# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Oestrogel 0.60 mg/g metered dose Gel Pump Pack

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One gram of gel contains 0.6 mg of the active ingredient, Estradiol (0.06% w/w).
The active substance is estradiol hemihydrate.
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 or ovariectomised women: vasomotor disorders (hot flushes, night sweats), urogenital atrophic changes (vulvovaginal atrophy, dyspareunia, urinary incontinence) and psychiatric disorders (sleep disturbances, asthenia)

- Prevention of osteoporosis in menopausal women at high risk of fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis.

- 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 are recommended.

In women without a uterus, continuous oestrogen-only treatment is indicated in those who have been hysterectomised or if pronounced oestrogen deficiency symptoms recur on the withdrawal of treatment. In this last case, progesterone may be administered for the first 12 to 14 days of each month.

Unless endometriosis has been diagnosed previously, it is not recommended to combine a progestagen in hysterectomised women.
The dosage will be readjusted after 2 or 3 cycles of treatment, if necessary, depending on the clinical symptoms, i.e.:

- Reduced dose in the event of signs of hyperoestrogenism such as breast tension, abdominal or pelvic swelling, anxiety, nervousness, aggressiveness.
- Increased dose in the event of signs of hypoestrogenism, such as

persistence of hot flushes, vaginal dryness, headache and sleep disturbances, asthenia, depressive tendency.

If you forget a dose, do not double the dose the following day to make up for the missed dose. If your next dose is due within the next 12 hours, wait for the time of the next application. If your next dose is due in more than 12 hours, apply the missing dose immediately and apply the next dose at the usual time. Forgetting a dose may increase the likelihood of spotting or bleeding.

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 750 cm2.

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.

<u>Medical examination and follow-up</u>:

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 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 examinations, 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 tumours (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

When administered concomitantly with a progestagen, the potential contraindications of the latter should be considered: pregnancy for androgenic progestagens, breast, ovarian or endometrial carcinoma for oestrogenic progestagens.

Caution should be exercised in the presence of risks for cardiovascular, coronary artery and/or cerebrovascular diseases, which are increased in the event of hypertension and/or smoking.

The observation of a change on breast palpation requires an additional gynaecological examination at any time during treatment. Similarly, the doctor should be consulted in the event of irregular vaginal blood loss (outside the monthly treatment withdrawal period), headache and visual disorders, painful swelling of the lower limbs or abdominal pain.

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 the 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, the risk may remain elevated for at least 10 years.

- The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.
- Break-through bleeding and spotting may occur during the first months of treatment. If break-through bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated, which may involve an 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 a progestagen to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis if they are known to have residual foci of endometriosis.

Breast cancer:

The overall evidence suggests an increased risk of breast cancer in women taking combined oestrogen- progestagen and possibly also oestrogen-only HRT that is dependent on the duration of taking HRT.

*Combined oestrogen-progestagen therapy*

The randomised placebo-controlled trial, the *Women's Health Initiative* (WHI), and epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen that becomes apparent after about 3 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 substantially lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

This excess risk becomes apparent within a few years of use but returns to baseline within a few (at most five) years after stopping treatment.

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

**Ovarian cancer:**

Ovarian cancer is much rarer than breast cancer. The epidemiological evidence from a large meta- analysis suggest a slightly increased risk in women on oestrogen-only HRT or as combined oestrogen- progestagen therapy, which becomes apparent within 5 years of use and decreases over time after stopping.

Other studies, including the WHI trial, seem to suggest that the use of combined HRTs may confer a similar, or slightly smaller, risk (see section 4.8).

**Venous thromboembolism:**

HRT is associated with a 1.3- to 3-fold increased 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 abnormalities are exposed to 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.

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 patient 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 of the patient 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 ratio of use of HRT.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctor immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

<u>Coronary artery disease:</u>

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

*Combined oestrogen-progestagen therapy*

The relative risk of coronary artery disease during use of combined oestrogen + progestagen HRT is slightly increased. As the baseline absolute risk of coronary artery disease is strongly dependent on age, the number of extra cases of coronary artery disease due to oestrogen + progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

*Oestrogen-only treatment*

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

**Ischemic stroke**

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

Other conditions:

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

• Women with pre-existing 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.

• Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by PBI (protein-bound iodine), T4 levels (measured by column or by radioimmunoassay) or T3 levels (measured by radioimmunoassay). 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).

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

## 4.5. Interaction with other medicinal products and other forms of interaction

Oestrogel does not cause excessive hepatic enzyme stimulation at the usual doses: it exerts no deleterious effect on the lipid balance, coagulation factors (fibrinogen, antithrombin III activity), circulating levels of renin substrate or sex hormone-binding globulins; it therefore does not exert a hypertriglyceridaemic, diabetogenic or hypertensive effect.

Conversely, the metabolism of oestrogens may be increased by concomitant use of enzyme inducers, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine, meprobamate, phenylbutazone) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong enzyme inhibitors, exhibit inducing properties when used concomitantly with steroid hormones.

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

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

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

**4.6. Fertility, pregnancy and lactation** **Pregnancy**

Oestrogel is not indicated during pregnancy. If pregnancy occurs or is suspected, treatment should be withdrawn immediately. Threatened abortion and suppression of breast-feeding do not constitute indications for oestrogen therapy.

The results of most epidemiological studies to date re indicate no teratogenic of foetotoxic effects in pregnant women inadvertently exposed to therapeutic doses of oestrogens.

**Breast-feeding**

This medicinal product is not indicated during breast-feeding.

**Fertility**

Oestrogel is not indicated in fertility given the indication for HRT in menopausal women.

## 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 tissue disorders | Muscle cramps, pain in the limbs | Arthralgia |
| 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 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 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 | | | |

The following adverse reactions have been reported in association with oestrogen/progestagen treatment:
– gallbladder disease;
– skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura;
– probable dementia over the age of 65 (see section 4.4).

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

### 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: OESTROGENS (genitourinary system and sex hormones), 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.

Transdermal administration of OESTROGEL avoids the "hepatic first-pass" effect responsible for the increased synthesis of angiotensinogen, VLDL lipoproteins (triglycerides) and certain coagulation factors.

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.

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 progestagen – given to predominantly healthy women –, reduces the risk of hip, vertebral and other osteoporotic fractures. HRT may also prevent the risk of fractures in women with low bone density and/or established osteoporosis, but the evidence for this is limited.

  After 2 years of treatment with 2.5g of Oestrogel, the increase in lumbar spine bone mineral density (BMD) was between 1.2 ± 0.5 % and 5.6 ± 2.9% (mean ± SD). After three years of treatment with 2.5 g of Oestrogel, the increase in lumbar spine bone mineral density (BMD) was between 1.2 ± 0.9 %/year and 4.7 ± 3.2 %. This change in BMD was similar to that shown with oral Conjugated Equine Estrogens at the daily dose of 0.625mg/day. The percentage of women who maintained or gained BMD in lumbar zone during treatment was 90%. Oestrogel also had an effect on hip BMD. A significant loss of 1.3 ± 0.3 %/year was observed at the proximal femur in the control-estriol group whereas no significant change was observed in the Oestrogel arm. The difference between both groups was significant ($P<0.05$).

## 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 2.5 g 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/m². 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 metabolitesare 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**

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.

**5.4. List of excipients**

Ethanol, Carbomer, Triethanolamine, Purified Water.

**5.5. Incompatibilities**

Not applicable.

**5.6. Shelf life**

3 years

**5.7. Special precautions for storage**

Do not store above 25$^0$ C

**5.8. Nature and contents 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.

### 5.9. Special precautions for disposal and 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.

## 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 AUTHORISATION HOLDER

BESINS HEALTHCARE SA
Avenue Louise, 287
1050 Brussels
BELGIUM

## 8. MARKETING AUTHORISATION NUMBER(S)

CTD8112

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