1. NAME OF THE MEDICINAL PRODUCT

DERMESTRIL 25 micrograms/24 hours transdermal patches
DERMESTRIL 50 micrograms/24 hours transdermal patches
DERMESTRIL 100 micrograms/24 hours transdermal patches

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch contains oestradiol as an active ingredient in the following quantities:

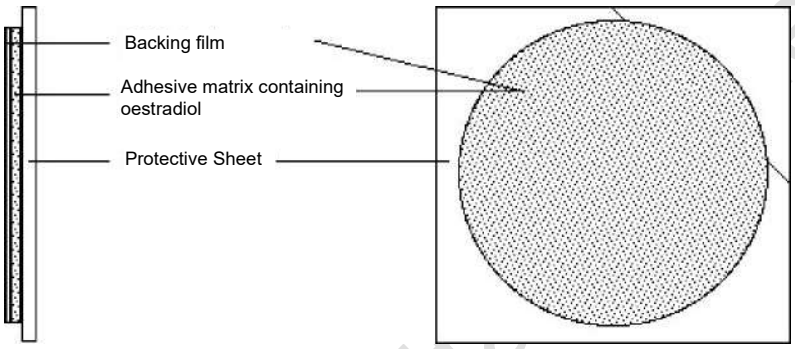
DERMESTRIL 25 micrograms: 2 mg
DERMESTRIL 50 micrograms: 4 mg
DERMESTRIL 100 micrograms: 8 mg

3. PHARMACEUTICAL FORM

Transdermal patch.

A transdermal patch consists of a transparent, slightly opaque backing film, an adhesive matrix containing oestradiol, and a protective sheet that must be removed before use.
The composition of the 3 systems (Dermestril 25 micrograms, 50 micrograms, 100 micrograms) per unit area is identical. The three different dosages of DERMESTRIL differ both in surface area and in the daily in vivo release of the active ingredient.

Visual representation:



	DERMESTRIL		
	25	**50**	**100**
Surface area (release area)	9 cm^2	18 cm^2	36 cm^2
Nominal daily release of oestradiol (*in vivo*):	25 µg	50 µg	100 µg

4. CLINICAL INFORMATION

4.1 Therapeutic Indications

DERMESTRIL 25, 50, 100
Hormone replacement therapy (HRT) for symptoms resulting from oestrogen deficiency in women at least 6 months after their last menstruation.
DERMESTRIL 50, 100
Second-line treatment to prevent osteoporosis in postmenopausal women at high risk of future fractures who have specific intolerances or contraindications to other medicinal products authorised for the prevention of osteoporosis (see section 4.4).

Treatment experience in women over 65 years of age is limited.

4.2 Posology and method of administration

- POSOLOGY

Treatment is normally started with 1 patch of DERMESTRIL 50 applied to the skin twice a week to ensure continuous administration of the hormone. The patch must be removed every 3-4 days and replaced by a new one. Three dosages of DERMESTRIL are available: DERMESTRIL 25 micrograms, 50 micrograms and 100 micrograms.

The dosage must be adjusted on an individual basis during treatment in relation to efficacy or overdose symptoms (e.g. the onset of breast tenderness and/or vaginal bleeding). For the initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose should be used for the shortest possible treatment period (see also section 4.4).
In the event of adverse effects or symptoms of overdose (e.g. breast tenderness and/or vaginal bleeding), the dose must be reduced.
The maximum dose of 100 µg per day should not be exceeded.
The lowest effective dose should be used for maintenance therapy.
DERMESTRIL is generally used for treatment cycles of 3 weeks (6 applications) followed by one week without treatment. Vaginal bleeding may occur during this week.
Continuous, non-cyclic treatment is recommended for women who have undergone hysterectomy or in cases where severe oestrogen deficiency symptoms reappear during therapy-free intervals.
DERMESTRIL should be combined with a progestogen at least in women with an intact uterus, according to the instructions of the patient's doctor, as outlined as follows, for example:
In women with an intact uterus, a progestogen approved for adjunctive use with oestrogen should also be administered for at least 12-14 days of each month/28-day cycle to counteract the development of hyperplasia or endometrial cancer due to oestrogen stimulation (see section 4.4).
Unless the patient has been previously diagnosed with endometriosis, the addition of a progestogen is not recommended for women without a uterus.
Three different treatment regimes can be employed:

'Cyclic'
Dermestril is administered cyclically, with an interval during which treatment is discontinued, usually 21 days of treatment and 7 days of discontinuation. The progestogen is usually administered for 12-14 days of the cycle; bleeding may occur during the withdrawal period.

