SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FemSeven 75,
75 micrograms/24 hours,
transdermal patch.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch contains 2.25 mg of estradiol hemihydrate in a patch size of 22.5 cm2, releasing 75 micrograms of estradiol 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.

Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. (See also section 4.4)

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

FemSeven is an oestrogen-only patch that should be applied to the skin once weekly on a continuous basis, i.e. each patch is replaced with a new one after 7 days.

In women with an intact uterus, the addition of a progestogen for at least 12 to 14 days every month/28 day cycle is essential to help prevent any endometrial hyperplasia induced by the oestrogen. For more detailed information, please refer to section 4.4 (Special warnings and precautions for use - "Endometrial hyperplasia").

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

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. Therefore, therapy should normally be started with one FemSeven patch (delivering 50 micrograms of estradiol in 24 hours). If the prescribed dose does not eliminate the menopausal symptoms, the dose should be adjusted stepwise after the first few months by using a transdermal patch delivering 75 or 100 micrograms estradiol per day. A maximum of 100 micrograms estradiol per day should not be exceeded. If there are persistent signs of overdose, such as breast tenderness, the dose should be reduced accordingly.

Hysterectomised women not taking HRT or transferring from another HRT product may start treatment with FemSeven on any convenient day. The same holds true for non-hysterectomised women not taking HRT or transferring from a continuous combined HRT product. In non-hysterectomised women switching from sequential HRT regimens, treatment with FemSeven should start after the previous treatment regimen has ended.

Consecutive new patches should be applied to different sites. It is recommended that sites are chosen below the waist where little wrinkling of the skin occurs e.g., buttocks, hip or abdomen. FemSeven must not be applied on or near the breasts. The patch should be applied to clean, dry, healthy and intact skin. The patch should be applied to the skin as soon as it is removed from its wrapping. The patch is applied by removing both parts of the protective liner and then holding it in contact with the skin for at least 30 seconds (warmth is essential to ensure maximal adhesive strength).

Should part or all of a patch detach prematurely (before 7 days) it should be removed and a new patch applied. To aid compliance it is recommended the patient then continues to change the patch on the usual day. This advice also applies if a patient forgets to change the patch on schedule. Forgetting a patch may increase the likelihood of break-through bleeding or 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 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 substance 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 benefit outweighs the risk.
Evidence regarding the risk 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 FemSeven 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

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 administrated 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 months/28 day cycle or continuous combined oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

For oral doses of estradiol > 2 mg, conjugated equine oestrogens > 0.625 mg and patches > 50 µg/day the endometrial safety of added progestogens has not been demonstrated.

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 shows an increased risk of breast cancer in women using oestrogen-progestogen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestrogen therapy

The randomised placebo-controlled trial the Women's Health Initiative study (WHI) and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestogen for HRT that becomes apparent after about 3 (1-4) years (see. Section 4.8).

Oestrogen-only therapy

The WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of oestrogen-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 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 the 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 > 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 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-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 healty women close to menopause, but will rise 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 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.

Exogenous estrogens 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 of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65.

ALT elevations

During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other

oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. 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 may lead to decreased effect and changes in the uterine bleeding profile.

Effect of HRT with oestrogens on other medicinal products

Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interpretation exists, which may lead to a reduction in seizure control among women taking both medicinal products together

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

4.6 Fertility, Pregnancy and lactation

- Pregnancy :

FemSeven is not indicated during pregnancy. If pregnancy occurs during medication with FemSeven treatment should be withdrawn immediately.
The results of most epidemiological studies to date relevant to inadvertent fœtal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

- Lactation :

FemSeven is not indicated during lactation.

4.7 Effects on ability to drive and use machines

There is no evidence from the clinical data available on oestrogen therapy to suggest that FemSeven 75 should have any effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

The most frequently reported undesirable effects (> 10 %) in clinical trials during treatment with FemSeven were application site reactions, e.g. pruritus, erythema, eczema, urticaria, oedema and changes in skin pigmentation. They were mostly mild skin reactions and usually disappeared 2 – 3 days after patch removal. These effects are usually observed with transdermal oestrogen replacement therapy.
All adverse events considered to be drug-related, which were observed during the Phase III (> 500 patients) and Phase IV (> 10 000 patients) clinical trials or from the spontaneous reporting system and literature, are summarised in the following table:

