

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

DERMESTRIL-Septem 75 micrograms/24 hours Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One transdermal patch contains:

7.74 mg of estradiol hemihydrate equivalent to 7.5 mg estradiol/33.75 cm² delivering 75 micrograms of estradiol in 24 hours.

Excipient(s):

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch. Each patch is transparent, colourless, slightly opaque with an elliptical shape and a printed identification code, and covered by a rectangular, transparent protective liner.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in women at least 6 months since last menses. The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Posology

DERMESTRIL-Septem is an oestrogen-only patch applied to the skin once weekly in order to ensure a continuous supply of estradiol to the body; thus each used system is removed after seven days and replaced by a new one. Three strengths of DERMESTRIL-Septem are available, i.e. DERMESTRIL-Septem 25, 50, 75. 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. Treatment is usually initiated with DERMESTRIL-Septem 25. If after a treatment of 1-2 months with DERMESTRIL-Septem 25 applied once weekly the symptoms of oestrogen deficiency appear not to be neutralised, a higher dosage can be given. In case of undesirable effects or symptoms of overdose (e.g. breast tenderness and/or vaginal bleeding), the dose should be reduced.

In women with an intact uterus, a progestagen approved for addition to oestrogen treatment must be additionally administered for at least 12-14 days every month/28 day cycle to oppose the development of an oestrogen-stimulated hyperplasia of the endometrium (*see Section 4.4 Special Warnings and Special Precautions for Use*). Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestagen in hysterectomised women.

The treatment with DERMESTRIL-Septem may be initiated at any convenient time for women who are not currently on any oestrogen therapy. Women currently using cyclic or sequential oestrogen/progestagen therapy should complete the on-going treatment cycle before beginning treatment with DERMESTRIL-Septem; the appropriate time to begin treatment with DERMESTRIL-Septem would be the first day of a withdrawal bleeding.

Women who are already using continuous combined oestrogen/progestagen therapy may be switched to DERMESTRIL-Septem directly.

Method of administration

Apply DERMESTRIL-Septem to the skin of the hip, upper quadrant of the buttock, lumbar region or abdomen and press firmly over the whole surface and along the edges to ensure good adhesion. The absorption capacity of the skin is the rate-determining factor in the release of estradiol from DERMESTRIL-Septem. The application on another (higher) skin region than on the mentioned preferred regions is not recommended, as this might have an influence on the release of estradiol. The skin of the application site should be clean, dry, not-greasy and free of redness or irritation. Areas of the body which form folds or are subject to friction during movement should be avoided.

DERMESTRIL-Septem *should not be applied on or near the breasts.*

Patches should not be applied twice consecutively to the same skin site.

If the patch is correctly applied, it will adhere to the skin for the required one-week period without problems. In the event that a patch does come off, it should be replaced with a new patch for the rest of the one-week dosing period. The patch should then be changed again at the regular time to re-establish the patient's routine schedule. Similarly, if the patch is not changed on the scheduled day, it should be replaced as soon as possible and changed again on the next scheduled day. Forgetting to apply a new patch at the scheduled time may increase the likelihood of break-through bleeding and spotting.

If the patch is correctly applied, the patient may bathe or shower. However, the patch may become detached after a very hot bath or sauna. If this occurs, the patch should be replaced with a new one (as described above). Possibly the sauna should be planned for a day scheduled for the change of the patch.

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 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.

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 DERMESTRIL-Septem, 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 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 month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

- For patches releasing more than 50 micrograms/day the endometrial safety of added progestagens 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 progestagens 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 taking combined oestrogen-progestagen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestagen 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-progestagen 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-progestagen 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-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.

Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen 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 a history of VTE or 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/m²), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

-As in all postoperative patients, prophylactic measures need 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, 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.

