

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

FemSeven Conti, 50 micrograms/ 7 micrograms/24 hours, transdermal patch.

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch contains 1.5 mg of estradiol hemihydrate and 0.525 mg levonorgestrel in a patch size of 15 cm<sup>2</sup>, releasing 50 micrograms of estradiol and 7 micrograms of levonorgestrel per 24 hours.

For the full list of excipients, see 6.1.

## 3 PHARMACEUTICAL FORM

Transdermal patch

Octagonal, transparent, flexible, rounded-edge transdermal matrix patch located on an oversized removable protective liner.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women more than one year after menopause.

Experience of treating women older than 65 years is limited.

### 4.2 Posology and method of administration

For transdermal use.

Fem7 Plus has to be applied once a week, i.e. each patch is replaced every 7 days. Fem7 Plus is a continuous combined hormone replacement therapy (HRT) treatment without a treatment-off phase: as one patch is removed, the next is applied immediately. Forgetting to change a patch on schedule may increase the likelihood of break-through bleeding or spotting.

In women with amenorrhoea and not taking HRT or women transferring from another continuous combined HRT product, treatment with Fem7 Plus may be started on any convenient day.

In women transferring from sequential HRT regimens, treatment should start right after their withdrawal bleeding has ended.

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.

#### Method of administration

Fem7 Plus should be applied to clean, dry, healthy skin (which is neither irritated nor grazed), free from any cream, lotion or other oily product.

Fem7 Plus should be applied to an area of skin without major skin folds, i.e. the buttocks or hips, and not subject to chafing by clothing (avoid the waist and also avoid wearing tight clothing that could loosen the transdermal patch).

**Fem7 Plus must not be applied either on or near the breasts.** It is advisable to avoid applying the patch to the same

site twice running. At least one week should be allowed to elapse between applications to the same site.

After opening the sachet, one-half of the protective foil is peeled off, being careful not to touch the adhesive part of the transdermal patch with the fingers. Then the patch must be applied directly to the skin. After that the other half of the protective foil is peeled off, and the patch must be firmly **pressed with the palm of the hand for at least 30 seconds, concentrating on the edges. Pressure and the warmth of the hand are essential to ensure maximal adhesive strength of the patch.**

It is possible to take a shower or have a bath without removing the transdermal patch. In the event that the transdermal patch should become detached prematurely, i.e. before the seventh day (due to vigorous physical activity, excessive sweating, abnormal chafing of clothing), a new patch should be applied (to aid compliance it is recommended that the patient then continues to change the patch on the original scheduled day).

Once applied, the transdermal patch has to be covered by clothes to avoid direct exposure to sunlight.

Removal of the transdermal patch should be carried out slowly to avoid irritating the skin. In the event of some of the adhesive remaining on the skin, this can usually be removed by gently rubbing with a cream or an oily lotion.

After use, Fem7 Plus is to be folded in two (with the adhesive surface to the inside) and disposed of with normal household solid waste.

### 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;
- Porphyrria.

### 4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

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

#### Medical examination/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 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 Fem7 Plus, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for, thromboembolic disorders (see below)
- Risk factors for oestrogen-dependent tumours, e.g. 1<sup>st</sup> 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:

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- 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 progestagen cyclically for at least 12 days per months/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 include an endometrial biopsy to exclude endometrial malignancy.

#### Breast cancer

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

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-progestagen for HRT that becomes apparent after about 3 years (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/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. Long term (at least 5-10 years) use of oestrogen-only HRT products has been associated with a slightly increased risk of ovarian cancer (see section 4.8). Some studies including the WHI trial suggest that the long-term use of combined HRTs may confer a similar or slightly smaller risk (see section 4.8).

#### Venous thromboembolism

- HRT is associated with a 1.3-3 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 > 30 kg/m<sup>2</sup>), 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 for 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.
- In women with no personal history of VTE but with a first-degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).  
If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S or protein C deficiencies or a combination of defects) HRT is contraindicated.
- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

#### Coronary artery disease (CAD)

- There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT.  
The relative risk of CAD during use of combined oestrogen+progestagen 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+progestagen use is very low in healthy women close to menopause, but will rise with more advanced age.

#### Ischaemic stroke

- Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk in ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependant, 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 hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T<sub>4</sub> levels (by column or by radio-immunoassay) or T<sub>3</sub> levels (by radio-immunoassay). T<sub>3</sub> resin uptake is decreased, reflecting the elevated TBG. Free T<sub>4</sub> and free T<sub>3</sub> 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 progestagens 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 progestagens.

At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens and progestagens HRT 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

Fem7 Plus is not indicated during pregnancy. If pregnancy occurs during treatment with Fem7 Plus, treatment should be withdrawn immediately.

Clinically, data on a large number of exposed pregnancies indicate no adverse effects of levonorgestrel on the foetus.

The results of most epidemiological studies to date that are relevant to inadvertent foetal exposure to combination of oestrogens + progestagens indicate no teratogenic or foetotoxic effect.

Lactation

Fem7 Plus is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

4.8 Undesirable effects

The most frequently reported undesirable effects (> 10 %) in clinical trials during treatment with Fem7 Plus were application site reactions, breast tenderness and bleeding or spotting. The application site reactions were mostly mild skin reactions and usually disappeared 2 – 3 days after patch removal. In the majority of cases breast tenderness was reported as mild or moderate and tends to decrease during treatment time.

