SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Estradiol Besins Pump-Pack 750 micrograms/actuation Gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of gel contains 0.6 mg of the active ingredient, estradiol (0.06% w/w).

Each pump actuation delivers 1.25 g of gel which contains 0.75 mg of estradiol.

Excipients with known effect: Ethanol.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Transdermal gel.

A clear, colourless gel with an odour of alcohol.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Hormone replacement therapy (HRT) for oestrogen 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. (see also Section 4.4)

The experience treating women older than 65 years is limited.

4.2. Posology and method of administration

Posology

Estradiol Besins should be administered daily on a continuous basis.

Dosing in women without a uterus:

Estradiol Besins is an estrogen-only product particularly indicated for women without a uterus. Estradiol Besins should be administered daily on a continuous basis.
Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

Dosing in women with an intact uterus:

In women with a uterus, consideration should be given to the addition of a progestogen including progesterone for at least 12 to 14 days every month / 28-day cycle to reduce the risk of endometrial hyperplasia and carcinoma. Estradiol Besins should be administered daily on a continuous sequential basis.

Menopausal and postmenopausal symptoms:

Each metered dose (1 pump actuation) from the dispenser is 1.25 g of Estradiol Besins. Two pumps (2.5 g) of Estradiol Besins once daily (1.5 mg estradiol) is the usual starting dose, which in the majority of women will provide effective relief of symptoms. If after one month's treatment effective relief is not obtained, the dosage may be increased accordingly to a maximum of four pumps (5 g) of Estradiol Besins daily (3.0 mg estradiol).
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.

Initiation of treatment:

Women who have never taken HRT and are post-menopausal or have very infrequent menstrual cycles:

- Treatment with Estradiol Besins can be started on any day.

Switching from a continuous oestrogen-progestogen combined HRT:

- Treatment with Estradiol Besins can be started on any day of the cycle.

Switching from a cyclic or continuous sequential HRT treatment:

- Finish the therapeutic sequence before beginning treatment with Estradiol Besins.

Postmenopausal osteoporosis:

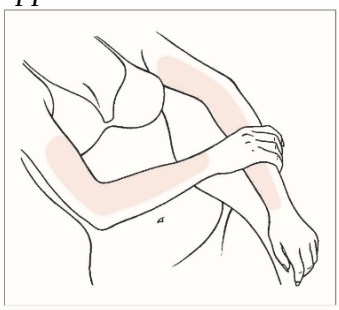
- The usual dose is two actuations (2.5 g of gel, which contains 1.5 mg estradiol) once daily. The lowest effective dose for the prevention of osteoporosis is not known.

<u>Method of Administration</u>

For local cutaneous use:
Before using a new pump pack, it will require priming; the first dose of gel dispensed should be discarded.
The gel should be applied by the patient herself, not by anyone else, and skin contact, particularly with a male partner, should be avoided for one hour after application.
Wash hands with soap and water after applying the gel.

Washing the skin or contact with other skin products should be avoided until at least one hour after application of Estradiol Besins.
Secondary exposure to estradiol can potentially occur as a result of passive transfer following skin-to-skin contact. Patients should be informed that others, especially children, should not come in contact with the area of the body where Estradiol Besins was applied on (see section 4.4).
The gel dose should be dispensed and applied to clean, dry, intact areas of skin *e.g.* on the arms and shoulders, or inner thighs. A thin layer of the gel should be applied to the entire arm on the inside and outside from wrist to shoulder or inner thigh. The area of application should be as large as possible
Estradiol Besins should **NOT** be applied on or near the breasts or on the vulval region. A frequent change in application sites is recommended.

Application Areas:



Arms from wrist to shoulder *Inner thighs*

Estradiol Besins must be allowed to dry for 5 minutes before covering the skin with clothing.
If the patient forgets to apply a dose and it is more than 12 hours until the next dose, the missed dose should be applied and normal dosing resumed the next day. If the next dose is less than 12 hours away, it is best just to wait and apply the next dose normally.
Forgetting a dose may increase the likelihood of break-through bleeding and spotting.
Patients should be advised not to apply two doses at the same time.
Elderly People
As for adults. The experience treating women older than 65 years is limited.
Paediatric population
There is no relevant use of Estradiol Besins in children aged less than 12 years.

4.3. Contra-indications

- Known hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- 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 (*e.g.* 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;
- Porphyria

4.4. Special warnings and precautions for use

This medicine is for external use only and should not therefore be swallowed. Care should be taken to ensure cleanliness of the skin and hands during application.

Do not apply to damaged skin.

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 and 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 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 "Breast 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 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 Besins, 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 (SLE)
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered (see Section 4.3) and in the following situations:

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

Warnings:

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 progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestogen 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 progestogens 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 shows an increased risk of breast cancer in women taking combined oestrogen-progestogen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen therapy

The randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see Section 4.8).

Oestrogen-only therapy

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 lower than that found in users of oestrogen-progestogen combinations (see section 4.8).

Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the

duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more.
HRT, especially oestrogen-progestogen 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. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women oestrogen-only or combined oestrogen-progestogen HRT which becomes apparent within 5 years of use and diminishes over time after stopping.
Some other studies, including the WHI trial suggest that use of combined HRTs may be associated with 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 recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30kg/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 (*e.g.* painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary Artery Disease (CAD)

There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen- progestogen or oestrogen-only HRT.
Oestrogen-only:
Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.
Combined oestrogen-progestogen therapy:
The relative risk of CAD during use of combined oestrogen+progestogen 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+progestogen use is very low in healthy women close to menopause, but will rise with more advanced age.

Ischaemic Stroke

Combined oestrogen-progestogen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischemic 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).

Potential Estradiol Besins transfer to children

Estradiol Besins can be accidentally transferred to children from the area of the skin where it was applied on.

Post-marketing reports of breast budding and breast masses in prepubertal females, precocious puberty, gynaecomastia and breast masses in prepubertal males following unintentional secondary exposure to estradiol gel have been reported. In most cases, the condition resolved with removal of estradiol exposure.

Patients should be instructed:

- not to allow others, especially children, to come into contact with the exposed area of the skin and to cover the application site with clothing if needed. In case of contact the child's skin should be washed with soap and water as soon as possible.
- to consult a physician in case of signs and symptoms (breast development or other sexual changes) in a child that may have been exposed accidentally to Estradiol Besins.

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.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

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 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.

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and without ribavirin, ALT elevations greater than 5 times the upper limit of normal

(ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. See section 4.5.

Precautions:

This medicine contains 0.5 g alcohol (ethanol) in each dose of 1.25 g gel.
It may cause burning sensation on damaged skin.
This product is flammable until dry.

4.5. Interactions with other medicinal products and other forms of interaction

Treatment with surface active agents (*e.g.* sodium lauryl sulphate), or other drugs which alter barrier structure or function, could remove drug bound to the skin, altering transdermal flux. Therefore, patients should avoid the use of strong skin cleansers and detergents (*e.g.* benzalkonium or benzothonium chloride products), skin care products of high alcoholic content (astringents, sunscreens) and keratolytics (*e.g.* salicylic acid, lactic acid).
The use of any concomitant skin medication which alters skin production (*e.g.* cytotoxic drugs) should be avoided.
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.
At transdermal administration, the first-pass effect in the liver is avoided and thus, transdermally applied oestrogens HRT might be less affected than oral hormones by enzyme inducers.
Clinically, an increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in the uterine bleeding profile.

Effect of HRT with oestrogens on other medicinal products

Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as

CHCs. Additionally, also with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin,glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4)
At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens HRT might be less affected than oral hormones by enzyme inducers.

4.6. Fertility, pregnancy and lactation

Pregnancy

Estradiol Besins is not indicated during pregnancy. Pregnancy should be excluded before initiating HRT. If pregnancy occurs during medication with Estradiol Besins, treatments should be withdrawn immediately.
The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic of foetotoxic effects.

Lactation

Estradiol Besins is not indicated during lactation.

Fertility

Not relevant

4.7. Effects on ability to drive and use machines

Estradiol Besins has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable Effects

Undesirable effects are generally mild and rarely require treatment withdrawal. Undesirable effects, if any, usually occur during the first months of treatment.
Adverse effects have been ranked under headings of frequency using the following convention: very common (≥ 1/10); common (≥ 1/100; ≤ 1/10); uncommon (≥ 1/1,000; ≤ 1/100); rare (≥ 1/10,000; ≤ 1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data).

Table 1: Adverse Reaction Tabulation based on the Frequency Report for Estradiol total spontaneous cumulative

MeDRA Term	Frequency calculations based on the Frequency Report for Estradiol total spontaneous cumulative ADRs: 20,193 ADR Frequency report - 01/01/1900 - 07/31/2023					
Organ System Class	Adverse reactions – preferred terms					
	Very Common (≥10) (No adverse	Common (≥1/100, <1/10)	Uncommon (≥1/1000, <1/100)	Rare (≥1/10000 to ≤1/1000)	Very rare (<1/10,000)	Frequency not known (No adverse reactions

	reactions noted for this frequency)					noted for this frequency)
Metabolism and nutrition disorders				Glucose intolerance		
Psychiatric disorders			Depression, Mood swings	Change in libido		
Nervous system disorders		Headache	Vertigo, migraine	Aggravation of epilepsy		
Gastrointestinal disorders		Nausea, abdominal pain	Flatulence, vomiting			
Eye disorders					Contact lens intolerance	
Vascular disorders			Venous thromboembolic disease	Arterial hypertension		
Hepatobiliary disorders				Liver function test abnormalities, cholestasis and jaundice		
Skin and subcutaneous tissue disorders			Pruritus	Skin discolouration, acne		
Musculoskeletal and connective tissue disorders				Bone pain		
Reproductive system and breast disorders		Breast swelling/pain, breast enlargement,	increased volume of uterine fibroids,			

		dysmenorrhoea, menorrhagia, metrorrhagia, leucorrhoea discharge, endometrial hyperplasia	leiomyoma, vaginitis/vaginal candidiasis			
General disorders and administration site conditions		Weight change (increase or decrease), water retention with peripheral oedema	Asthenia	Anaphylactic reaction (in women a history of allergic reaction)		

Breast cancer risk

- 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.
- The increased risk in users of oestrogen-only therapy is 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).
- Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented.

