereditary for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or sever headache

- Systemic lupus erythematosis
- A history of endometrial hyperplasia
- Epilepsy
- Asthma
- Otoscerlosis

Reasons for immediate withdrawal of therapy:
Therapy should be discontinued in cases where 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

Endometrial Hyperplasia
The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The addition of a progestagen for at least 12 days per cylce (for cyclic or sequential products) or every day in non-hysterectomised women greatly reduces, but may not eliminate, this risk.

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 treament 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 Woman's Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS) and other epidemiological studies have reported an increased risk of breast cancer in women taking estrogens, estrogen-progestagen combinations or tibolone for HRT for several years *(see section 4.8).* In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestagen was added, compounds. Either sequentially or continuously, and regardless of type of progestagen. There is no evidence of a difference in risk between the different routes of administration.

For all HRT, an excess risk becomes apparent within a few years of use and increases with the duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

The oestrogen + progestagen treatment in the WHI study was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases.

HRT, especially oestrogen-progestagen 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 (VET), i.e. deep venous 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 five year period is about 3 per 1000 women aged 50-59 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 (BMI>30kg/m^2) and systemic lupus erythrematous (SLE). There is no consensus about the possible role of varicose vein in VTE.

Patients with 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 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 use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative 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 orthapaedic surgery to lower limbs, consideration should be given to temporarily HTR 4 to 6 weeks earlier, if possible. Treatement should not be restarted until the woman is completely moblilised.

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 potential thromboembolic symptoms (e.g., painful swelling of a leg, sudden pain in the chest, dyspnoea).

Corornary artery disease (CAD)

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogen and medroxyprgestrone acetate (MPA). Two large clinical trials (WHI and HERS ie 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 and 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. 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 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 oestrogen 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 1iated with an increased risk of ovarian cancer in some 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 different risk than oestrogen-only products.

Other conditions

Oestrogen 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. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in the Estopause is increased.

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

Oestrogens increase thyroid binding globulin (TGB), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be eleveated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or

biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/rennin substrate, alpha-I-antitrypsin, ceruloplasmin).

There is no evidence for improvement of cognitive function. There is some evidence of increased risk of probable dementia in women older than 65 years using continuous combined conjugated oestrogen and MPA.

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

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. Phenobarbital, phenytoin, and carbamazepine) anti-infectives (e.g. 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.

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

4.6 Pregnancy and lactation

Estopause is not indicated during pregnancy. If pregnancy occurs during treatment with Estopause, treatment should be withdrawn immediately. Data on a limited number of exposed pregnancies indicate adverse effects of medroxyprogesterone acetate on sexual differentiation of the foetus Studies in animals have shown reproductive toxicity *(see section 5.3).* The potential risk for humans is unknown. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of estrogens progestagen indicate no teratogenic or foetotoxic effect.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens and progestagens indicate no teratogenic or fetotoxic effect.

<u>Lactation</u>
Estopause is not indicated during lactation

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

The most frequently reported undesirable effect during Estopause treatment was breast tenderness, which occurred in 10.6% of users. Undesirable effects according to system organ class associated with Estopause treatment are presented in the table below.

Organ group	**Common>1/100**	**Uncommon>1/1000, <1/100**	**Rare>1/10,000; <1/1,000**
Gastrointestinal	Nausea, abdominal pain	Dyspepsia, vomiting, flatulence, gallbladder disease/gall stones	

Skin		Chloasma	Alopecia, hirsutism, rash, itching
CNS	Headache	Dizziness, migraine	
Urogenital	Uterine bleeding, increase in size of uterine fibroids	Vaginal candidiasis, changes in vaginal secretion	
Cardiovascular		Increase in blood pressure	Venous thromboemolism
Miscellaneous	Weight increase/decrease, oedema, breast tenderness, breast enlargement, changes in mood including anxiety and depressive mood, changes in libido.	Leg cramps, cholestasis	

Breast cancer
The risk of breast cancer increases with the number of years of HRT usage. The Million Women Study showed that , compared to never-users, use of oestrogen-progestagen combined HRT is associated with a higher risk of breast cancer (RR= 2.00, 95% CI: 1.88-2-12) that use of oestrogen alone (RR=1.30, 95% CI: 1.21-1.40).

For women not using HRT about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 65 years. Among those with with current or recent use of HRT, the number of additional cases from this study is shown in table 1. The number of additional cases of breast cancer due to HRT is broadly similar for women who start HRT irrespective of age at start of use (between ages of 45-65).

Endometrial cancer
In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogen. According to data from epidemiological studies, the test estimate of the risk of endometrial cancer 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. Among those with current or recent HRT, the number of additional cases is shown in table 1 Adding a progesterone to oestrogen-only therapy greatly reduces, but may not eliminate, this increased risk.

