Professional information for FEMIGEL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FEMIGEL transdermal gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FEMIGEL is a hydro-alcoholic gel containing 1,5 mg of 17β-oestradiol (as hemihydrate) in 2,5 g of gel (0,06 % *m/m*).

Each pump actuation delivers 1,25 g of gel which contains 0,75 mg of oestradiol.

Excipients with known effect

Contains 40 % *m/m* absolute ethanol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal gel.

Translucent, slightly opalescent 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 at high risk of future fractures who are intolerant of, or contraindicated for, other medicines 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

FEMIGEL is an oestrogen-only product indicated only for women without a uterus. FEMIGEL 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 metered dose (1 pump actuation) from the dispenser is 1,25 g of FEMIGEL.

Two pumps (2,5 g) of FEMIGEL once daily (1,5 mg 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 pumps (5 g) of FEMIGEL daily (3,0 mg 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 section 4.4) should be used.

Postmenopausal osteoporosis:

The minimum effective dose is 2,5 g FEMIGEL once daily for most patients.

Use with progestogen:

In women with an intact uterus the recommended dose of progesterone should be administered for at least 12 days of each month, in accordance with the manufacturer's recommendations. FEMIGEL should be administered daily on a continuous sequential basis.

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

Initiation of treatment:

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

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

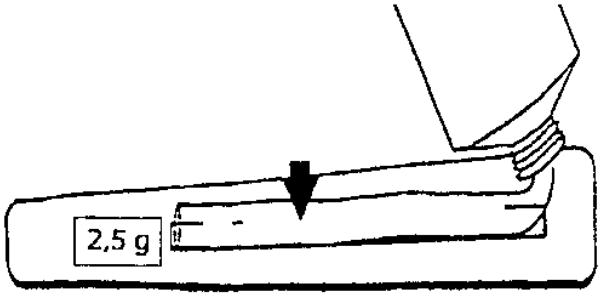
Method of administration

For external use only. FEMIGEL is applied topically to the skin.

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 (2,5 g) should be administered from the pump, where one plunge delivers 1,25 g of gel and applied to clean dry or intact areas of skin e.g. on the arms and shoulders, or inner thighs. The area of application should be at least 750 cm^2. One pump actuation from the dispenser, or half the prescribed dose, should be applied to each arm/shoulder (or thigh). FEMIGEL should NOT be applied on or near the breasts or on the vulval region. A frequent change in application sites is recommended. Not recommended for use in children.

FEMIGEL 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 FEMIGEL.

Patients should be informed that children should not come in contact with the area of the body where FEMIGEL was applied on (see section 4.4).

For people not being treated with FEMIGEL:

In the event of contact with an application area, which has not been washed or is not covered with clothing, wash the area of skin onto which FEMIGEL may have been transferred as soon as possible, using soap and water.

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 hypersensitivity to oestradiol or to any of the excipients (see section 6.1).
- Pregnancy (see section 4.6).
- Personal and family history of breast cancer.
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer).
- Undiagnosed genital bleeding.
- Untreated endometrial hyperplasia.
- Current venous thromboembolism (e.g. deep venous thrombosis, pulmonary embolism).
- Previous proven deep vein thrombosis (DVT).
- Previous pulmonary embolism.
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency, see section 4.4).
- Inherited thrombophilia.
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction).
- Active liver disease, or a history of liver disease as long as liver function tests have failed to

return to normal.

- Porphyria.
- Patients known with inherited genetic mutations: BRCA1 and BRCA2 genes.
- Early menstrual periods (before the age of 12 years).
- History of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma) *in situ.*
- Previous treatment using radiation therapy to the chest or breast.
- Previous exposure to diethylstilbestrol (DES).

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, FEMIGEL 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.

Evidence regarding the risks associated with FEMIGEL 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 FEMIGEL, a complete personal and family 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 medical practitioner 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 considered that these conditions may recur or be aggravated during treatment with FEMIGEL, in particular:

- leiomyoma (uterine fibroids) or endometriosis,
- risk factors for thromboembolic disorders (see below),
- risk factors for oestrogen dependent tumours, e.g. first-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 and in the following

situations (see section 4.3):

- 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 with FEMIGEL 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

FEMIGEL contains oestrogen only which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 2018 reported a significant increase in the risk of developing breast cancer in 55 575 women 40 – 59 years of age who used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for oestrogen-progestogen than oestrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for oestrogen-progestogen preparations was 1,60 at 1 – 4 years and RR = 2,08 at 5 – 14 years, while that for oestrogen only preparations was 1,17 at 1 – 4 years and 1,33 at 5 – 14 years. There was no risk to develop breast cancer in women who started MHT at 60 years of age.

All women on FEMIGEL should receive yearly breast examinations by a health care provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors and prior mammogram results.

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 (body mass index [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 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, FEMIGEL should be discontinued.

Patients should be told to contact their medical practitioners 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 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).

Potential FEMIGEL transfer to children

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

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.

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 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-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 years.

Ethanol

FEMIGEL contains 0,5 g alcohol (ethanol) in each dose of 1,25 g gel. It may cause burning sensation on damaged skin. FEMIGEL is flammable until dry.

4.5 Interaction with other medicines and other forms of interaction

Treatment with surface active medicines (e.g. sodium laurilsulfate), or other medicines which alter barrier structure or function, could remove medicine 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 medicine which alters skin production (e.g. cytotoxic medicine) 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

FEMIGEL is not indicated during pregnancy (see section 4.3). If pregnancy occurs during the use of FEMIGEL, treatment should be discontinued immediately.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to oestrogens indicate no teratogenic of fetotoxic effects.

