Annex III

Amendments to relevant sections of the summary of product characteristics and package leaflets

Note:

The changes to the relevant sections of the summary of product characteristics and package leaflet is the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Part A. - 0.01% w/w estradiol containing medicinal products for topical use(as per Annex I)

[The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below]

I. Summary of Product Characteristics

Section 4.1 - Therapeutic indications

[The wording of the indication should be deleted and the text below should be inserted in its place]

Treatment of vaginal atrophy due to oestrogen deficiency in postmenopausal women.

Section 4.2 Posology and method of administration

[The text below should be inserted by replacing the existing text of this section]

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.

Route of administration: cream for vaginal use

[invented name] should be applied with an applicator.

One filled applicator dose (= 2 g cream) is inserted before retiring to bed. In the first week of treatment, [invented name] should be applied on every other day, i.e. at 48-hourly intervals, and twice weekly thereafter (maintenance dose). The applicator should be cleaned with warm water each time after use.

Treatment may be started on any convenient day.

The maximum duration of treatment is 4 weeks.

The endometrial safety of prolonged treatment and repeated treatment courses is unknown. Given that systemic exposure occurs during treatment with [Invented name], prolonged treatment beyond 4 week is not recommended. If symptoms persist beyond 4 weeks, alternative therapies should be considered.

If unexpected bleeding should occur, treatment with [invented name] must be suspended until the cause of bleeding has been clarified (see section 4.4 on endometrial safety).

If a dose is forgotten, it should be taken as soon as the patient remembers. A double dose should be avoided.

The experience treating women older than 65 years is limited.

Section 4.3 Contraindications

[The text below should be inserted by replacing the existing text of this section]

[invented name] should not be used in the following cases:

- 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 thrombosis, 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.

Section 4.4 Special warnings and precautions for use

[All current text in this section should be deleted and replaced by the text below]

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.

[Invented name] should not be used in patients who are treated with systemic Hormone Replacement Therapy (HRT).

During treatment with [invented name], after each application there is a transient increase in plasma oestradiol levels above the physiological range of postmenopausal women.

Therefore, for safety reasons, the maximum duration of treatment is limited to 4 weeks. Vigilance is required for possible systemic effects.

Medical examination/follow-up

Before initiating or reinstituting hormone therapy, a complete personal and family medical history should be obtained. 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. 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.

The pharmacokinetic profile of [Invented name] shows that there is systemic absorption of estradiol during treatment, in concentrations which are transiently above the postmenopausal levels (see Section 5.2). However, being a HRT product, the following need to be considered:

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 oestrogen treatment, 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

During treatment with [invented name], after each application there is an increase in plasma oestradiol levels above the physiological range of postmenopausal women. Therefore, for safety reasons the maximum duration of treatment is limited to 4 weeks. Vigilance is required for possible systemic effects.

[Invented name] should not be used in patients who are treated with systemic Hormone Replacement Therapy (HRT).

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

Women with an intact uterus with abnormal bleeding of unknown aetiology or women with an intact uterus who have previously been treated with unopposed oestrogens should be examined with special care in order to exclude hyperstimulation/malignancy of the endometrium before initiation of treatment with [invented name]

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 systemic oestrogen-only users varies from 2- to 12-fold compared with non-users, depending on both duration of treatment and on oestrogen dose. After stopping treatment risk remain elevated for at least 10 years.

Endometrial safety of long-term (more than one year) or repeated use of local vaginally administered oestrogen is uncertain. Therefore, before a 4-week treatment course with [invented name] is repeated, treatment should be reviewed, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

If bleeding or spotting appears at any time on therapy, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

The woman should be advised to contact her doctor in case bleeding or spotting occurs during treatment with [invented name].

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

Risk estimates have been drawn from systemic exposure (HRT) and it is not known how these apply to local treatment.

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 WHI trial found no increase in 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 found in users of oestrogen-progestagen combinations.

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.

A relationship between breast cancer risk and local vaginal oestrogen therapy is uncertain.

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

Risk estimates have been drawn from systemic exposure (HRT) and it is not known how these apply to local treatment.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Long-term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer. 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).

A relationship between ovarian cancer risk and local vaginal oestrogen therapy is uncertain.

Risk estimates have been drawn from systemic exposure (HRT) and it is not known how these apply to local treatment.

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.

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 recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation 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.

A relationship between venous thromboembolism and local vaginal oestrogen therapy is uncertain.