'*Continuous sequential*':
Dermestril is administered without interruption. The progestogen is usually administered sequentially for 12-14 days during each month/28-day cycle. Bleeding may occur during the withdrawal period.

'*Continuous-combined*':
Dermestril and the progestogen are administered daily without interruption.

Treatment with DERMESTRIL can begin at any time for women who have not already undergone HRT. Women who have received cyclic or sequential oestrogen/progestogen therapy should complete ongoing treatment before starting treatment with DERMESTRIL; the most suitable time to start treatment with DERMESTRIL is on the first day of withdrawal bleeding. Women who are already receiving continuous oestrogen-progestogen combination therapy may switch directly to treatment with DERMESTRIL.

- METHOD OF ADMINISTRATION

Each box contains 8 transdermal therapeutic systems (patches) individually packaged in sachets.
Open the sachet by tearing it from the marked notch and pull the patch out (do not use scissors to avoid damaging the patch).
Each DERMESTRIL patch consists of two parts: the actual transdermal system (containing the active ingredient) and a transparent protective sheet with a circular dot relief and a white logo.
Hold the patch between your thumb and forefinger at the smaller part of the protective sheet marked by a notch. Peel off the larger part of the protective sheet with your other hand and remove it. Avoid touching the adhesive part of the patch.
Apply the patch to the skin of the hips or the lumbar or abdominal region, always holding the patch between the thumb and forefinger at the part still covered by the protective sheet.
Peel off the remaining part of the protective sheet and press firmly over the entire surface of the plaster for about 10 seconds. Press firmly using a finger along the edges to ensure good adhesion.
The skin at the application site must be clean, dry and not greasy and must not present any redness or irritation.
The patch should not be applied to parts of the body that form large folds during movement and body areas from which the patch could come off due to movement or rubbing.
DERMESTRIL should not be applied to the breasts.
Patches should not be applied twice consecutively at the same site.
DERMESTRIL should be replaced twice a week to ensure continuous administration of oestradiol. For example, if therapy is started on a Monday or Thursday, the patch must be replaced on the following Thursday or Monday, respectively.
When the instructions above are followed carefully, the patch should adhere to the skin without any problems for a period of 4 days. If the patch comes off, it must be replaced with a new patch. In any case, regular patch replacement should take place according to the initial schedule. If the patient forgets to replace the patch on the scheduled day, it must be replaced as soon as possible. A new patch should then be applied regularly according to the previously established dates. Failure to take one or more doses may increase the likelihood of breakthrough bleeding and spotting.

When the patch is applied correctly, bathing or showering should not cause any problems; however, it may come off after a very hot bath or sauna. If this happens, it will have to be replaced with a new one. If possible, sauna visits should be scheduled for the day set for the patch change.
Used patches must be folded with the adhesive part inside and discarded.

4.3 Contraindications

- hypersensitivity to the active ingredient or to any of the excipients listed in section 6.1
- ;
- past, suspected or known breast cancer;
- suspected or known oestrogen-dependent malignant tumours (e.g. endometrial cancer);
- undiagnosed genital bleeding;
- untreated endometrial hyperplasia;
- current or previous venous thromboembolism (e.g. deep vein 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 history of liver disease, until liver function tests have returned to normal;
- porphyria.

4.4 Special warnings and precautions for use

- For the treatment of postmenopausal symptoms, the patient should only begin HRT if they are suffering from symptoms that adversely affect their 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 benefits outweigh the risks.
- 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 risks and benefits for these women may be more favourable than in older women.

Medical examination and follow-up checks

Before starting or resuming HRT, a complete family and personal history must be taken by the patient's doctor. A general and gynaecological examination (including pelvic and breast examination) must also be performed, taking into consideration the patient's medical history and the contraindications and warnings for use.
During treatment, periodic clinical examinations of a nature and frequency appropriate to the individual case are recommended. Women should be advised to report any changes in their breasts to their doctor (see 'breast cancer' below). Clinical investigations, including the use of appropriate imaging tools, e.g. mammography, must be performed in line with currently accepted clinical protocols and the clinical needs of the individual case.