Breastfeeding

FEMIGEL is not indicated during lactation.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Summary of the safety profile

The reporting rate of adverse drug reactions with FEMIGEL was calculated as 5/10 000 patient year's corresponding to approximately five spontaneously reported cases in every 10 000 patients exposed to FEMIGEL (Periodic Benefit Risk Evaluation Report 01 September 2016 to 30 November 2017).

Tabulated list of adverse reactions

Clinical trial data

The table below lists adverse experiences which were reported in > 10 % of patients (regardless of relationship to treatment) who received percutaneous 17ß-oestradiol gel 1,25 g (containing 0,75 mg of oestradiol) or 2,5 g (containing 1,5 mg of oestradiol) or placebo gel applied once daily for 12 weeks, in a multi-centre, randomised, double-blind, placebo-controlled clinical trial in 221 postmenopausal women.

Adverse experiences (> 10 %) reported in a 221 patient placebo-controlled trial in postmenopausal women over a 12-week period			
Adverse experience	**Placebo (n = 73)**	**0,75 mg oestradiol (n = 75)**	**1,5 mg oestradiol (n = 73)**
Headache	13	13	14
Nausea	3	4	9
Breast pain	7	8	8
Infection	5	12	5
Pain	8	5	4
Vaginitis	3	8	1

Post-marketing experience

The information given below is based on extensive post-marketing experience from the administration of FEMIGEL.

System organ class	**Frequency not known (cannot be estimated from the available data)**
Gastrointestinal disorders	Nausea
Nervous system disorders	Dizziness, headache
Skin and subcutaneous tissue disorders	Alopecia, pruritus

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).

Undesirable effects observed with FEMIGEL used in menopause are reported in the table below:

System organ class	**Frequency of occurrence of adverse reactions**		
	Common (≥ 1/100; < 1/10)	Uncommon (≥ 1/1 000; < 1/100)	Rare (≥ 1/10 000; < 1/1 000)
Metabolism and nutrition disorders			Glucose intolerance
Psychiatric disorders		Depression, mood swings	Change in libido
Nervous system disorders	Headache	Vertigo, migraine	Aggravation of epilepsy
Vascular disorders		Venous thromboembolic disease	Arterial hypertension
Gastrointestinal disorders	Nausea, abdominal pain	Flatulence, vomiting	
Hepatobiliary disorders			Liver function tests abnormalities
Skin and subcutaneous tissue disorders		Pruritus	Skin decolouration, acne
Reproductive system and breast disorders	Breast swelling/pain, breast enlargement, dysmenorrhoea, menorrhagia,	Benign breast neoplasm, increased volume of uterine, leiomyoma,	Galactorrhoea

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

Description of selected adverse reactions

The following risks apply in relation to systemic oestrogen/ progestogen treatment:

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 1 000 never-users of HRT over a 5 year period (50 – 54 years)*[1]	Risk ratio	Additional cases per 1 000 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

*[1] 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/m^2)

Age at start HRT (years)	Incidence per 1 000 never-users of HRT over a 10 year period (50-59 years)*[2]	Risk ratio	Additional cases per 1 000 HRT users over 10 years
		Oestrogen only HRT	
50	26,6	1,3	7,1
		Combined oestrogen-progestogen	
50	26,6	1,8	20,8

*[2] 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.

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1 000 women in placebo arm over 5 years	Risk ratio and 95 % CI	Additional cases per 1 000 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)

*[3] 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 1 000 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 1 000 women between the ages of 50 and 65 years.

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

The use of oestrogen-only or 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 2 000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2 000 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 FEMIGEL (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 1 000 women in placebo arm over 5 years	Risk ratio & 95 % CI	Additional cases per 1 000 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 years (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 FEMIGEL will increase with age (see section 4.4).

WHI studies combined - Additional risk of ischaemic stroke*[5] over 5 years' use

Age range (years)	Incidence per 1 000 women in placebo arm over 5 years	Risk ratio and 95 % CI	Additional cases per 1 000 HRT users over 5 years
50 – 59	8	1,3 (1,1– 1,6)	3 (1 – 5)

*[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 FEMIGEL is important. It allows continued monitoring of the benefit/risk balance of FEMIGEL. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA's website.

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

Category and class: A 21.8.1 Oestrogens

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 FEMIGEL is applied 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.

Distribution

Daily application of 2,5 g of FEMIGEL over a surface area of 400 – 750 cm^2 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 their respective ration to those obtained during the early-mid follicular phase of the menstrual cycle.

FEMIGEL 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 (C_{max}) of oestradiol and oestrone on day 12 were 117 pg/mL and 128 pg/mL, respectively.

The time-averaged serum oestradiol and oestrone concentrations ($C_{average}$) over the 24-hour dose interval after administration of 2,5 g of FEMIGEL on day 12 were 76,8 pg/mL and 95,7 pg/mL, respectively.

Biotransformation

Metabolism of oestradiol takes place mainly in the liver under oestriol, oestrone and their conjugated metabolites (glucuronides, sulphates).

These metabolites also undergo enterohepatic recirculation.

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

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

Elimination

Oestriol is the major urinary oestradiol metabolite. However, glucuronide and sulphate metabolites of oestradiol 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

Absolute ethanol (40 % *v/v*)

Carbomer

Trolamine

Purified water.

6.2 Incompatibilities

Not known.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

6.5 Nature and contents of container

FEMIGEL is packed into a metering canister composed of a polypropylene (PP) bottle, a low-density polyethylene (LDPE) pouch, a polypropylene (PP) metering pump and closed with a polypropylene (PP) cap in a pack size of 80 g.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Medi Challenge (Pty) Ltd.

493 De Jonge Street

Elardus Park

Pretoria, Gauteng

0181

8. REGISTRATION NUMBER

28/21.8.1/0600

9. DATE OF FIRST AUTHORISATION

8 February 1996.

10. DATE OF REVISION OF THE TEXT

17 February 2026