As in all postoperative patients, prophylactic measures need to 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 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 (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Risk estimates have been drawn from systemic exposure (HRT) and it is not known how these apply to local treatment.

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only.

Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Risk estimates have been drawn from systemic exposure (HRT) and it is not known how these apply to local treatment.

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 increase with age.

A relationship between ischaemic stroke and low dose local vaginal oestrogen therapy is uncertain.

Risk estimates have been drawn from systemic exposure (HRT) and it is not known how these apply to local treatment.

Other conditions

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

Women with pre-existing hypertriglyceridaemia 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.

The relationship between pre-existing hypertriglyceridaemia and low dose local vaginal oestrogen therapy is unknown.

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 biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

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

In rare cases benign, and in even rarer cases malignant liver tumours leading to isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as those contained in [invented name]. If severe upper abdominal complaints, enlarged liver or signs of intra-adominal haemorrhage occur, a liver tumour should be considered in the differential diagnosis.

Note:

Intravaginal applicator may cause minor local trauma, especially in women with serious vaginal atrophy.
[Invented name] should not be used immediately prior to sexual intercourse or as a lubricant, in order to avoid possible undesirable effects in the partner.

Using [invented name] together with latex products (e.g. condoms, diaphragms) can reduce the functionality of such products thereby making them less reliable as [invented name] contains excipients (other ingredients, particularly stearates).

Cetyl stearyl alcohol can cause local skin irritation (e.g. contact dermatitis).

Section 4.5 Interaction with other medicinal products and other forms of interaction

[All current text in this section should be deleted and replaced by the text below]

Interactions of [invented name] with other medicinal products were not investigated.

However, 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, carbamazepine) 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.

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

Section 4.6 Fertility, Pregnancy and lactation

[The text below should be inserted in this section and the existing text should be deleted]

Pregnancy

[invented name] is not indicated during pregnancy. If pregnancy occurs during medication with [invented name], treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effect.

Lactation

[invented name] should not be used during breast feeding.

Section 4.7 Effects on ability to drive and use machines

[The text below should be inserted in this section and the existing text should be deleted]

[invented name] is unlikely to have any effect on alertness or coordination.

Section 4.8 Undesirable effects

[The text below should be inserted in this section and the existing text should be deleted]

Post-marketing experience

The following undesirable effects related to [invented name] have been reported:

System organ class (MedDRA)	Uncommon (≥ 1/1,000 to < 1/100)	Very rare (< 1/10,000),
General disorders and administration site conditions	Transient, mild local irritation (e.g. pruritus, burning). Slight discharge	Hypersensitivity skin reaction (allergic contact eczema)

The following adverse reactions have been associated with oral and/or transdermal oestrogen therapy (class effects):

System Organ Class	Common ≥ 1/100 to < 1/10 (≥ 1% and <10%	Uncommon > 1/1000 to <1/100 (> 0.1% and <1%)
Infections and infestations		Vaginitis, including vaginal candidiasis
Immune system disorders		Hypersensitivity
Psychiatric disorders	Depression	Changes in libido, mood disturbances
Nervous system disorders		Dizziness, headache, migraine, anxiety
Eye disorders		Intolerance to contact lenses
Vascular disorders		Venous thrombosis, pulmonary embolism
Gastrointestinal disorders		Nausea, bloating, abdominal pain
Hepatobiliary disorders		Gallbladder disease
Skin and subcutaneous tissue disorders	Alopecia	Chloasma/melasma, hirsutism, pruritus, rash
Musculoskeletal, connective tissue and bone disorders	Arthralgias, leg cramps	
Reproductive system and breast disorders	Abnormal uterine bleeding (breakthrough bleeding/spotting), breast pain, breast tenderness, breast enlargement, breast discharge, leukorrhoea	

General disorders and administration site conditions		Oedema
Investigations	Changes in weight (increase or decrease), increased triglycerides	

Breast cancer risk

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments.

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen 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-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised 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 users of HRT over 5 year period***	**Risk ratio**	**Additional cases per 1000 HRT user 5 years (95% CI)**
		Oestrogen only HRT	
50 – 65	9 – 12	1.2	1 – 2 (0 – 3)
		Combined oestrogen-progestogen	
50 – 65	9 – 12	1.7	6 (5 – 7)
* Taken from baseline incidence rates in developed countries. # Overal risk ratio. The risk ratio is not constant but will increase with increasing duration of 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 (years)	**Incidence per 1000 women placebo arm over 5 year period***	**Risk ratio and 95% CI**	**Additional cases per 1000 HRT user 5 years (95% CI)**
		CEE oestrogen-only	
50 – 79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA oestrogen & progestogen $	
50 – 79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

* WHI study in women with no uterus, which did not show an increase in risk of breast cancer.
$ When the analysis was restricte 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 non-users

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. See sction 4.2 and 4.4.