Largest meta-analysis of prospective epidemiological studies
Estimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years) *	Risk ratio	Additional cases per 1000 HRT users after 5 years
		Oestrogen only HRT	
50	13.3	1.2	2.7
		Combined oestrogen-progestogen	
50	13.3	1.6	8.0

*: Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2).
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years) *	Risk ratio	Additional cases per 1000 HRT Users after 10 years
Oestrogen only HRT			
50	26.6	1.3	7.1
		Combined oestrogen-progestagen	
50	26.6	1.8	20.8

*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m2).
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 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) *
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 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.

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with a 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 progestogen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study (MWS) 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

Use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who

are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

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 combined - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT 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

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

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 in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT 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*			

The following adverse reactions have also been reported in association with systemic oestrogen/ progestogen treatment:

- Rash
- Chloasma/ melasma
- Vomiting

- Abdominal pain
- Breast tenderness
- Breast enlargement
- Fluid retention/ oedema
- Weight changes
- Changes in libido
- Depression
- Gall bladder disease
- Probable dementia over the age of 65 (see section 4.4)
- Skin and subcutaneous disorders: erythema multiforme, erythema nodosum, vascular purpura

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 Yellow Card Scheme, website www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Overdosage is unlikely with transdermal applications.

Overdoses of oestrogen may cause breast tenderness, nausea and withdrawal bleeding. These signs disappear when the treatment is stopped or when the dose is reduced.

Treatment

There are no specific antidotes and treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system - natural and semisynthetic oestrogens, plain.

ATC Code: G03CA03.

The onset of menopause results from a decline in the secretion of oestradiol and other oestrogens by the ovary resulting initially in the cessation of menstruation, followed by menopausal symptoms such as vasomotor symptoms (hot flushes and sweating),

muscle cramps, myalgias, arthralgias, anxiety, atrophic vaginitis and kraurosis vulvae. Oestrogens are also an important factor in preventing bone loss and after the menopause women lose bone mineral content at an average rate of 15-20% in a ten year period.

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

Clinical trial information

- Relief of oestrogen deficiency symptoms and bleeding patterns

Relief of menopausal symptoms was achieved during the first few weeks of treatment. The rate of regular withdrawal bleeding or amenorrhoea depends on the individual posology and may vary on the individual patient.

- Prevention of osteoporosis

- Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass.
- The effect of oestrogens on the 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 similar rate 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 this is limited.

5.2 Pharmacokinetic properties

Absorption

Pharmacokinetic studies indicate that, when applied topically to a large area of skin in a volatile solvent, approximately 10% of the estradiol is percutaneously absorbed into the vascular system, regardless of the age of the patient.

Distribution

Daily application of 2.5 g or 5 g oestradiol over a surface area of 400-750 cm2 results in a gradual increase in oestrogen blood levels to steady state after approximately 3-5 days and provides circulating levels of both estradiol and estrone equivalent in

absolute concentrations and in their respective ratio to those obtained during the early-mid follicular phase of the menstrual cycle.

Estradiol was administered to 17 postmenopausal women once daily on the posterior surface of one arm from wrist to shoulder for 14 consecutive days.

Maximum serum concentrations (Cmax) of estradiol and estrone on Day 12 were 117 pg/ml and 128 pg/ml, respectively.

The time-averaged serum estradiol and estrone concentrations (Caverage) over the 24hour dose interval after administration of 2.5 g of Estradiol Besins l on Day 12 were 76.8 pg/ml and 95.7 pg/ml, respectively.

Biotransformation

Metabolism of estradiol takes place mainly in the liver under oestriol, estrone and their conjugated metabolites (glucuronides, sulphates). These metabolites also undergo enterohepatic recirculation.

When treatment is stopped, estradiol and urinary conjugated estradiol concentrations return to baseline in about 76 hours.

Elimination

Oestriol is the major urinary estradiol metabolite. However, glucuronide and sulphate metabolites of estradiol and oestrone are also found in urine and bile. Metabolites excreted in bile undergo enterohepatic recirculation or are excreted in the faeces.

5.3 Preclinical safety data

Nonclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

-Ethanol

-Carbomer

-Trolamine

-Purified water

6.2 Incompatibilities

Not known.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Metering canister composed of a polypropylene bottle, a LDPE pouch, a polypropylene metering pump and closed with a polypropylene cap, containing 80 g of gel.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Besins Healthcare UK Limited

Lion Court, 25 Procter Street

Holborn, London

WC1V 6NY

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 42714/0008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/04/2024

10 DATE OF REVISION OF THE TEXT

19/01/2026