Table 1: Best estimate of absolute risk (number of cases expected in 1000 women from age of 50-65) of breast and endometrial cancer in women not taking HRT and number of additional cases (+95% CIs for breast cancer) in women taking HRT by regimen and duration of intake

Exposure	**Breast**	**Endometrium**
No HRT	32	
Oestrogen only	**Additional cases**	**Additional cases**
5 years	+2(0-3)	+4
10 years	+5(3-7)	+10
Oestrogen +Progestagen	**Additional cases**	**Additional cases**
5 years	+6 (5-7)	0
10 years	+19(18-20)	<2

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

- Oestrogen-dependant neoplasm's benign and malignant, e.g. endometrial cancer
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent

among hormone replacement therapy users than among non-users. For further information, *see section 4.3 Contraindications and 4.4 Special warnings and precautions for use*

- Myocardial infarction and stroke
- Gall bladder disease
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia

4.9 Overdose

Oestrogen overdose may cause nausea, headache and uterine bleeding. Numerous reports on high doses of oestrogen-containing oral contraceptives ingested by young children indicate that serious harmful effects do not occur. Treatment of oestrogen overdose is symptomatic. High doses of medoxyprogestrone acetate (MPA) used for cancer treatment have not resulted in serious undesirable effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and oestrogens

ATC Code: G03fA12

The active form of oestradiol (sythetic 17β-oestradiol) is chemically and biologically identical to endogenous human oestradiol. It substitutes for the loss of oestrogen production in menopausal women and alleviates menopausal symptoms.

Oestrogen prevents bone loss following menopause or ovariectomy.

Medroxyprogesterone acetate is a derivative of the natural progesterone, 17-alpha-hydroxy-6-methylprogesterone. Medroxyprogesterone acetate binds to progestin-specific receptors and acts on the endometrium to convert the status of the endometrium from proliferative to secretory.

As oestrogen promotes the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of medroxyprogesterone acetate greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

<u>Relief of oestrogen deficiency symptoms and bleeding patterns.</u>

Relief of menopausal symptoms was achieved during the first weeks of treatment. Bleeding and/or spotting appeared in 31% of the women receiving 1 mg oestradiol valerate and 51% of women receiving 2mg oestradiol valerate during the first three months of treatment and in 9% of the women receiving 1mg oestrogen valerate and in 20% of women receiving 2mg oestradiol valerate after 10-12 months of treatment.

Amenorrhoea was seen in 91% of women receiving 1 mg oestradiol valerate and in 80% of women receiving 2mg oestradiol valerate after 10-12 months treatment.

<u>Prevention of osteoporosis</u>

Oestrogen deficiency of menopause is associated with an increasing bone turnover and decline of the bone mass. The effect of oestrogens on bone mineral density (BMD) is dose dependant. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost a rate similar to that in untreated women.

Evidence for the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progesterone-given to predominantly healthy women-reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but he

evidence for this limited.

Information on serum lipid

No benefit has been demonstrated in primary and secondary coronary heart disease. The clinical relevance of lipid changes is unknown and the relevance for the safety of Estopause therefore highly questionable.

5.2 Pharmacokinetic properties

Following oral administration, oestradiol is absorbed from the gastrointestinal tract and rapidly hydrolysed to oestradiol by esterases. In postmenopausal women aged 50-59 years the maximum concentration of oestradiol in serum (C_{max}) was reached within 4 hours after multiple dosing of 1 mg or 2 mg oestradiol valerate. After 1 mg dose C_{max} was about 166pmol/l, trough conecentration (C_{max}) about 101pmol/l and average concentration ($C_{average}$) about 123 pmol. For 2mg dose C max was 308 pmol/l, C_{min} 171 pmol/l and $C_{average}$ 228 pmol. Comparable oestradiol concentrations were observed in women over 65 years.

After oral administration, progesterone is absorbed from the gastrointestinal tract, but is rapidly metabolised by small intestine and liver. After multiple dosing of 2.5mg or 5mg medoxyprogesterone acetate to women aged 50-65 years, maximum concentration in serum was reached in less than 2 hours. After 2.5mg dose C_{max} was about 0.37ng/ml, c min about 0.05ng/ml and c average about o.11ng/ml. After 5mg dose C_{max} was about 0.64ng/ml, c min about 0.12ng/ml and $C_{average}$ about 0.21 ng/ml. Comparable medroxyprogesterone acetate concentrations were observed in women over 65 years.

Medroxyprogestrone acetate is over 90% bound to plasma proteins, mainly to albumin. The elimination half-life of oral medroxyprogesterone acetate is approximately 24 hours. Medroxyprogesterone acetate is extensively metabolised by hepatic hydroxylation and conjugation and excreted in the urine and the bile. Metabolism is poorly documented and the pharmacological activity of the metabolites is not known.

5.3 Preclinical safety data

Animal studies with oestradiol and medroxyprogesterone have shown expected estrogenic effects. Both compounds induced adverse effects in reproductive toxicity studies. Chiefly, estradiol showed embryotoxic effects and induced feminization of male fetuses. Medroxyprogesterone acetate showed embryotoxic effects and induced anti-androgenic effects in male fetuses. The relevance of these data for human exposure is unknown *(see section 4.6).*

Concerning other preclinical effects, the toxicity profiles of estradiol and medroxyprogesterone acetate are well known and reveal no particular human health risks beyond those already discussed in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each white tablet contains:

Lactose monohydrate
Crospovidone (type A)
Povidone K25
Talc
Magnesium stearate
Opadry White Y-1-7000
hypromellose
macrogol 400
titanium dioxide (E171)

Each pale-blue tablet contains:

Lactose monohydrate
Crospovidone (type A)
Povidone K25
Talc
Magnesium stearate
Opadry White Y-1-7000
hypromellose
macrogol 400
titanium dioxide (E171)
Indigo carmine lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25^{o}C. Store in the original package.
Keep container in the outer carton.

6.5 Nature and contents of container

Calendar pack consisting of 16 round, white, biconvex, film-coated tablets and 12 round, pale-blue, biconvex, film-coated tablets within a PVC/aluminum foil blister pack.

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 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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