Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Estradiol Implants 50 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each implant contains 50 mg estradiol (as hemihydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Implant.
White to pale brown opaque or translucent cylinder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal women.
- 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.

4.2 Posology and method of administration

Frequency of replacement depends on the duration of activity of the implants administered and the severity of the symptoms. Patients require a further implant when symptoms return, usually every 4 to 8 months.

Estradiol implants should be inserted subcutaneously under local anesthetic either by means of a trocar and cannula or in the wound at the time of laparotomy, into an area where there is little movement, such as the upper outer part of the buttock or the lower abdominal wall.

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.

Because of the sustained absorption of Estradiol, the endometrium of post-menopausal or ovariectomized women is liable to progressive hypertrophy. Therefore, in women with an intact uterus, additional administration of a progestogen is essential, for 12 – 14 days every month, to prevent endometrial hyperplasia. Literature data suggests that co-administration of progestogens with Estradiol implants does prevent endometrial hyperplasia. Only progestogens approved for addition to estrogen treatment are recommended. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomized women.

When the patient no longer requires or seeks re-implantation with Estradiol implants, it is recommended that, in those women with an intact uterus, cyclical administration of an oral progestogen should be continued until there is a cessation of the withdrawal bleeding, in order to the prevent the possibility of continued endometrial stimulation.

Depending on the duration and dosage used, withdrawal bleeding may occur up to 1-2 years after the last implantation.

Since the implants consist entirely of Estradiol without any auxiliary ingredients, they are biodegradable and no

removal procedure is required. In the rare event that removal of the implant should be necessary, the implant may be located by palpation or if not successful by Magnetic Resonance Imaging technique. This technique can identify the implant by its size and structure and the implant can exactly be localized by insertion of a localizer wire with the tip ending at the implant. After localization, the implant can be removed after a small incision under local anesthetic.

4.3 Contraindications

- Known, past or suspected breast cancer.
- Known or suspected estrogen-dependent 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 (eg 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 Estradiol.
- Porphyria.

4.4 Special warnings and precautions for use

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.

Medical examination/follow-up
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 *(section 4.3)* and warnings for use *(section 4.4)*. 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). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

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 Estradiol implants in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or risk factors for, thromboembolic disorders (see below).
- Risk factors for estrogen dependent 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 (severe) headache.
- Systemic lupus erythematosis.
- A history of endometrial hyperplasia (see below)
- Epilepsy.
- Asthma.
- Otosclerosis.

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case 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 estrogens are administered alone for prolonged periods *(see Section 4.8).* The addition of a progestogen for at least 12 days per cycle in non-hysterectomized women greatly reduces the 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 treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Unopposed estrogen stimulation may lead to pre-malignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to estrogen replacement should be considered in women who have undergone hysterectomy because of endometriosis, if they are know to have residual endometriosis.

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 estrogens, estrogen-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 estrogens (CEE) or Estradiol (E_2) 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 estrogen 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 estrogen-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 2-3 fold 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 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 and severe obesity (Body Mass Index > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.

Patients with a history of VTE or known thrombophillic 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 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 orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT, if possible. Treatment should not be restarted until the woman is completely mobilised.

If VTE develops after initiating therapy the drug should be discontinued and/or adequate anticoagulant treatment should be given. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (eg painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)
There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated estrogens and medroxyprogesterone 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 ischemic stroke in healthy women during treatment with continuous combined conjugated estrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a five 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 estrogen 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 estrogen-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 than estrogen-only products.

Other conditions
Estrogen 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 active ingredients in Estradiol implants is increased.

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

Estrogen increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (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 elevated 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/renin substrate, alpha-I-antitrysin, ceruloplasmin).

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 combine CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

4.5 Interaction with other medicinal products and other forms of interaction

Since Estradiol implants are administered parentally, the first-pass effect in the liver is avoided and, thus, parentally administered estrogens might be less affected than oral hormones by enzyme inducers. The metabolism of estrogens in general may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. Phenobarbital, phenytonin, carbamezapine) and anti-infectives (e.g. rifampicin, ritabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparation containing St John's wort (Hyperticum Perforatum) may induce the metabolism of estrogens.

