Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ESTREVA 0.1% w/w gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g of gel contains 1.0325 mg of estradiol hemihydrate, corresponding to 1.0000 mg of anhydrous estradiol.
Each dose delivers 0.5 g of gel, ie 0.5 mg of estradiol (as 0.516 mg of estradiol hemihydrate).
Excipients: contains Propylene glycol (6.0 mg).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Gel
Translucent and odourless gel

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

ESTREVA® 0.1% w/w gel is presented in tube-bottles with dosing pumps.

It may be necessary to prime the pump when beginning a new bottle. The first dose may not be accurate and should be discarded.

Each push delivers 0.5 g of gel, i.e. 0.5 mg of estradiol.

The average dose is 1.5 g of gel per day, i.e 3 consecutive doses, for 24 to 28 days.

The starting dose is 0.5 g of gel per day for 24 to 28 days.

This starting dose can be adapted to individual needs.

The individual dose can range from 0.5 to 3 g of gel per day.

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.

In non-hysterectomised women, it is highly recommended that a progestogen be combined for at least 12 to 14 days of use of estradiol gel to prevent an endometrial hyperplasia induced by the oestrogen.
Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

Two therapeutic regimens can be used:
1) Cyclic for 24 to 28 days, followed by a 2 to 7 days treatment free period. The progestogen should be administered at least during the last 12 days of the estradiol treatment in non-hysterectomised women. Withdrawal bleeding may occur during this period.
2) Continuous: with no treatment free period. In non-hysterectomised women the progestogen should be administered for at least 12 days per month. Withdrawal bleeding may occur when the progestogen is withdrawn.
Continuous, non-cyclic, treatment may be recommended in cases where marked symptoms of oestrogen deficiency recur during the treatment-free period.

The application surface should be 2 times the size of the hand. The patient applies the gel onto clean, dry and intact skin, preferably after washing in the morning or evening, on the abdomen, thighs, arms, or shoulders. The gel should not be applied on the breasts or to the mucosa. Eye contact must be avoided. It is not necessary to rub the gel in, however it is recommended that subjects wait for 2 minutes before dressing.
The gel does not stain clothing. Hands should be washed after application.
Forgetting a dose may increase the likehood of break-through bleeding and spotting.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia ;
- Previous or current venous thromboembolism (deep venous thombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- 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 substances or to any of the excipients;
- 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.
Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

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 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 what changes in their breasts should be reported to their doctor or nurse (see “Breat cancer” below). Investigations, including appropriate imaging tools, e.g. 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 occured 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 ESTREVA® 0.1% w/w gel, in particular:
- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer

- Hypertension
- Liver disorders (e.g. 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

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 and carcinoma

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.

- The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

- 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 oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

Breast cancer

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT.
The randomized placebo-controlled trial the Women's Health Initiative study (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (see Section 4.8).
The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT.
Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-progestagen combinations (see section 4.8).
The excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.
HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. In long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8).
Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar, or slightly smaller, risk (see section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).

- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

- Generally recognized risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilization, obesity (BMI > 30 kg/m^2)), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

- As in all postoperative patients prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).
  If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is ‘severe’ (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

- 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 (eg, painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

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- There is no evidence from randomised controlled trials of protection against myorcardial infarction in women with or without CAD who received combined oestrogen-progestagen or oestrogens-only HRT.
  The relative risk of CAD during use of combined oestrogen+progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestagen use is very low in healthy women close to menopause, but will rise with more advanced age. Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke

- Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Other conditions

- Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

- 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 (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-antitrypsin, ceruloplasmin).

- HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

Potential estradiol transfer

If no precaution is taken, estradiol gel can be transferred to other persons by close skin to skin contact.

The following precautions are therefore recommended:

- for the patient:
  - wash hands with soap after applying the gel,
  - cover the application area with clothing once the gel has dried,
  - shower before any situation in which this type of contact is foreseen.
- for people not being treated with ESTREVA 0.1% w/w gel:
  - in the event of contact with an application area which has not been washed or is not covered with clothing, wash the area of skin onto which estradiol may have been transferred, using soap and water.

Excipients known to have a recognized action or effect

- The presence of propylene glycol, may cause skin irritation.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens 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, carbamazepin) and 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.

At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens might be less affected than oral hormones by enzyme inducers.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:

ESTREVA® 0.1% w/w gel is not indicated during pregnancy. If pregnancy occurs during medication with ESTREVA® 0.1% w/w gel treatment should be withdrawn immediately.
The results of most epidemiological studies to date relevant to inadvertent fœtal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Lactation:

ESTREVA® 0.1% w/w gel 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

During phase III clinical trials, the following adverse drug reactions have been reported, with a frequency under 10% for all of them. These adverse drug reactions are those which are reported during oestrogen replacement therapy.

