

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oestrogel 750 micrograms/metered dose Gel Pump-Pack.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each metered dose contains 750 micrograms Estradiol (as hemihydrate)

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Gel.

A colourless, transparent gel with an alcoholic odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Prevention of osteoporosis in postmenopausal women considered at risk of developing fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis (see section 4.4).

Oestrogel is indicated for women with or without a uterus. Advice on the addition of a progestogen is given in section 4.2 for women with a uterus.

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Posology

Oestrogel is an oestrogen-only product indicated only for women without a uterus.

Oestrogel should be administered daily on a continuous basis.

In women with an intact uterus it is recommended to add a progestogen (e.g. a progesterone) for at least 12 days of each month, in accordance with the manufacturers recommendations.

Menopausal and postmenopausal symptoms:

Each measure from the dispenser is 1.25g of Oestrogel. Two measures (2.5g) of Oestrogel once daily (1.5mg 17 β -oestradiol) 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 measures (5g) of Oestrogel daily (3.0mg 17 β -oestradiol). The lowest effective dose should be used for maintenance therapy.

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.

Postmenopausal osteoporosis:

The minimum effective dose is 2.5g of Oestrogel once daily for most patients.

Use with Progestogen:

In women with an intact uterus the recommended dose of progestogen should be administered for 12 days of each month, in accordance with the manufacturers recommendations. Oestrogel should be administered daily on a continuous sequential basis.

Unless there is a previous diagnosis of endometriosis, it is not recommended to add progestogen in hysterectomised women.

Initiation of treatment:

Women who have never taken HRT and have regular menstrual cycles: treatment with Oestrogel can be started within 5 days of start of bleed.

Women who have never taken HRT and are post-menopausal or have very infrequent menstrual cycles: treatment with Oestrogel can be started on any day.

Switching from a continuous oestrogen-progestogen combined HRT: treatment with Oestrogel 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 Oestrogel.

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 at least 750cm^2 , twice the area of the template provided. One measure 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. A frequent change in application sites is recommended.

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.

Washing the skin or contact with other skin products should be avoided until at least one hour after application of Oestrogel.

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.

Patients should be advised not to apply two doses at the same time.

Forgetting a dose may increase the likelihood of break-through bleeding and spotting.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;
- Known hypersensitivity to the active substances or to any of the excipients;
- Porphyria

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 benefits outweigh the risks.

Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination / follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including appropriate imaging tools, e.g. mammography, should be carried out in accordance with currently accepted practices, modified to the clinical needs to 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 disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy

Treatment should be discontinued where a contra-indication is discovered and if the following occur:

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

Endometrial hyperplasia and carcinoma

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

The addition of a 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 suggests an increased risk of breast cancer in women taking combined oestrogen-progestogen and possibly also 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 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 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-progestogen combinations (see section 4.8).

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

HRT, especially oestrogen-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 taking 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/m²), 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 to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with 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 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, dyspnea).

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.

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.

Oestrogen-only

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

Ischaemic stroke

Combined oestrogen-progestogen 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 protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

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

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens (and progestogens) 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 (and progestogens).

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

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.

The requirement for oral antidiabetics or insulin may change as a result of the effect on glucose tolerance.

There are also some laboratory tests that can be influenced by oestrogens, such as tests for glucose tolerance or thyroid function.

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 cleansers and detergents (e.g. benzalkonium or benzethonium chloride products), skin care products of high alcohol 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Oestrogel is not indicated during pregnancy. If pregnancy occurs during medication with Oestrogel, treatment should be withdrawn immediately.

The results of most epidemiological studies to date, relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Lactation

Oestrogel is not indicated during lactation.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Most of the following severe events reported were seen mainly with artificial oestrogens and after oral use. Such incidents were very rare. However treatment should be stopped if one of the following develops:

- Cardiovascular or thrombo-embolic events
- Cholestatic jaundice
- Benign mastopathy, uterine tumour, (eg increase in the volume of a fibroma)
- Hepatic adenoma: this can give rise to intra-abdominal haemorrhage
- Galactorrhoea, if this develops a search should be made for a pituitary adenoma.

More frequent but minor incidents can occur which do not usually require treatment to be stopped but the dose to be adjusted depending on whether the symptoms or signs suggest excess or insufficient oestrogen.

Signs of insufficient oestrogen:

- Persistent hot flushes
- Simple headaches, migraines
- Dryness of the vagina
- Ocular irritation due to contact lenses.