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

4.6 Pregnancy and lactation

Not applicable, because estradiol implants are only indicated in women without a Uterus.

4.7 Effects on ability to drive and use machines

As far as known Estradiol implants have no effect on alertness or concentration.

4.8 Undesirable effects

No recent clinical trials have been conducted with Estradiol implants that would allow a reliable estimation of the percentage of the patients expected to experience adverse reactions. From literature and from monitoring during market use the prevalence appears to less than 1%. The following undesirable effects have been reported in association with estrogen-progestogen treatment.

Breast: Tenderness, pain, swelling, secretion.

General: Fluid retention, weight gain.

Skin: Transient erythema, chloasma, rash, vascular purpura

Central Nervous System: Headache, migraine, fatigue, nervousness and changes in mood, probable dementia *(see Secti 4.4).*

Digestive tract and liver: Nausea, bloating, cholelithiasis, cholestaticicterus, changes in serum liver enzyme levels.

Urogenital area: Aggravation of endometriosis,

Cardiovascular system: Venousthromboembolism, 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 Section 4.3 and 4.4*

Myocardial infarction and stroke

Eyes: Discomfort when contact lenses are used.

Neoplasms Estrogen-dependent neoplasms benign and malignant e.g. breast cancer and endometrial cancer (see below).

With implants, occasionally subdermal hematoma may occur at the implantation site.

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 *estrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was estrogen-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 *estrogen-progestogen* combined HRT, several epidemiological studies have reported and overall higher risk for breast caner than with estrogen's alone.

The MWS reported that, compared to never users, the use of various types of estrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR=2.00, 95%CI: 1.88 – 2.12) than use of estrogens 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 estrogen-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 estrogen-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 estrogen-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 to 79 years, and additional 8 cases of invasive breast cancer would be due to estrogen-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 estrogen-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 hypeplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens. 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 estrogen dose, the reported increase in endometrial cancer risk among unopposed estrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestogen to estrogen-only therapy greatly reduces this increased risk.

4.9 Overdose

Generally, estrogens are well tolerated even in massive doses. Possible symptoms of overdosage include those listed under undesirable effects *(Section 4.8)*. Treatment is symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03C A03

The active ingredient, synthetic 17β-estradiol is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women, and alleviates menopausal symptoms.

Estrogen prevents bone loss following menopause or ovariectomy.

Clinical trial information.

- Relief of estrogen-deficiency symptoms.
- Relief of menopausal symptoms was achieved usually during the first week of treatment.

Prevention of osteoporosis

Estrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of estrogens on bone mineral density is dose-dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestogen - 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 the evidence for that is limited.

Studies have reported significant increases in bone mineral density at spine and hip after treatment with Estradiol implants (25-100 mg every 6 months) for 1 to 15.5 years.

5.2 Pharmacokinetic properties

After insertion of a 50 mg implant into the subcutaneous fat the Estradiol plasma level reaches its maximum of about 430 pmol/1 in a few days and shows a slow and gradual decline to about 200 pmol/1 at six months. As with other estrogens and progestagens, there are large inter-individual differences in hormone levels, but intra-individual variability appears to be small.

After repeated implantation Estradiol levels reach higher values than after the initial implantation, but they remain well within the midfollicular range as found in premenopausal women. With two implants at a time and/or implantation intervals shorter than 6 months, occasionally higher Estradiol levels may occur. Subcutaneous administration of Estradiol bypasses the gastrointestinal tract, where orally administered Estradiol is converted into estrone.

In addition, the first-pass effect of the liver is avoided. Therefore, more unconjugated Estradiol is available and a more physiological ratio between Estradiol and estrone levels is achieved than with oral Estradiol therapy.

5.3 Preclinical safety data

There is no preclinical data of relevance to the prescriber which is additional to that included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

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

The sterile implant is supplied in a sealed glass tube.

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

Full aseptic “no touch” technique should be used.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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