Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Oestrogel 0.60 mg/g metered dose Gel Pump Pack

2. Qualitative and quantitative composition
The active substance is estradiol hemihydrate.

Excipients with known effect:Ethanol

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Gel

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
The dosage varies according to individual need.

For the treatment of postmenopausal symptoms, the minimum effective dose of 1.25 g of gel per day(= 0.75 mg of estradiol) should be recommended for 21 to 28 days per month. As the dose varies according to need, the mean dose is 2.5 g of gel per day. For initiation and continuation of treatment of menopausal symptoms, the lowest effective dose should be used for the shortest possible time (see also section 4.4).

In women with an intact uterus, continuous oestrogen treatment without progesterone cover is not recommended because of the risks to the endometrium (cystic glandular hyperplasia, dysplasia with increased risk of endometrial cancer). Treatment must be continued for at least three consecutive weeks followed by withdrawal for one week in combination with an oral progesterone for 12 to 14 days per month/28-day cycle. Treatment may be applied from day 1 to day 25 of the month in combination with an oral progesterone if necessary. Withdrawal bleeding may occur during the treatment withdrawal week.

Only progestagens authorised in combination with an oestrogen arerecommended.

Method of Administration
Transdermal route.

The pump pack will require priming before using a new pump pack for the first time. The first dose dispensed should be discarded.

The correct dose of gel should be dispensed and applied to clean, dry, intact areas of skin e.g. on the arms and shoulders, or inner thighs.The area of application should be as large as possible at least 750cm2.

One pump actuation from the dispenser, or half the prescribed dose, should be applied to each arm/shoulder (or thigh).

Oestrogel should NOT be applied on or near the breasts or on the vulval region. Oestrogel should be allowed to dry for 5 minutes before covering the skin with clothing.

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 Oestrogel.

4.3 Contraindications

• Known, past or suspected breast cancer;
• Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer);
• Undiagnosed genital bleeding;
• Untreated endometrial hyperplasia;
• Previous or current idiopathic venous thromboembolism (e.g. deep vein 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;
• Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.;
• Porphyria.

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.
Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination and follow-up:
Before initiating or reinstituting hormone replacement therapy (HRT), a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see '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 Oestrogel, in particular:
• leiomyoma (uterine fibroids) or endometriosis;
• risk factors for thromboembolic disorders (see below);
• risk factors for oestrogen dependent tumors (e.g. 1st degree heredity for breast cancer);
• hypertension;
• liver function 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 if a contraindication is discovered and in the following situations:
• jaundice or deterioration in liver function;
• significant increase in blood pressure;
• new episode of migraine-type headache;
• pregnancy.

Endometrial hyperplasia and carcinoma:

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (see section 4.8). After stopping treatment risk may remain elevated for at least 10 years.
- The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.
- Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.
- Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis.

Breast cancer:
The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestagen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

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

Ischaemic stroke

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

Other conditions

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

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

- Exogenous oestrogens 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-1-antitrypsin, ceruloplasmin).

- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should minimise exposure to the sun or ultraviolet radiation whilst taking HRT.

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

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, 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.

When co-administered with sex hormones, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors including combinations with HCV inhibitors, can increase or decrease plasma concentrations of oestrogen. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant medications including HIV/HCV antivirals should be consulted to identify potential interactions and any related recommendations.

Herbal preparations containing St. John's wort (Hypericum perforatum) may induce the metabolism of oestrogens.

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

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

4.6 Pregnancy and Lactation

Pregnancy

Oestrogel is not indicated during pregnancy. If pregnancy occurs or is suspected, treatment should be withdrawn immediately.

The results of most epidemiological studies to date indicate no teratogenic of foetotoxic effects in pregnant women inadvertently exposed

Breastfeeding

This medicinal product is not indicated during breast-feeding.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The table below reproduces all the adverse drug reactions, and specifically those observed in at most 10% of patients.