Ovarian cancer

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments.

Long-term use of oestrogen-only and combined oestrogen-progestogen 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

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments.

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

*Study in women with no uterus

Risk of coronary artery disease

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments.

The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestogen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments.

The use of oestrogen-only and oestrogen + progestogen 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* over 5 years' use

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

* No differentiation was made between ischaemic and haemorrhagic stroke

Other adverse reactions have been reported in association with oestrogen/progestogen treatment. Risk estimates have been drawn from systemic exposure and it is not known how these apply to local treatments:

- Skin and subcutaneous disorders: erythema multiforme, erythema nodosum, vascular purpura
- Probable dementia over the age of 65 (see section 4.4)
- Gallbladder disease

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

[*For the printed material, please refer to the guidance of the annotated QRD template.]

Section 4.9 Overdose

[The text below should be inserted in this section. Any existing section should be deleted.]

Undesirable effects - such as gastrointestinal complaints, nausea, etc - may occur after accidental or intentional administration of large amounts of [invented name]. Treatment is symptomatic.

Section 5.1 Pharmacodynamic properties

[…]

[The text below should be deleted from this section]

As its active substance, [invented name] contains 17ß-estradiol, a natural sex hormone, at a concentration of 0.01%. Estradiol is the most potent natural oestrogen to act intracellularly. As well as its typical hormonal effects during the reproductive period, estradiol also exerts characteristic effects on the skin. At around ≥ 0.01% topically or systemically, estradiol widens the capillary vessels and promotes general blood perfusion. Oestrogens stimulate epithelial cell proliferation in the genital area and urinary tract, as well as increasing collagen synthesis in the skin.

Similarly to other steroid hormones, estradiol acts directly on genetic information (DNA) via specific receptors. Thus, estradiol affects transcription (RNA synthesis) and therefore stimulates the synthesis of specific proteins. In addition, estradiol also has rapid, non-genomic effects (signal transduction).

[The text below should be inserted in this section.]

The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol.

Endogenous 17β-estradiol induces and maintains the primary and secondary female sexual characteristics. The biological effect of 17β-estradiol is carried out through a number of specific oestrogen receptors. The steroid receptor complex is bound to the cells' DNA and induces synthesis of specific proteins.

Maturation of the vaginal epithelium is dependent upon oestrogens. Oestrogens increase the number of superficial and intermediate cells and decrease the number of basal cells in vaginal smear.

Oestrogens maintain vaginal pH around normal range (4.5) which enhances normal bacterial flora.

Section 5.2 Pharmacokinetic properties

[The text below should be inserted in this section. Any existing section should be deleted.]

When applied vaginally, estradiol is absorbed from the vaginal epithelium and enters the bloodstream in concentrations which are transiently above the postmenopausal range.

The following values were determined after single-dose administration of 2 g [invented name], equivalent to 200 µg E2: $AUC_{\delta 0-\infty}$ = 887.5 pg/ml*h; $AUC_{\delta 0-tz}$ = 799.5 pg/ml*h; $C_{\delta max}$ = 86.2 pg/ml. The geometric mean half-life of E2 was 5.05 hours, with high interindividual variability. In another study, mean estradiol serum concentrations at baseline and at day 31 (i.e. about 36 h after administration of study medication on day 29) were 6.4 pg/ml and 15.1 pg/ml, respectively, in the [invented name] group and 4.4 pg/ml and 6.2 pg/ml, respectively, in the placebo group.

Estradiol is rapidly metabolised in the liver and intestinal tract to estrone and subsequently to estriol. Estradiol conversion to estriol is irreversible. Over 95% of estriol is excreted in the urine, mainly in the form of glucuronides.

Section 5.3 Preclinical safety data

[The text below should be inserted in this section. Any existing section should be deleted.]

17β-Estradiol is a well-known substance. Nonclinical studies provided no additional data of relevance to clinical safety beyond those already included in other sections of the SmPC.