Organ system class (e.g. MedDRA SOC level)	**Common ADRs > 1/100 ; < 1/10**	**Uncommon ADRs >1/1 000 ; < 1/100**	**Rare ADRs >1/10 000 ; < 1/1 000**
Skin and subcutaneous tissue		Hair changes, sweating increased	
Muscular and skeletal		Arthralgia, leg cramps	
Central & peri nervous system	Headache	Dizziness, paresthesia, migraine	
Psychiatric disorders		Anxiety, appetite increase, depression, insomnia, nervousness	
Gastrointestinal system dis.		Nausea, dyspepsia, abdominal pain, vomiting	
Cardiovascular		Blood pressure changes	
Myo-, endo-, pericards		Chest pain	
Vascular (extracardial)		Vein disorders	
Reproductive disease female	Breast discomfort (e.g. Mastalgia/	Vaginal discharge, breakthrough bleeding	Worsening of uterine fibroids

	mastopathies, breast tenderness, breast enlargement)		
Body as a whole/general dis.		Oedema, fatigue, weight changes	

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 1000 never-users of HRT over a 5 year-period (50-54 years)*	Risk ratio	Additional cases per 1000 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
*Taken from baseline incidence rates in England in 2015 in developed countries women with BMI 27 (kg/m2)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)	Additional cases Incidence per 1000 never-users of HRT over a 10 year period (50-59 years) *	Risk ratio	Additional cases per 1000 HRT users after 10 years
Oestrogen only HRT			
50	26.6	1.3	7.1
Combined oestrogen-progestogen			
50	26.6	1.8	20.8

*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 (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)*
CEE+MPA oestrogen & progestogen‡			
50-79	14	1.2 (1.0 – 1.5)	+4 (0 – 9)

*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.

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 1 000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1 000 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 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* 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)

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

Other adverse reactions have been reported in association with oestrogen/progestogen 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).

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Goggle Play or Apple App Store.

4.9 Overdose

The mode of administration makes significant overdose unlikely; removal of the patches is all that is required should it occur.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03 A03

Oestrogens

The active ingredient, synthetic 17 -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 menopause or ovariectomy.

Clinical Trial Information:

Relief of oestrogen-deficiency symptoms and bleeding patterns:

Relief of menopausal symptoms was achieved during the first few weeks of the treatment. In non-hysterectomised women, the bleeding profile depends on the type and dose of the progestogen and duration used in combination with FemSeven.

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

After application of the transdermal system containing estradiol, therapeutic concentrations of estradiol are achieved within 3 hours and maintained throughout the entire application period of the transdermal patch (7 days). Estradiol peak plasma concentrations (Cmax) range from 59 to 155 pg/ml (baseline corrected geometric mean 92 pg/ml) and AUC0-168h values were

between 2478 and 10694 h*pg/ml (baseline corrected geometric mean 5188 h*pg/ml). The mean average plasma concentration (Cav) is 42 pg/ml (range: 20 to 145 pg/ml) and mean Cpre (trough concentration before next patch application) is 29 pg/ml. After removal of the transdermal patch, estradiol concentrations return to pre-treatment values (below 10 pg/ml) within 12 hours.

By transdermal administration of FemSeven, there is no hepatic first-pass effect and the estradiol reaches the bloodstream directly in unchanged form and in physiological amounts. With the use of FemSeven, the estradiol concentrations are raised to values similar to those of the early to middle follicular phase.

The liver is the major site for estradiol metabolism. The primary metabolites are estrone, estriol and their conjugates (glucuronide and sulfate). Estradiol is excreted into the urine mostly as glucuronide and sulfate. The urinary excretion approaches pre-treatment levels within 24 hours after patch removal.

5.3 Preclinical safety data

Animal studies with estradiol have shown expected estrogenic effects.
There are no preclinical data of relevance to the prescriber that are additional to those already included in other sections of the SPC (see notably section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

None known.

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

The container (primary packaging) consists of a sealed laminated sachet. This comprises layers of food grade paper/polyethylene/aluminium/ethylene copolymer.

Package sizes: Carton of 4 and 12 patches.

6.6 Special precautions for disposal

After removal from the laminated sachet, peel off the two part protective liner. Try to avoid touching the adhesive. Stick the adhesive side down to the upper left or right buttock on a clean and dry area of skin. Hold the applied patch to the skin with the palm of the hand for at least 30 seconds, in order to ensure optimal adhesion to the skin.

Recommended application sites are clean, dry and intact areas of skin on the trunk below the waistline. FemSeven should not be applied on or near the breasts. After removal the used patch should be folded and disposed of with the normal household solid waste.

7 MARKETING AUTHORISATION HOLDER

Theramex Ireland Limited

3rd Floor, Kilmore House,

Park Lane,

Spencer Dock,

Dublin 1,

D01 YE64,

Ireland

8 MARKETING AUTHORISATION NUMBER(S)

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