Signs of excess oestrogen:

- Nausea, vomiting, abdominal cramps/pain, flatulence
- Tension in the breasts
- Irritability
- Oedema, heaviness of the legs
- Increased secretions from the uterine cervix

Other undesirable effects:

- Metrorrhagia, which should suggest a search for a subjacent disease, in particular endometriosis
- Exacerbation of epilepsy
- Chloasma/melasma which can be persistent.
- Skin irritation at the application site; in individual cases an allergic contact dermatitis with post-inflammatory pruritus and generalised exanthema
- Bloating
- Alterations in body weight
- Headache
- Dizziness
- Anxiety/depressive symptoms
- Hypertension
- Altered libido
- Growth of pre-existing fibroids
- Some women are predisposed to cholestasis during steroid therapy.

Other adverse reactions have been reported in association with oestrogen/progestogen treatment:

- Oestrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer.
- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4 Special warnings and precautions for use.
- Myocardial infarction and stroke
- Gall bladder disease.
- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4)

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.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestogen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Results of the largest randomised placebo-controlled trial (WHI-study) and largest epidemiological study (MWS) are presented.

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

<u>Age range (years)</u>	Additional cases per 1000 never-users of HRT over a 5 year period* ²	Risk ratio & 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-progestogen			
50-65	9-12	1.7	6 (5-7)
[#] Overall risk ratio. The risk ratio is not constant but will increase with increasing duration on use.			

Note: since the background incidence of breast cancer differs by EU country, the number of additional case of breast cancer will also change proportionately.

^{*2} Taken from baseline incidence rates in developed countries.

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) ^{*3}
CEE+MPA oestrogen & progestogen‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

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

^{*3} WHI study in women with no uterus, which did not slow an increase in risk of breast cancer.

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1000 women with 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 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 HRT (see section 4.4). Results of the WHI studies are presented:

WHI Studies – Additional risk of VTE over 5 years’ use

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

^{*4} 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*⁵ over 5 years’ use

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

**⁵No 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

No reports of ill effects from overdosage have been recorded and remedial action is generally unnecessary. There are no specific antidotes and treatment should be symptomatic. The effects of overdosage are usually a sensation of tension in the breasts, abdominal and pelvic swelling, anxiety and irritability. These signs disappear when treatment is stopped or when the dose 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.

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

Oestrogens prevent bone loss following menopause or ovariectomy.

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.

As the major oestrogen secreted by the human ovary, oestradiol is crucial to the development and maintenance of the female reproductive system and secondary sex characteristics, it promotes growth and development of the vagina, uterus and fallopian tubes, and enlargement of the breasts. Indirectly it contributes to the shaping of the skeleton, maintenance of tone and elasticity of urogenital structures, changes in the epiphyses of the long bones that allow for pubertal growth spurt and its termination, growth of axillary and pubic hair and pigmentation of the nipples and genitals.

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.

Clinical trial information

Relief of oestrogen-deficiency symptoms and bleeding patterns

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

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 rate similar 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 that is limited.

5.2 Pharmacokinetic properties

Pharmacokinetic studies indicate that, when applied topically to a large area of skin in a volatile solvent, approximately 10% of the oestradiol is percutaneously absorbed into the vascular system, regardless of the age of the patient. One pressure dose corresponds to the absorption of 75µg of oestradiol. There is temporary storage in the horny layer of the epidermis. From this site, there is slow diffusion into the systemic circulation via the capillaries in the dermis. Daily application of 2.5g or 5g Oestrogel over a surface area of 400-750cm² results in a gradual increase in oestrogen blood levels to steady state after approximately 3-5 days and provides circulating levels of both oestradiol and oestrone equivalent in absolute concentrations and in their respective ratio to those obtained during the early-mid follicular phase of the menstrual cycle.

Avoidance of first pass metabolism by the percutaneous route not only results in a physiologic ratio of oestradiol and oestrone, but also reduces the impact on hepatic biosynthesis of protein that has been demonstrated with orally administered oestrogens.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer (Carbopol 980 NF)
Trolamine
Ethanol
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. Do not refrigerate or freeze.

6.5 Nature and contents of container

Rigid polypropylene container, encasing a collapsible LDPE pouch fitted with a mechanical metering valve, closed with a polypropylene cap. Each contains 80g.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Besins Healthcare
Avenue Louise 287
1050 Brussels
Belgium

8 MARKETING AUTHORISATION NUMBER

PA1341/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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