Section 6.5 Nature and contents of container

[The text below should be deleted from this section]

[…] and cutaneous use in the external genital area.

II. Package Leaflet

[The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below]

1. WHAT [invented name] IS AND WHAT IT IS USED FOR

[The text below should be all deleted from this section]

[invented name] is a cream containing estradiol for vaginal use.

[invented name] is used:
For the treatment of atrophic disorders of the vagina and vulva, which are due to a lack of oestrogen, e.g. atrophic vaginitis, coital problems, vaginal stenosis (narrowing), vulvar atrophy with burning and itching

[The text below should be inserted in this section.]

[invented name] is a cream for vaginal use which contains estradiol

- Estradiol is a female sex hormone.
- It belongs to a group of hormones called oestrogens.
- It is exactly the same as the estradiol produced by the ovaries of women.

[invented name] belongs to a group of medicines called local Hormone Replacement Therapy (HRT).

It is used to relieve menopausal symptoms in the vagina such as dryness or irritation. In medical terms this is known as ‘vaginal atrophy’. It is caused by a drop in the levels of oestrogen in your body. This happens naturally after the menopause.

[invented name] works by replacing the oestrogen which is normally produced in the ovaries of women. It is inserted into your vagina, so the hormone is released where it is needed. This may relieve discomfort in the vagina.

2. Before you use [invented name]

[The currently existing text should be deleted from this section and be replaced by the text below.]

During treatment with [invented name], after each application there is a transient increase in plasma estradiol levels above the physiological range of postmenopausal women. Therefore, for safety reasons, you should use [invented name] no longer than 4 weeks.

Do not use [invented name] when you use other HRT products such as estrogen tablets, patches or gel for treatment of hot flushes or prevention of osteoporosis

Medical history and regular check-ups

The use of HRT carries risks which need to be considered when deciding whether to start taking [invented name], or whether to carry on taking it.

Before you start (or restart) HRT, your doctor will ask about your own and your family's medical history. Your doctor may decide to perform a physical examination. This may include an examination of your breasts and/or internal examination, if necessary.

Go for regular breast screening as recommended by your doctor.

Do not use [invented name] if

- You are **allergic** (hypersensitive) to **estradiol** or any of the other ingredients of [invented name] (listed in Section 6 Further information)
- You have or have ever had **breast cancer**, or you are suspected of having it
- You have or have ever had **cancer which is sensitive to oestrogens**, such as cancer of the womb lining (endometrium), or you are suspected of having it
- You have any **unexplained vaginal bleeding**
- You have excessive **thickening of the womb lining** (endometrial hyperplasia) that is not being treated
- You have or have ever had a **blood clot in a vein** (thrombosis), such as in the legs (deep venous thrombosis) or the lungs (pulmonary embolism)
- You have a **blood clotting disorder** (such as protein C, protein S, or antithrombin deficiency)
- You have or have recently had a disease caused by blood clots in the arteries, such as a **heart attack, stroke** or **angina**
- You have or have ever had a **liver disease** and your liver function tests have not returned to normal
- You have a rare blood problem called "**porphyria**", which is passed down in families (inherited).

If any of the above conditions appear for the first time while using [invented name] , stop using it at once and consult your doctor immediately.

Take special care with [invented name]

Tell your doctor if you have or have ever had any of the following problems before you start the treatment. If so, you should see your doctor more often for check-up's. [Invented name] , is for short-term (4 weeks) local treatment in the vagina and the absorption into the blood is lower. It is therefore less likely that the conditions mentioned below will get worse or come back during treatment with [invented name].

- Asthma
- Epilepsy
- Diabetes
- Gallstones
- High blood pressure
- Migraines or severe headaches
- A liver disorder, such as a benign liver tumour

- Growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia)
- A disease affecting the eardrum and hearing (otosclerosis)
- A disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE)
- Increased risk of getting an oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer)
- Increased risk of developing blood clots (see "Blood clots in a vein (thrombosis)")
- Fibroids inside your womb
- A very high level of fat in your blood (triglycerides)
- Fluid retention due to cardiac or kidney problems.

Do not use [invented name] when you use other HRT products such as estrogen tablets, patches or gel for treatment of hot flushes or prevention of osteoporosis.