Conditions requiring special monitoring

If any of the following conditions are present, or have been diagnosed in the past, and/or have been aggravated by pregnancy or previous hormone treatment, the patient should be closely monitored. The following conditions in particular may reoccur or worsen during treatment with DERMESTRIL:

- leiomyoma (uterine fibroids) or endometriosis;
- risk factors for thromboembolic diseases (see below);
- risk factors for oestrogen-dependent tumours (e.g. first degree relative with breast cancer);
- hypertension;
- hepatopathies (e.g. hepatic adenoma);
- diabetes mellitus with or without vascular involvement;
- cholelithiasis;
- migraines or (severe) headaches;
- systemic lupus erythematosus;
- history of endometrial hyperplasia (see below);
- epilepsy;
- asthma;
- otosclerosis.

Reasons for immediate discontinuation of treatment

Treatment must be discontinued immediately if a contraindication arises and in the following cases:

- jaundice or deterioration in liver function;
- significant increase in blood pressure;
- onset of migraine-type headaches;
- pregnancy.

Endometrial hyperplasia and carcinoma

- In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma increases if oestrogen is administered alone for prolonged periods. The increased risk of endometrial cancer among oestrogen-only users is 2 to 12 times higher than among non-users, depending on duration of treatment and the oestrogen dose (see section 4.8). After discontinuing treatment, the risk remains elevated for at least 10 years. The addition of a progestogen for at least 12 days per month/28-day cycle or continuous-combined oestrogen therapy in women with an intact uterus greatly reduces this risk. The endometrial safety of added progestogens for patches that deliver more than 50 µg per day has not been studied.
- Breakthrough bleeding and spotting may occur during the first few months of treatment. If these symptoms appear after the start of therapy, or continue after the discontinuation of treatment, the cause should be investigated, which may include endometrial biopsy to rule out endometrial malignancy.
- Unbalanced oestrogen stimulation may lead to premalignant or malignant transformation of residual foci of endometriosis. The addition of progestogens to HRT with oestrogen should therefore be considered for women who have undergone hysterectomy due to endometriosis, especially in cases of residual endometriosis.

Breast cancer

The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestogen or oestrogen-only HRT that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen therapy

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

Oestrogen-only therapy

- The WHI study found no increased risk of breast cancer for women who have undergone hysterectomy using oestrogen-only HRT. Observational studies have mainly reported a slightly increased risk of breast cancer diagnosis, which is lower than in women taking oestrogen-progestogen combinations (see section 4.8).

The results of an extensive meta-analysis show that after stopping treatment, the excess risk will decrease with time, and the time it takes to return to baseline values depends on the duration of previous HRT use. When HRT has been taken for more than 5 years, the risk may persist for 10 years or more.

HRT, in particular combined oestrogen-progestogen therapy, 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 indicates a slight increase in risk for women taking oestrogen-only or oestrogen therapy combined with progestogen. This risk is greatest within 5 years of therapy use and decreases over time after stopping. Some other studies, including the WHI study, suggest that the use of combined HRT may be associated with a similar or slightly smaller risk (see section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3 to 3-fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. This is more likely to occur in the first year of HRT than later (see section 4.8).
- Patients with a history of venous thromboembolism or with known thrombophilic states are at 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 oestrogen use, older age, major surgery, prolonged

immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/the postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus as to the possible role of varicose veins in VTE.

As in all postoperative patients, prophylactic measures must be considered to prevent VTE following surgery. If elective surgery is to be followed by prolonged immobilisation, it is recommended that HRT be temporarily suspended for a period of 4 to 6 weeks before surgery. Treatment should not begin again until the patient has regained full mobility.

- In women with no personal history of VTE, but with a first-degree relative with a history of thrombosis at a young age, screening may be recommended after thorough advice regarding its limitations (only a fraction of thrombophilic defects are identified by screening). If a thrombophilic defect is identified that isolates with thrombosis among family members or if the alteration is 'severe' (e.g. antithrombin, protein S or protein C deficiencies or a combination of deficiencies), HRT is contraindicated.

- For women already treated with chronic anticoagulant therapy, the risk-benefit ratio of HRT use should be carefully considered.

- If VTE develops after starting therapy, the drug must be discontinued. Patients should be told to contact their doctor immediately if they experience a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden chest pain, dyspnoea).

Coronary artery disease (CAD)
- Randomised controlled trials showed no protection from myocardial infarction in women with or without existing CAD who received combined oestrogen-progestogen therapy or oestrogen-only HRT.