Other potential systemic undesirable effects are those commonly observed with oestrogen and progestin treatments.

Organ system class (e.g. MedDRA SOC level)	Common ADRs > 1/100, < 1/10	Uncommon ADRs > 1/1000, < 1/100	Rare ADRs > 1/10.000, < 1/1000
General disorders		Fluid retention/	

		oedema/weight increase/loss, fatigue, leg cramps	
Nervous system disorders	Headache	Dizziness, migraine	
Gastrointestinal disorders	Dyspepsia	Bloating, abdominal cramps, nausea	Cholelithiasis, cholestatic jaundice
Cardiovascular disorders		Hypertension	
Reproductive system and breast disorders	Mastodynia	Endometrial hyperplasia, benign breast tissue changes,	Increase in size of uterine fibrosis
Psychiatric disorders		Depression	

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.

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 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-progestagen			
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 cases of breast cancer will also change proportionately.			

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

Age range (yrs)	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 & progestagen‡			
50-79	14	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.

2 \*Taken from baseline incidence rates in developed countries

3 \*WHI study in women with no uterus, which did not show 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 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 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. In the Million Women Study 5 years of HRT resulted in 1 extra case per 2500 users.

**Risk of venous thromboembolism**

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

**WHI Studies - Additional risk of VTE over 5 years’ use**

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 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-progestagen			
50-59	4	2.3 (1.2-4.3)	5 (1-13)

**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.

**WHI studies combined - Additional risk of ischaemic stroke\*5 over 5 years’ use**

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

4 \*Study in women with no uterus

5\*no differentiation was made between ischaemic and haemorrhagic stroke.

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

- 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).

**4.9 Overdose**

The method of administration makes significant overdose unlikely. Signs of an overdose are generally breast tenderness, swelling of the abdomen/pelvis, anxiety, irritability, nausea and vomiting. Removal of the transdermal patches is all that is required should it occur.

**5 PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

Pharmacotherapeutic group:

Progestagens and oestrogens, combinations, levonorgestrel and oestrogen

ATC code: G03F A11

Fem7 Plus contains a continuous combined combination of oestrogen and progestagen for continuous use, combining estradiol hemihydrate and levonorgestrel.

- Estradiol: The active ingredient, synthetic 17 $\beta$ -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.
- Levonorgestrel: As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of levonorgestrel greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical trial information

Relief of oestrogen-deficiency symptoms and bleeding patterns:

- Under treatment with Fem7 Plus, relief of menopausal symptoms was achieved during the first weeks of treatment.
- Fem7 Plus is a continuous-combined HRT given with the intent of avoiding the regular withdrawal bleeding associated with cyclic or sequential HRT.

Amenorrhoea was seen in 59-68 % of the women during months 10-12 of treatment.. Irregular bleeding and/or spotting appeared in 28-39 % of the women during the first three months of treatment and in 37 % during months 10-12 of treatment.

**5.2 Pharmacokinetic properties**

By transdermal administration there is no hepatic first-pass effect as observed with oral administration; estradiol reaches the bloodstream in unchanged form and in physiological amounts. Therapeutic estradiol concentrations are comparable to those observed in the follicular phase.

After continuous application of FemSeven Conti, maximum plasma concentration of estradiol (C<sub>max</sub>) reaches 82 pg/ml and average plasma concentration (C<sub>av</sub>) is about 34 pg/ml. Trough plasma concentration (C<sub>trough</sub>) at the end of a 7-day wearing period is 27 pg/ml. After removal of the transdermal patch, estradiol concentrations return to their baseline

values within 12 to 24 hours.

The maximum plasma concentration of levonorgestrel is reached after three to four days and C<sub>max</sub> is approximately 113 pg/ml at steady state. The average plasma concentration of levonorgestrel during a 7-day period is approximately 88 pg/ml and trough plasma concentration (C<sub>trough</sub>) reaches 72 pg/ml.

After percutaneous absorption, levonorgestrel is bound to plasma proteins, i.e. albumin (50%), and sex hormone-binding globulin (SHBG) (47.5%). Affinity to SHBG is higher than for other commonly used progestagens.

### 5.3 Preclinical safety data

In experimental animals estradiol displayed an embryo-lethal effect already at relatively low doses; malformations of the urogenital tract and feminisation of male foetuses were observed. Levonorgestral displayed an embryo-lethal effect in animal experiments and, in high doses, a virilising effect on female fetuses. Because of marked differences between animal species and between animals and humans, preclinical results are of limited predictive value for the treatment of humans with oestrogens.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Backing layer: Polyethylene terephthalate (PET) foil.  
 Adhesive matrix: Styrene-isoprene-styrene block copolymer, glycerine esters of completely hydrogenated resins.  
 Protective liner: Siliconized polyethylene terephthalate (PET) foil.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Do not store above 30°C.

### 6.5 Nature and contents of container

Sachet (Paper/PE/aluminium/ethylene copolymer). Carton of 4 or 12 sachets.

### 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

*See section 4.2, Posology and method of administration. No special requirements.*

## 7 MARKETING AUTHORISATION HOLDER

Merck Serono Ltd  
 Bedfont Cross  
 Stanwell Road  
 Feltham  
 Middlesex, TW14 8NX  
 United Kingdom

## 8 MARKETING AUTHORISATION NUMBER

PA 0654/015/001

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 19 March 2004

Date of last renewal: 5 November 2007

**10 DATE OF REVISION OF THE TEXT**

March 2012