Stop using [invented name] and see a doctor immediately

If you notice any of the following when using HRT:
- Migraine-like headaches which happen for the first time
- Yellowing of your skin or the whites of your eyes (jaundice). These may be signs of a liver disease
- A large rise in your blood pressure (symptoms may be headache, tiredness, dizziness)
- Any of the conditions mentioned in the 'Do not use [invented name] ' section

If you become pregnant

If you notice signs of a blood clot, such as:

- painful swelling and redness of the legs
- sudden chest pain
- difficulty in breathing

For more information, see 'Blood clots in a vein (thrombosis)'.

The following risks apply to HRT medicines which circulate in the blood. It is not known how these risks apply to locally administered treatments such as [invented name] .

HRT and cancer

Excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the lining of the womb (endometrial cancer)

Taking oestrogen-only HRT tablets for a long time can increase the risk of developing cancer of the womb lining (the endometrium). It is uncertain whether long term (more than one year) or repeated use of local vaginally administered oestrogen products possess a similar risk.

If you get **breakthrough bleeding or spotting**, it's usually nothing to worry about, but you should make an appointment to see your doctor. It could be a sign that your endometrium has become thicker.

Breast cancer

Evidence suggests that taking combined oestrogen-progestagen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long you take HRT. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

For women who have had their womb removed and who are using oestrogen-only HRT for 5 years, little or no increase in breast cancer risk is shown.

Compare

Women aged 50 to 79 who are not taking HRT, on average, 9 to 14 in 1000 will be diagnosed with breast cancer over a 5-year period. For women aged 50 to 79 who are taking oestrogen-progestagen HRT over 5 years, there will be 13 to 20 cases in 1000 users (i.e. an extra 4 to 6 cases).

Regularly check your breasts. See your doctor if you notice any changes such as:

- dimpling of the skin
- changes in the nipple
- any lumps you can see or feel

Ovarian cancer

Ovarian cancer is rare. A slightly increased risk of ovarian cancer has been reported in women taking HRT for at least 5 to 10 years.

Women aged 50 to 69 who are not taking HRT, on average about 2 women in 1000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been taking HRT for 5 years, there will be between 2 and 3 cases per 1000 users (i.e. up to 1 extra case).

Effect of HRT on heart and circulation

Blood clots in a vein (thrombosis)

The risk of blood clots in the veins is about 1.3 to 3- times higher in HRT users than in non-users, especially during the first year of taking it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

You are more likely to get a blood clot in your veins as you get older and if any of the following applies to you. Inform your doctor if any of these situations applies to you:

- you are unable to walk for a long time because of major surgery, injury or illness
- you are seriously overweight (BMI >30 kg/m^2)
- you have any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots
- if any of your close relatives has ever had a blood clot in the leg, lung or another organ
- you have systemic lupus erythematosus (SLE)
- you have cancer.

For signs of a blood clot, see “Stop taking [invented name] and see a doctor immediately”.

Compare

Looking at women in their 50s who are not taking HRT, on average, over a 5-year period, 4 to 7 in 1000 would be expected to get a blood clot in a vein.

For women in their 50s who have been taking oestrogen-progestagen HRT for over 5 years, there will be 9 to 12 cases in 1000 users (i.e. 5 extra cases)

For women in their 50s who have had their womb removed and have been taking oestrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1000 users (i.e. 1 extra case).

Heart disease (heart attack)

There is no evidence that HRT will prevent a heart attack.

Women over the age of 60 years who use oestrogen-progestagen HRT are slightly more likely to develop heart disease than those not taking any HRT.

For women who have had their womb removed and are taking oestrogen-only therapy there is no increased risk of developing a heart disease.

Stroke

The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Compare

Looking at women in their 50s who are not taking HRT, on average, 8 in 1000 would be expected to have a stroke over a 5-year period. For women in their 50s who are taking HRT, there will be 11 cases in 1000 users, over 5 years (i.e. 3 extra cases).

Other conditions

HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Note

Cetyl stearyl alcohol can cause local skin irritation (e.g. contact dermatitis)

Do not use [invented name] immediately before sexual intercourse or as a lubricant, to prevent possible side effects in your partner.

Take special care when using [invented name] together with latex products (e.g. condoms, diaphragms), as it contains excipients (other ingredients, particularly stearates) which can reduce the functionality of such products, thereby making them less reliable.

If your vaginal skin is very vulnerable, be careful when inserting the applicator into the vagina.

Using other medicines

Interactions of [invented name] with other medicinal products were not investigated.