Combined oestrogen-progestogen therapy
The relative risk of CAD during combined oestrogen-progestogen use increases slightly. Since the absolute baseline risk of CAD is highly dependent on age, the number of additional cases due to oestrogen+progestogen use is very low in healthy women approaching the menopause but will increase with advancing age.

Oestrogen-only therapy
Randomised controlled data found no increased risk of CAD in women who have undergone hysterectomy taking oestrogen-only therapy

Ictus
- Combined oestrogen-progestogen and oestrogen-only therapy are associated with up to a 1.5-fold increase in the risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, since the risk of stroke at baseline is highly dependent on age, the overall risk of stroke in women using HRT will increase with age (see section 4.8).

Other conditions
- Oestrogens can cause fluid retention, therefore patients with renal or cardiac dysfunction should be carefully monitored. Patients with terminal renal failure must be closely monitored, as circulating levels of the active substance in DERMESTRIL are expected to increase.
- Women with pre-existing hypertriglyceridaemia should be closely monitored during oestrogen therapy or HRT, as rare cases of major increases in plasma triglycerides leading to pancreatitis have been reported following oestrogen therapy in patients with this condition.
- Oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Oestrogens increase levels of thyroid hormone-binding globulin (TBG), leading to increased levels of circulating thyroid hormone, as measured by iodine-binding protein (PBI), T4 levels (column or RIA method) or T3 levels (RIA method). T3 resin uptake is reduced, reflecting the increase in TBG. The free T3 and T4 fractions are not affected. Other binding proteins, such as corticosteroid-binding globulin (CBG) and sex hormone-binding globulin (SHBG), may increase and result in increased circulating levels of corticosteroids and sex hormones, respectively. The free, biologically active hormone fractions are not affected. 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 an increased risk of probable

dementia for 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 programme 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 programme ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the programme glecaprevir/pibrentasvir. See section 4.5.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogen (and progestogens) may be boosted by the concomitant use of substances known to induce drug-metabolising enzymes, particularly cytochrome P450, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (rifampicin, rifabutin, nevirapine, efavirenz). In contrast, ritonavir and nelfinavir, though known as strong inhibitors, exhibit induction properties when used in conjunction with steroid hormones. Herbal remedies such as Hypericum perforatum can induce oestrogen (and progestogen) metabolism.
Transdermal preparations are affected to a lesser extent by enzyme inducers than oral preparations as they avoid the hepatic first-pass effect. Clinically, an increased metabolism of oestrogen and progestogens may reduce their efficacy and lead to changes in the uterine bleeding profile.

Pharmacodynamic interactions
During clinical trials with the HCV combination drug programme 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 programme ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the programme n with glecaprevir/pibrentasvir (see section 4.4).

4.6 Fertility, pregnancy and breastfeeding

Pregnancy
DERMESTRIL is not indicated during pregnancy. If pregnancy occurs during treatment with DERMESTRIL, treatment must be discontinued immediately. The results of most available epidemiological studies indicate that accidental foetal exposure to oestrogen does not result in teratogenic or foetotoxic effects.

Breastfeeding

DERMESTRIL is not indicated during breastfeeding.

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 were treated with the product during clinical trials.
Approximately 10-15% of patients treated with DERMESTRIL in clinical trials experienced systemic adverse reactions that were mild and transient. Breast tenderness was reported in 20-35% of patients. Local reactions at the application site, mainly mild erythema with or without itching, were observed in 10-25% of patients.
Serious adverse reactions associated with the use of HRT are also mentioned in section 4.4 '**Special warnings and precautions for use**'.

The following table shows the list of adverse reactions that have been observed in HRT users according to the MedDRA system and organ classification (MedDRA SOCs).

Classification by systems and organs	Common (≥1/100, <1/10)	Uncommon (≥1/1.000,	Rare (<1/1.000)
Infections and infestations		Candidiasis of the vagina	
Immune system disorders		Hypersensitivity reaction	
Metabolism and nutrition disorders	Increase or decrease in body weight		
Psychiatric disorders		Depression	Anxiety Decreased or increased libido
Neurological disorders	Headaches	Dizziness	Migraine
Eye disorders		Visual disorders	Contact lens intolerance
Cardiac disorders		Palpitations	
Gastrointestinal disorders	Abdominal pain Nausea	Indigestion	Bloating Vomiting
Hepatobiliary disorders		Gallbladder disorders	
Skin and subcutaneous tissue disorders	Pruritic Rash	Erythema nodosum Urticaria	Hirsutism Acne
Diseases of the skeletal muscle and connective tissue			Muscle cramps
Reproductive system and breast disorders	Metrorrhagia Uterine/vaginal bleeding incl. spotting	Breast pain Breast tenderness	Dysmenorrhoea Vaginal discharge Premenstrual syndrome Increase in breast volume
Systemic diseases and conditions related to the site of administration		Oedema	Fatigue

The most appropriate MedDra term is used to describe a particular reaction and its synonyms and conditions.