Organ system class (e.g. MedDRA SOC level)	Common ADRs > 1/100 ; < 1/10	Uncommon ADRs >1/1,000 ; < 1/100
Reproductive system and breast disorders	Metrorrhagia Uterine haemorrhage Breast pain	Benign breast neoplasm Vaginal discharge
Gastrointestinal disorders	Nausea Abdominal distension	Vomiting
Nervous system disorders	Headache	-
Musculoskeletal and connective tissue disorders	Sensation of heaviness	Musculoskeletal pain
Psychiatric disorders	-	-
Vascular disorders	-	Thrombophlebitis -
Respiratory, thoracic and mediastinal disorders	-	Pulmonary embolism
Investigations	-	Weight increase
General disorders and administration site conditions	-	Oedema peripheral Fatigue

Skin and sub cutaneous tissue disorders	-	Pruritus

Based on the post-marketing data, cases of allergic reactions, contact dermatitis at the application site have been reported (unknown effect).

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration (see section 4.4).
- Results of the largest randomized placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

Million Women study– Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 neverusers of HRT over a 5 year period*2	Risk ratio	Additional cases per 1000 HRT users over 5 years (95%CI)
Oestrogen only HRT			
50-65	9-12	1.2	1-2 (0-3)
Combined oestrogen-progestagen			
50-65	9-12	1.7	6 (5-7)
#Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*3
CEE+MPA oestrogen & progestagen‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

*2 *Taken from baseline incidence rates in developed countries*
*3 *WHI study in women with no uterus, which did not show an increase in risk of breast cancer*

Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1000 women with an uterus not using HRT.
In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only*4			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined oestrogen-progestagen			
50-59	4	2.3 (1.2-4.3)	5 (1-13)

Risk of coronary artery sidease
The risk of coronary artery disease is slightly increased in users of combined oestrogenprogestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke*5 over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1 1.6)	3 (1-5)

*4 *Study in women with no uterus*
5**no differentiation was made between ischaemic and haemorrhagic stroke.*

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).

4.9 Overdose

Signs of an overdose are generally breast tenderness, swelling of the abdomen/pelvis, anxiety and irritability (see posology and method of administration).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03CA03
OESTROGENS (Genitourinary system and sex hormones)
Natural oestrogen by transdermal route.

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

Clinical Trial Information :

Relief of menopausal symptoms was achieved during the first few weeks of treatment.

5.2 Pharmacokinetic properties

In a pharmacokinetic study, application a single dose of 1.5 g of ESTREVA® 0.1% w/w gel (i.e. 1.5 mg) over a surface area of 400 cm2 of abdominal skin is followed by a progressive increase in estradiolaemia which reaches a mean peak of 40 pg/ml after a single administration. With repeated administration of the same dose over the same area, steady state is reached in 4 days. Average levels 24 hours after the last application are in the order of 40 pg/ml and the mean peak at the 22nd day is 70 pg/ml.

Repeated administration of 3 g of ESTREVA® 0.1% w/w gel leads to a doubling of the area under the curve observed with 1.5 g of gel.

The bioavailability of percutaneous estradiol is dependent on the area of application and varies from one subject to another making it necessary to adapt the dosage to each individual case as a function of the clinical symptomatology.

5.3 Preclinical safety data

Acute toxicity of estrogens is low. Because of marked differences between animal species and between animals and humans preclinical results possess a limited predictive value for the application of estrogens in humans.
In experimental animals estradiol displayed an embryolethal effect already at relatively low doses; malformations of the urogenital tract and feminization of male fetuses were observed.
Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenetic potential revealed estrogenic effects in relationship with the pharmacological activity of the molecule.
The finished product is a mild irritant for the skin, an irritant for the eyes, shows good tolerance with repeated topical administration and is non-sensitizing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96 per cent, Purified water, Propylene glycol, Diethylene glycol monoethyl ether (Transcutol), Carbomer (Carbopol 1382), Trolamine, Disodium edetate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

High-density white polyethylene tube-bottle containing 50 g of gel, with a dosing pump.
Box of one or three bottles of 50g.
The pump delivers pushes of 0.5 g of gel corresponding to 0.5 mg of estradiol.
Not all pack sizes may be marketed.

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

BELPHARMA S.A.
Winston Churchill Av., 67
1180 Brussels
Belgium

8 MARKETING AUTHORISATION NUMBER

PA 0908/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 January 1999

Date of last renewal: 15 July 2010

10 DATE OF REVISION OF THE TEXT

July 2011