Pregnancy and the breast-feeding

[Invented name] is for use in postmenopausal women only. If you become pregnant, stop using [invented name] and contact your doctor. [Invented name] should not be used during breastfeeding.

Driving and using machines

No known effect.

3. How to use [invented name]

[The text below should be inserted in this section and any existed text should be deleted]

Always use [invented name] exactly according to the instructions given in this leaflet. You should check with your doctor or pharmacist if you are not sure.

Dosage instructions, method and duration of administration

The following information applies, unless you have been prescribed [invented name] otherwise by your doctor. You must always follow the directions for use; if not, [invented name] may not work properly.

How to use [invented name]

[invented name] is a cream for vaginal use.

The experience treating women older than 65 years is limited.

You can start using [invented name] on any day which is best for you.

[invented name] should be applied with an applicator.

Insert the contents of 1 filled applicator (= 2 g cream) before bedtime. During the first week of treatment, [invented name] should be applied every other day - i.e. at 48-hourly intervals - and twice a week thereafter (maintenance dose). The applicator should be cleaned with warm water each time after use. Treatment should not exceed 4 weeks. Do not use up any remaining content after completing treatment course.

[In this section the use of the cream with the applicator is inserted. This part of section 3 has not been modified during this procedure]

[…]

[The following text should be inserted after the section "Clean the applicator after use"]

In case the applicator is damaged you should not use it and inform the manufacturer.

How long should you go on using [invented name]?

[Invented name] should not be used for more than 4 weeks.

It is unknown whether prolonged treatment or repeated treatment courses will cause thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb (endometrial cancer). Therefore, prolonged treatment beyond 4 weeks is not recommended. If symptoms of vaginal atrophy persist beyond 4 weeks, alternative therapies should be considered. Please talk to your doctor.

If you get breakthrough bleeding or spotting, you should stop using [invented name]. Usually, it's nothing to worry about, but you should make an appointment to see your doctor.

If you use more [invented name] than you should

If you use too much [invented name] on one occasion, side effects such as nausea may occur. Talk to a doctor or pharmacist.

If you forget to use [invented name]

Do not use a double dose of [invented name] to make up for a forgotten single dose. Continue with your treatment as normal.

If you stop using [invented name]

Your doctor will explain the effects of stopping treatment and when to stop it. He or she will also discuss other possibilities for treatment with you.

4. Possible side effects

[The text below should be inserted in this section and any existed text should be deleted]

Like all medicines, [invented name] can cause side effects, although not everybody gets them.

The following categories are used to express the frequency of side effects:

Very common:	more than 1 in 10 patients treated
Common:	1 to 10 patients treated out of 100
Uncommon:	1 to 10 patients treated out of 1,000
Rare:	1 to 10 patients treated out of 10,000
Very rare:	less than 1 in 10,000 patients treated
Not known:	frequency cannot be estimated from the available data

Uncommon: temporarily mild local irritation (e.g. itching, burning) and slight discharge may occur.
Very rare: allergic reactions.

The following side effects can occur with oral and/or transdermal oestrogen treatment:

- Gall bladder disease
- Various skin disorders:
  - discoloration of the skin especially of the face or neck known as “pregnancy patches (chloasma)
  - painful reddish skin nodules (erythema nodosum)
  - rash with target-shaped reddening or sores (erythema multiforme)

Common
Depression, hair loss, joint pain, leg cramps, abnormal uterine bleeding, breast pain, breast tenderness, breast enlargement, breast discharge, weight increase or decrease, increased blood fats (triglycerides)

Uncommon
Vaginitis including infection of the genitals caused by a fungus, changes in sexual drive, mood disturbances, dizziness, headache, migraine, anxiety, intolerance to contact lenses, blood clots in a vein (thrombosis), nausea, bloating, abdominal pain, hirsutism, pruritus, rash, oedema

The following adverse events have also been associated with oral and/or transdermal oestrogen therapy:

- breast cancer
- endometrial hyperplasia and carcinoma
- ovarian cancer
- blood clots in the veins of the legs of lungs (venous thromboembolism)
- heart disease
- stroke
- probable memory loss if Hormone Replacement Therapy is started over the age of 65

For more information about these side effects, see Section 2

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse> . This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

[*For the printed material, please refer to the guidance of the annotated QRD template.]

