

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0654/010/001

Case No: 2075955

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Merck Serono Limited

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

an authorisation, subject to the provisions of the said Regulations, in respect of the product

FemSeven Sequi 50 micrograms/10 micrograms/24 hours, transdermal patch

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **09/04/2010** until **26/09/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

FemSeven Sequi 50 micrograms/10 micrograms/24 hours, transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Phase 1:

Each patch contains 1.5 mg of estradiol hemihydrate in a patch size of 15 cm², releasing 50 micrograms of estradiol per 24 hours.

Phase 2:

Each patch contains 1.5 mg of estradiol hemihydrate and 1.5 mg of levonorgestrel in a patch size of 15 cm², releasing 50 micrograms of estradiol and 10 micrograms of levonorgestrel per 24 hours.

For 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 post-menopausal women.

Experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

For transdermal use.

Apply FemSeven Sequi once a week, i.e. replace each patch every 7 days. FemSeven Sequi is a continuous sequential hormone replacement therapy (HRT) without a treatment-off phase: as one patch is removed, the next is applied immediately.

Each treatment cycle with FemSeven Sequi consists of the successive application of two transdermal patches containing estradiol (phase 1) and then two transdermal patches containing estradiol and levonorgestrel (phase 2).

Accordingly, the following treatment cycle should be observed:

- one phase 1 patch once a week for the first two weeks
- then one phase 2 patch once a week for the following two weeks.

In women who are not taking HRT or women who switch from a continuous combined HRT product, treatment may be started on any convenient day.

In women transferring from a sequential HRT regimen, treatment should begin the day following completion of the prior regimen.

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

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

FemSeven Sequi should be applied to an area of skin without major skin folds, e.g. 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).

FemSeven Sequi must not be applied either on or near the breasts. It is advisable to avoid applying the patch to the same site twice. At least one week should be allowed to elapse between applications to the same site.

After opening the sachet, peel off one-half of the protective foil, being careful not to touch the adhesive part of the transdermal patch with the fingers. Apply directly to the skin. Now peel off the other half of the protective foil and press the patch on firmly with the palm of the hand for at least 30 seconds, concentrating on the edges. The 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.

Should a patch detach prematurely, before 7 days (due to vigorous physical activity, excessive sweating, abnormal chafing of clothing), it should be removed and a new patch of the same phase applied. To aid compliance it is recommended the patient then continues to change the patch on the usual day and according to the initial treatment cycle. 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.

Once applied, the transdermal patch should not be exposed 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, fold FemSeven Sequi in two (with the adhesive surface to the inside) and dispose of it 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) ;
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction) ;
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal ;
- Known hypersensitivity to the active substances or to any of the excipients ;
- Porphyria.

4.4 Special warnings and precautions for use

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

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 mammography, should be carried out in accordance with currently accepted screening practices, modified according 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 Sequi, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- A history of, or 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 if 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

- The risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestagen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk.
- 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.

Breast cancer

A randomised placebo-controlled trial, the Women’s Health Initiative study (WHI), and epidemiological studies, including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking oestrogens, oestrogen-progestagen combinations or tibolone for HRT for several years (see section 4.8). For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine oestrogens (CEE) or estradiol (E2) was greater when a progestagen was added, either sequentially or continuously, and regardless of type of progestagen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine oestrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

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

Venous thromboembolism

- HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. One randomised controlled trial and epidemiological studies found a two- to threefold higher risk for users compared with non-users. For non-users it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.
- Generally recognized risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m²) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE.
- Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contra-indicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.
- The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all postoperative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.
- If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnea).

Coronary artery disease (CAD)

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated oestrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated oestrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated oestrogens and MPA for 5 years, the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9 (best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer

Long-term (at least 5-10 years) use of oestrogen-only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than oestrogen-only products.

Other conditions

Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in FemSeven Sequi transdermal patch is increased.

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), 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).

There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger post-menopausal women or other HRT products.

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 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 Pregnancy and lactation

Pregnancy:

FemSeven Sequi is not indicated during pregnancy. If pregnancy occurs during medication with FemSeven Sequi, 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 relevant to inadvertent foetal exposure to combinations of oestrogens and progestagens indicate no teratogenic or foetotoxic effects.

Lactation:

FemSeven Sequi 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 FemSeven Sequi were application site reactions. They usually disappeared 2 – 3 days after patch removal.