Combined oestrogen-progestagen therapy:

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.

oestrogen-only:

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

Ischaemic stroke

-Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Other conditions

-Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

-Women with pre-existing 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, alpha₁-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 interactions

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, carbamazepin) 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 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

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

Lactation

DERMESTRIL-Septem is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

More than 700 patients have been treated with the product in clinical trials.

Approximately 10 to 17% of the patients treated with DERMESTRIL-Septem in clinical trials experienced systemic adverse reactions, which were mild and transient. Breast tenderness was reported in 20-35% of patients. Local reactions at the application site, mostly mild erythema with or without pruritus, occurred in 10-25% of patients.

Serious undesirable effects associated with the use of hormone replacement therapy are also mentioned in section 4.4 Special warnings and precautions for use.

The table below reports undesirable effects that have been reported in users of hormone replacement therapy (HRT) by MedDRA system organ classes (MedDRA SOCs).

System Organ Class	Common ADRs, ($\geq 1/100$, <1/10)	Uncommon ADRs, ($\geq 1/1,000$, <1/100)	Rare ADRs ($< 1/1,000$)	Frequency unknown *
Infections and manifestations		Vaginal candidiasis		
Immune system disorders		Hypersensitivity reaction		
Metabolism and nutrition disorders	Weight increase or Weight decrease			
Psychiatric disorders		Depressed mood	Anxiety Libido decreased or Libido increased	
Nervous system disorders	Headache	Dizziness	Migraine	Probable dementia over the age of 65

				(see section 4.4), chorea, exacerbation of epilepsy
Eye disorders		Visual disturbances	Contact lens intolerance	
Cardiac disorders		Palpitations		
Gastrointestinal disorders	Abdominal pain, Nausea	Dyspepsia	Bloating, Vomiting	Pancreatitis (in women with preexisting hypertriglyceridaemia) Gastroesophageal reflux disease
Hepatobiliary disorders		Gall bladder disorder		Hepatic function abnormal, sometimes with jaundice
Skin and subcutaneous tissue disorders	Rash, Pruritus	Erythema nodosum, Urticaria	Hirsutism, acne	Angioedema, Erythema multiforme, Vascular purpura, Chloasma Application site reactions: erythema with or without pruritus
Musculoskeletal and connective tissue disorders			Muscle cramps	
Reproductive system and breast disorders	Uterine/Vaginal bleeding including Spotting	Breast pain, Breast tenderness	Dysmenorrhea, Vaginal discharge, Premenstrual-like syndrome, Breast enlargement	Fibrocystic breast disease
General disorders and administration site conditions		Oedema	Fatigue	
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)				Breast cancer ^a Oestrogen dependent neoplasms benign and malignant, e.g. endometrial cancer ^b , ovarian cancer ^c Increase in size of leiomyoma
Vascular disorders				Stroke ^f Arterial thromboembolism, i.e. angina and myocardial infarction ^e . For further information see sections 4.3 and 4.4. Venous thromboembolism ^d , i.e. deep leg or pelvic venous thrombosis and pulmonary embolism. For further

				information see sections 4.3 and 4.4.
Renal and urinary disorders				Urinary incontinence

The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

*Undesirable effects from spontaneous post-marketing reporting sources, which have not been observed in clinical trials.

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.
- The increased risk in users of oestrogen-only therapy is 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).
- 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/m²)

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-progestagen			
50	13.3	1.6	8.0
* 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/m²)

Age at start HRT (years)	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-progestagen			
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 (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
		CEE oestrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA oestrogen & progestagen#	

50-79	17	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 1000 women with an 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

Use of oestrogen-only or combined oestrogen-progestagen 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 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 & 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)
* 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-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 & 95%CI	Additional cases per 1000 HRT
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			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			

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL- Dublin 2; Tel: + 353 1 6764971; Fax: +353 16762517.

Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

Overdosage is unlikely with transdermal application. Nausea, vomiting, sleepiness, dizziness and withdrawal bleeding may occur in some women. There is no specific antidote and treatment should be symptomatic. The patch(es) should be removed. Aforementioned information is also applicable for overdosing in children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: G03CA03

Urogenital system and sex hormones

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

Clinical trial Information

- Relief of oestrogen-deficiency symptoms and bleeding patterns
- Relief of menopausal symptoms was achieved during the first few weeks of treatment

5.2 Pharmacokinetic properties

The average half-life of estradiol in plasma is about one hour. Plasma clearance is 650-900 litre/day/m₂. Estradiol is metabolised mainly in the liver, the most important metabolites are estriol, estrone and their conjugates (glucuronides, sulphates), which are much less active than estradiol.

The metabolites of estradiol are eliminated mainly by the kidney as glucuronides and sulphates. The metabolites of estradiol are also found in faeces, due to an entero-hepatic circulation.

Following cutaneous application of DERMESTRIL-Septem, estradiol is released from the drug-containing adhesive matrix through the skin and reaches the systemic circulation directly, avoiding first-pass metabolism by the liver. Consequently, the estradiol:estrone ratio in plasma, which falls to values below 1 after the menopause and during oral oestrogen replacement therapy, return to pre-menopausal levels (approximately 1) with transdermal estradiol.

The nominal daily *in vivo* release rate of DERMESTRIL-Septem 75 is 75 μ g of estradiol; the system is active for one week. This release rate results in physiological estradiol serum concentrations, i.e. in the range of those observed during the premenopausal early follicular phase, which are constantly maintained throughout the patch application period.

Physiological concentrations of estradiol were achieved 6 hours after application of DERMESTRIL-Septem 75 in postmenopausal women, with average concentrations ($C_{average}$) over 367 pmol/l after 12 hours.

Following repeated applications of DERMESTRIL-Septem 75 patches at one week intervals, mean maximum serum (C_{max}) estradiol concentrations of 404 pmol/l were obtained at steady-state. The serum concentration of estradiol remained within the physiological levels of premenopausal women throughout the seven days of application and returned to baseline within 12-24 hours after removal of the patch.

The average concentration (C_{average}) of estradiol in steady-state conditions was 242 pmol/l. The C_{min} (trough) of estradiol, shown to be at the steady state, was 125 pmol/l.

5.3 Preclinical safety data

Animal studies with estradiol have shown expected oestrogenic effects. There are no preclinical data of relevance to the prescriber that are additional to those already included in other sections of the SPC.

Local tolerance studies performed in the rabbit have demonstrated the good skin tolerability of the transdermal patch after single and repeated applications. The patch did not show any sensitisation potential in the guinea pig.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Estradiol-containing

adhesive matrix: acrylic copolymers (Durotak 387-2353; Durotak 387-2287)

Backing foil: polyethylene terephthalate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Do not store above 25°C.

DERMESTRIL-Septem should be stored in an intact sachet.

6.5 Nature and contents of container

DERMESTRIL-Septem 75 is packed in a cardboard box containing 4 or 12 transdermal delivery systems sealed individually in protective sachets consisting of 4 layers: Surlyn, heat-sealable material (inner layer), aluminium foil, polyethylene and paper (outer layer).

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

Tear open the sachet at the indentation (do not use scissors to avoid damaging the patch) and remove the patch. Hold the patch between the thumb and index finger at the corner of the pull-off-tag. Detach the protective liner with the other hand and discard it.

Do not touch the adhesive side of the patch. Apply the patch to the skin holding between the thumb and index finger the part still covered by the protective liner. Detach the remaining part of the protective liner and press firmly for about 10 seconds on the whole surface of the patch.

Pass a finger along the edges to assure good adhesion.

After use, the patch should be folded with the adhesive part inside and discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rottapharm Ltd

Damastown Industrial Park

29 October 2020

CRN009XGZ

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Mulhuddart
Dublin 15
Ireland

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 1st December 2008

10 DATE OF REVISION OF THE TEXT

October 2020