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Part B. - 0.005 % w/w estradiol / 0.4 % w/w prednisolone containing medicinal products

[The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below]

I. Summary of Product Characteristics

Section 4.1 - Therapeutic indications

[The wording of the indication should be deleted and the text below should be inserted in its place]

For the initial short-term external treatment of acute, mild, inflamed, burning and itching skin diseases of the external female genital area for which weak acting corticosteroids and estradiol are indicated, in postmenopausal patients.

Section 4.2 Posology and method of administration

[The text below should be inserted by replacing the existing text in the relevant paragraph]

[invented name] (approximately 1 cm of cream) is thinly applied once daily with the fingers onto diseased skin areas of the external female genital area and then gently rubbed in.

The maximum dose is once daily.

[invented name] should not be applied intravaginally or on other parts of the internal genital area.

In most cases, [invented name] is used for 2-3 weeks. Application beyond 4 weeks is not recommended, due to potential systemic exposure to estradiol during treatment. In addition, due to the content of the corticosteroid prednisolone in [invented name] , skin atrophy might occur with prolonged use, further increasing systemic exposure to oestradiol.

[The text below should be deleted from this section]

The doctor will decide on the duration of treatment, and whether further treatment is needed with a corticosteroid-free, high-dose oestradiol cream or a cream with no active substances.

[The text below should be inserted in this section]

[invented name] should not be used in children or adolescents.

Section 4.3 Contraindications

[This section should have all of the following text]

[invented name] should not be used in the following cases:

- known hypersensitivity to oestradiol, prednisolone, cetyl stearyl alcohol or to any of the excipients of [invented name] .
- known or suspected benign or malignant oestrogen-dependent tumours e.g. uterine leiomyoma, endometrial cancer)
- history of malignant oestrogen-dependent tumours
- Unspecified genital bleeding
- Untreated endometrial hyperplasia
- Skin diseases in the external genital area caused by bacterial, fungal, or viral infections

Section 4.4 Special warnings and precautions for use

[The text below should be inserted in this section. The existing relevant text need to be modified accordingly]

Therapy with [invented name] should only be administered together with clinical monitoring. If unexpected genital bleeding occurs, treatment should be discontinued, the reason should be investigated which may include vaginal ultrasound investigation and endometrial biopsy to exclude endometrial hyperplasia or malignancy.

Unopposed oestrogen stimulation may lead to premalignant transformation in the residual foci of endometriosis. Therefore, caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

[The text below should be deleted from this section]

[invented name] may only be used with special caution, after a thorough clinical evaluation of the risks and benefits, in the following cases:

- history of malignant oestrogen-dependent tumours
- tumours of the womb (leiomyoma, uterine myoma).

Prolonged use of [invented name] over extensive areas may only proceed with special caution, after a thorough clinical evaluation of the risks and benefits, in cases of:

- endometriosis.

[The text below should be inserted in this section. The existing relevant text need to be modified accordingly]

[invented name] should not be used immediately prior to sexual intercourse or as a lubricant.

[The text below should be deleted from this section]

During prolonged use, vigilance is required for possible systemic effects. As a precaution, [invented name] may not be used in children or adolescents.

Section 4.5 Interaction with other medicinal products and other forms of interaction

[The text below should be inserted in this section]

There are no data available.

[The text below should be deleted from this section]

None known.

Section 4.8 Undesirable effects

[The text below should be inserted in this section. The existing relevant text need to be modified accordingly]

Vigilance is required for possible systemic side effects and skin atrophy. Especially prolonged use (>4 weeks) is therefore not recommended.

System organ class (MedDRA)	Uncommon (≥1/1,000 to <1/100)	Very rare (<1/10,000),
General disorders and administration site conditions	Transient, mild skin irritation (e.g. burning, erythema).	Hypersensitivity skin reaction (allergic contact eczema)
Reproductive system and breast disorders	Spotting	

[…]

[The text below should be inserted in this section.]

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

[*For the printed material, please refer to the guidance of the annotated QRD template.]

Section 5.1 Pharmacodynamic properties

[…]

Estradiol

[The text below should be inserted in this section. The existing relevant text need to be modified accordingly]

As an active substance, [invented name] contains 17ß-estradiol (0.005%). Estradiol is the most potent natural oestrogen to act intracellularly.

[The text below should be all deleted from this section]

As well as its typical hormonal effects during the reproductive period, higher concentrations of estradiol also exert characteristic effects on the skin. At around ≥ 0.01% topically or systemically, estradiol widens the capillary vessels and promotes general blood perfusion. Oestrogens stimulate epithelial cell proliferation in the genital area and urinary tract, as well as increasing collagen synthesis in the skin.