Organ system	**Common adverse drug reactions (≥ 1/100, < 1/10)**	**Uncommon adverse drug reactions (≥ 1/1,000, < 1/100)**
Psychiatric disorders	Nervousness, depression	
Nervous system disorders	Headache	Migraine, dizziness, drowsiness
Vascular disorders		Superficial or deep vein thrombosis, thrombophlebitis
Gastrointestinal disorders	Abdominal pain, abdominal cramps, abdominal distension, nausea, vomiting	
Hepatobiliary disorders		Liver function test abnormalities, hepatic adenomas, cholelithiasis
Skin and subcutaneous tissue disorders		Skin rash, pruritus, chloasma
Musculoskeletal and connective	Muscle cramps, pain in the limbs	Arthralgia

tissue disorders		
Reproductive organ and breast disorders	Dysmenorrhoea, menorraghia, bleeding (spotting), menstrual disorders, leucorrhoea	Benign breast tumour, uterine polyp, increase in size of uterine fibroids, endometriosis, mastodynia, exacerbation of oestrogen-dependent tumours
General disorders and administration site conditions		Peripheral oedema, sodium retention, sensation of distension, weight change

Breast cancer risk

• An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.

• Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.

• The level of risk is dependent on the duration of use (see section 4.4).

• Results of the largest randomised placebo-controlled trial (WHI study) and largest epidemiological study (MWS) are presented below.

MWS (Million Women Study) – Estimated additional risk of breast cancer after 5 years' use

Age range (years)	Additional cases per 1000 never-users of HRT over 5 years*	Relative risk with 95% CI	Additional cases per 1000 HRT users over 5 years (95% CI)
Oestrogen-only HRT			

50-65	9-12	1.2	1-2 (0-3)
Combined oestrogen-progestagen			

HRT			
50-65	9-12	1.7	6 (5-7)

* Taken from baseline incidence rates in developed countries.
# Overall relative risk. The relative risk is not constant but increases with increasing duration of use.
Note: Since the baseline incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

United States WHI studies – additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Relative risk with 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-progestagen‡			
50-79	17	1.2 (1.0-1.5)	+4 (0-9)

* In hysterectomised women, the WHI study showed an increased risk of breast cancer.
*In women with no uterus, the WHI study did not show an increased 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 nonusers

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

Ovarian cancer

Long-term use of oestrogen-only and combined oestrogen-progestagen HRT has been associated with a slightly increased risk of ovarian cancer (see section 4.4). A meta-analysis of 52 epidemiological studies revealed an increased risk of ovarian cancer in women currently using HRT compared with never-users of HRT (RR 1.43, 95% CI: 1.31 to 1.56). For women aged between 50 and 54 years intake of HRT for 5 years is reflected in one extra case per 2000 users. In women aged 50 to 54 years not taking HRT, 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- to 3-fold increased relative risk of 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 HRT (see section 4.4). Results of the WHI studies are presented below:

WHI studies – additional risk of venous thromboembolism over 5 years' of use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Relative risk with 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-			

progestagen			
50-59	4	2.3 (1.2-4.3)	5 (1-13)
* Study in hysterectomised women			

Risk of coronary artery disease

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

Risk of ischaemic stroke

• The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5-fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

• This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4

All WHI studies combined – additional risk of ischaemic stroke*over 5 years' use

Age (years)	Incidence per 1000 women in placebo arm over 5 years	Relative risk with 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			

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

4.9 Overdose

Breast tension, bleeding or nervousness may constitute signs of overdose, which will generally disappear when the amount of gel applied is reduced.

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.

Mechanism of action

Oestrogel belongs to the group of natural physiological oestrogens. The active substance is chemically and biologically identical to endogenous human estradiol. It allows systemic administration of 17ß-estradiol by application to intact skin. It substitutes for the loss of oestrogen production in menopausal or ovariectomised women and alleviates menopausal symptoms. Oestrogens prevent bone loss following menopause or ovariectomy.

Oestrogens form a complex with a specific receptor that primarily stimulates DNA and protein synthesis at the intracellular level; they exert their metabolic effects on the "target" organs. The most active oestrogen at the receptor level is estradiol, which is produced predominantly by the ovarian follicles, from menarche to menopause. Oestrogel will therefore exert an oestrogenic effect on the main "target" organs – not only the ovaries, endometrium and breasts, but also the hypothalamus, pituitary, vagina, urethra and liver – similar to that usually observed in the follicular phase.