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

Organ system	Common ADRs > 1/100, < 1/10	Uncommon ADRs > 1/1000, < 1/100	Rare ADRs > 1/10.000, < 1/1000
Body as a whole	Headache, Mastodynia	Fluid retention/oedema/weight increase/loss, fatigue, dizziness, leg cramps, migraine	
Gastrointestinal	Nausea, Vomiting	Bloating, abdominal cramps	Cholelithiasis, cholestatic jaundice
Cardio-vascular		Hypertension	
Reproductive	Breakthrough bleeding, spotting	Dysmenorrhoea, endometrial hyperplasia, benign breast tumours	Increase in size of uterine fibrosis
Psychiatric	Increase/ decrease in libido		Depression

Breast cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For *oestrogen-only* HRT, estimates of relative risk (RR) from a reanalysis of original data from 51 epidemiological studies (in which >80% of HRT use was oestrogen-only HRT) and from the epidemiological Million Women Study (MWS) are similar at 1.35 (95%CI: 1.21 – 1.49) and 1.30 (95%CI: 1.21 – 1.40), respectively.

For *oestrogen plus progestagen* combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with oestrogens alone.

The MWS reported that, compared to never users, the use of various types of oestrogen-progestagen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use with oestrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45, 95%CI: 1.25 – 1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI: 1.01 – 1.54) after 5.6 years of use of oestrogen-progestagen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries that:

- For women not using HRT, about 32 in every 1000 are expected to have breast cancer diagnosed between the ages of 50 and 64 years.
- For 1000 current or recent users of HRT, the number of *additional* cases during the corresponding period will be:
 - For users of *oestrogens-only* replacement therapy
 - between 0 and 3 (best estimate = 1.5) for 5 years' use
 - between 3 and 7 (best estimate = 5) for 10 years' use.
 - For users of *oestrogen plus progestagen* combined HRT,
 - between 5 and 7 (best estimate = 6) for 5 years' use
 - between 18 and 20 (best estimate = 19) for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an *additional* 8 cases of invasive breast cancer would be due to *oestrogen-progestagen combined* HRT (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:

- For 1000 women in the placebo group,
 - about 16 cases of invasive breast cancer would be diagnosed in 5 years.
- For 1000 women who used oestrogen + progestagen combined HRT (CEE + MPA), the number of *additional* cases would be
 - between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed oestrogens. According to data from epidemiological studies, the best estimate of the risk is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and oestrogen dose, the reported increase in endometrial cancer risk among unopposed oestrogen users varies from 2-to 12-fold greater compared with non-users. Adding a progestagen to oestrogen-only therapy greatly reduces this increased risk.

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

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

4.9 Overdose

The mode 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:

Progestogens and oestrogens for sequential administration

ATC code: G03FB 09

Transdermal route.

Estradiol: the active ingredient, synthetic 17 β -estradiol is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in postmenopausal 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, a synthetic progestin, greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Under treatment with FemSeven Sequi, relief of menopausal symptoms was achieved during the first weeks of treatment.

At the end of one year treatment, 82.7% of women with bleeding reported regular withdrawal bleeding. The day of onset was rather constant 1 - 2 days before the end of the cycle with a mean duration of 4 - 5 days. The percentage of women with breakthrough bleeding and/or spotting was 17.3%. During the 13 cycles of therapy, 19.4% of women treated presented with amenorrhoea.

5.2 Pharmacokinetic properties

With 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 application of the transdermal system containing estradiol alone (phase 1), therapeutic concentrations of estradiol are achieved within 4 hours; these concentrations are maintained throughout the entire application period of the transdermal patch (7 days). When estradiol is administered simultaneously with levonorgestrel (phase 2), the pharmacokinetics of estradiol are unaltered by levonorgestrel.

Peak plasma concentrations of estradiol (C_{\max}) range from 58 to 71 pg/ml, average plasma concentration (C_{av}) is between 29 to 33 pg/ml and trough plasma concentration (C_{pre}) is about 21 pg/ml during both treatment phases. After removal of the transdermal patch, estradiol concentrations return to their baseline values within 12 to 24 hours.

After application of the transdermal system containing estradiol and levonorgestrel at a dose of 10 µg/day (phase 2), the maximum plasma concentration of levonorgestrel (C_{\max}) range from 156 to 189 pg/ml and is reached within 63 to 91 hours (t_{\max}). The average plasma concentration of levonorgestrel (C_{av}) during a 7-day period is between 121 and 156 pg/ml and the trough plasma concentration (C_{pre}) levels are 118 pg/ml. The half-life of levonorgestrel after transdermal application is approximately 28 hours (minimum: 16 hours, maximum: 42 hours).

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

5.3 Preclinical safety data

Animal studies with estradiol and levonorgestrel have shown expected estrogenic and gestagenic 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-styrene block copolymer, glycerine esters of completely hydrogenated resins
Protective liner:	Siliconized transparent polyethylene terephthalate (PET) foil.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Each phase 1 or phase 2 transdermal patch is contained in an individual sachet (Paper/PE/aluminium/ethylene copolymer). Each carton contains 4 or 12 sachets consisting of 2 x phase 1 patches and 2 x phase 2 patches or 6 x phase 1 patches and 6 x phase 2 patches.

Not all pack sizes may be marketed.

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 4.2 Posology and method of administration.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA 654/10/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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