Similarly to other steroid hormones, estradiol acts directly on genetic information (DNA) via specific receptors following systemic administration. Thus, estradiol affects transcription (RNA synthesis) and therefore stimulates the synthesis of specific proteins. In addition, estradiol also has rapid, non-genomic effects (signal transduction).

[…]

Prednisolone

[The text below should be inserted in this section. The existing relevant text need to be modified accordingly]

According to the current, standard classification system for topical corticosteroids, i.e. weak (I), moderately potent (II), potent (III) and very potent (IV), prednisolone - closely related to natural hydrocortisone (= cortisol) - belongs to the first group. Thus, prednisolone is particularly suitable for the treatment of inflammatory dermatoses in problem areas, as it has weak anti-inflammatory, antiallergic and antipruritic properties.

Section 5.2 Pharmacokinetic properties

Estradiol

[The text below should be inserted in this section. The existing relevant text need to be modified accordingly]

No studies have been performed on the dermal absorption of oestradiol within the external female genital area from [invented name].

[…]

II. Package Leaflet

[The existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below]

1. WHAT [invented name] IS AND WHAT IT IS USED FOR

[invented name] is a medicine that contains oestradiol and prednisolone.

Therapeutic indications (areas of use):

[The wording of the indication should be deleted and the text below should be inserted in its place]

For the initial short-term external treatment of acute, mild, inflamed, burning and itching skin diseases of the external female genital area for which weak acting corticosteroids and estradiol are indicated, in women beyond menopause.

[The text below should be deleted]

Cream [invented name] is used in women for the treatment of atrophic vulva disorders attributable to oestrogen deficiency and for Lichen sclerosus (long-term itchy skin signs) on external genitals.

2. BEFORE YOU USE [invented name]

Do not use [invented name]

[This section should have all of the following text only]

- if you are known to be allergic (hypersensitive) to oestradiol, prednisolone, cetyl stearyl alcohol or any of the other ingredients of [invented name]
- if you have an benign or malignant tumour which is sensitive to oestrogens, such as fibroids inside your womb or uterine or cancer of the womb lining, or if you are suspected of having one
- if you have ever developed malignant tumours which are sensitive to oestrogens
- if you have any unexplained vaginal bleedings
- if you have an untreated endometrial hyperplasia (i.e. thickening of the lining of the womb)
- if you have skin diseases in the external genital area caused by bacterial, fungal or viral infections

Take special care with [invented name]

[The text below should be inserted in this section. The existing relevant text need to be modified accordingly]

- You should only use [invented name] under medical supervision. In particular, if you experience unexpected genital bleeding you must discontinue treatment with [invented name] and consult a doctor
- if you suffer or have suffered from endometriosis and have undergone hysterectomy (removal of the womb)
- when using [invented name] at the same time as latex products (e.g. condoms, diaphragms). This medicine contains inactive ingredients (especially stearates) that may reduce the functionality of these products, thereby making them less reliable.
- You should not use [invented name] immediately before sexual intercourse or as a lubricant.

[The text below should be deleted]

During prolonged use, you should look out for possible systemic effects (affecting the whole body).

As a precaution, [invented name] may not be used in children or adolescents.

[…]

3. HOW TO USE [invented name]

[…]

[The text below should be inserted in this section. The existing relevant text need to be modified accordingly]

[invented name] is thinly applied (a string of ointment about 1 cm long) to affected skin areas of the external female genital area once daily with the fingers and then gently rubbed in. [invented name] should not be applied intravaginally or on other parts of the internal genital area.

The maximum dose is once daily.

In most cases, [invented name] is used for 2-3 weeks. Its use beyond 4 weeks is not recommended.

[The text below should be deleted]

Your doctor will decide how long you should use the cream, and whether further treatment is needed with a corticosteroid-free but high-dose oestradiol cream, or a cream containing no active substances.

[The text below should be inserted]

[invented name] should not be used in children or adolescents.

[…]

4. POSSIBLE SIDE EFFECTS

[…]

[The text below should be deleted]

In prolonged use (beyond 4 weeks), you should look out for possible systemic side effects (e.g. chest pain) and skin atrophy.

[…]

[The text below should be inserted]

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects, you can help provide more information on the safety of this medicine.

[*For the printed material, please refer to the guidance of the annotated QRD template.]