Clinical trial information
Relief of menopausal symptoms:
• Relief of menopausal symptoms was achieved during the first few weeks of treatment.
• The profile of withdrawal bleeding or rate of amenorrhoea depends on the individual oestrogen-progestagen dosage regime.

5.2 Pharmacokinetic properties

Absorption
Estradiol is metabolized by the p450NF family of enzymes. Cutaneous penetration of estradiol through the skin accounts for about 10% of the administered dose. Transdermal oestrogens are well absorbed through the skin. Because the oestrogens bypass the liver, transdermal oestrogens have been shown to have less oestrogen-induced liver effects on renin substrate, thyroxine binding globulin, sex hormone binding globulin, cortisol binding globulin, and lipid profile.
Serum estradiol concentrations were determined experimentally 24 hours after daily application of 2.5g or 5 g of gel over 750 cm^2 of skin: they reach on average 75 pg/ml and 98 pg/ml, respectively (interindividual variability from min. 42 to max. 122 pg/ml for 2.5 g of gel and from min. 67 to max.160 pg/ml for 5 g of gel). On average, these levels remained stable and comparable for 72 hours after a daily application of gel and even for six consecutive cycles in other experiments.

Blood estradiol levels remain constant in the same patient, even after an interval of several months (intraindividual variation of the order of 11%). Percutaneous administration of estradiol avoids the first pass in the liver: a physiological ratio of circulating E2 and E1 levels ranging between 0.78 and 0.97, and therefore close to unity, is maintained and is comparable to that observed before menopause.When treatment is stopped, serum levels and urinary conjugated estradiol concentrations return to baseline in about 76 hours.

Distribution
The volume of distribution at steady state was 73 ± 24 l for micronized estradiol. Volume of distribution was derived after intravenous administration of estradiol. Oestrogens are highly protein bound. Although some oestrogens are loosely bound to albumin, the majority of estradiol is tightly bound to sex hormone binding globulins. The binding affinity constants with sex hormone binding globulins is 0.29 for estradiol and 0.07 for estrone.
The quantities of estradiol delivered into the blood per 24 hours after daily cutaneous application of 2.5 g and 5 g of gel are of the order of 75 µg/day and 100 µg/day, respectively.

Biotransformation
The plasma elimination half-life of estradiol is about an hour. The plasma clearance rate of its metabolites ranges from 650 to 900 litres/day/m^2. Metabolism of estradiol takes place mainly in the liver in the form of oestriol, estrone and their conjugated metabolites (glucuronides, sulphates);

Elimination
Glucuronides and sulphates conjugated metabolites are markedly less active and are largely eliminated in the form of glucuronides and sulphates. The metabolites also undergo enterohepatic recirculation.

Linearity/non-linearity
During the first hours following application of the gel (between 2 and 12 hours), estradiol levels reach values directly proportional to the size of the dose and the application area.

5.3 Preclinical safety data
Data not supplied

6. Pharmaceutical Particulars
6.1 List of Excipients
Ethanol, Carbomer, Triethanolamine, Purified Water.
6.2 Incompatibilities
Not applicable.

6.3 Shelf-Life
3 years

6.4 Special Precautions for storage

Do not store above 25 °C.

6.5 Nature and Content of container

• bottle of 80 g, 2 x 80 g, 3 x 80 g fitted with a metering valve to deliver 1.25 g of gel
containing 0.75 mg 17β-estradiol.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

OESTROGEL must be applied:

• By the woman herself,

• In the evening or morning, preferably after washing, at the same time each day.

If the consistency remains sticky for more than three minutes after application, this means that an insufficient area of skin has been covered. Consider spreading the gel over a wider area on the next application.

7. Marketing Authorization Holder

BESINS HEALTHCARE SA
Avenue Louise, 287
1050 Brussels
BELGIUM

8. Marketing Authorization Number

CTD8112

9. Date of first authorization/renewal of the authorization

25/10/2023

10. Date of revision of the text

05/05/2025