Other side effects have been reported with the use of oestradiol (frequency not known)
Benign, malignant and unspecified tumours (incl. cysts and polyps)
Breast cancer[a]
benign and malignant oestrogen-dependent tumours, e.g. endometrial cancer[b], ovarian cancer[c]
Increased size of leiomyomas

Neurological disorders
Probable dementia over 65 years of age (see section 4.4), chorea, exacerbation of epilepsy

Vascular disorders
Ictus [f]
Arterial thromboembolism, such as angina and myocardial infarction. For further information, see sections

4.3 and 4.4.
Venous thromboembolism[d], such as deep vein thrombosis of the leg, pelvic venous thrombosis and pulmonary embolism. For further information, see sections 4.3 and 4.4.

Gastrointestinal disorders
Pancreatitis (in women with pre-existing hypertriglyceridaemia)
Gastro-oesophageal reflux disease

Hepatobiliary disorders
Abnormal liver function, sometimes with jaundice

Skin and subcutaneous tissue disorders
Erythema multiforme
Chloasma
Vascular purpura
Angioedema
Reactions at the application site: erythema with and without itching

Renal and urinary disorders
Urinary incontinence

Reproductive system and breast disorders
Fibrocystic mastopathy

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 women 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 below.

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 (years) at the start of HRT	Incidence per 1,000 HRT non-users over a 5-year period (50-54 years)*	Risk ratio	Additional cases per 1,000 HRT users after 5 years
		Oestrogen-only HRT	
50	13.3	1.2	2.7
		Combined oestrogen-progestogen	
50	13.3	1.6	8.0
*Taken from baseline incidence rates in England in 2015 in 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/m2)

Age (years) at the start of HRT	Incidence per 1,000 HRT non-users over a 5-year period (50-54 years)*	Risk ratio	Additional cases per 1,000 HRT users after 5 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/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.			

US WHI Studies – Additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1,000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1,000 HRT users over 5 years' use (95% CI)
		Oestrogen therapy (CEE)	
50-79	**21**	**0.8 (0.7-1.0)**	**-4 (6 - 0)** [2]
		Combined oestrogen-progestogen therapy (CEE + MPA)	
50-79	**17**	**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 evidence of increased risk during the first 5 years of treatment. After 5 years the risk was higher than in non-users.

[2] WHI study in women with no uterus which did not show an increase in risk of breast cancer.

Endometrial cancer

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 epidemiological 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 the 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 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

HRT is associated with a 1.3 to 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). The results of the WHI studies are presented below:

WHI Studies – Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1,000 women in the placebo arm	Risk ratio & 95%CI	Additional cases per 1,000 HRT users
Oral oestrogen-only therapy [3]			
50-59	7	1.2–0.6-2.4	1 (3 - 10)
Oral combined oestrogen-progestogen therapy			
50-59	4	2.3–1.2-4.3	5 (1-13)

3 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 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 [4] over 5 years' use

Age range (years)	Incidence per 1,000 women in the placebo arm	Risk ratio & 95%CI	Additional cases per 1,000 HRT users over 5 years' use
50-59	8	1.3 (1.1 -1.6)	3 (1 - 5)

4 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, as it allows for the continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via the national reporting system at https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Overdose
Overdose is unlikely with transdermal application. Nausea, vomiting, drowsiness, dizziness and amenorrhoea may occur in some women. There is no specific remedy and treatment should be symptomatic. The patch must be removed.
Symptoms of overdose include breast tenderness and/or the onset of vaginal bleeding. In such cases, a dosage reduction should be considered.
If necessary, an overdose can be quickly controlled by removing the patch.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: Natural and semisynthetic oestrogen, not combined
ATC: G03CA03
The active synthetic 17-β-estradiol is chemically and biologically identical to endogenous human oestradiol. It replaces the loss of oestrogen production in menopausal women and alleviates symptoms of the menopause. Oestrogen prevents the loss of bone tissue following the menopause or ovariectomy.
Information from clinical studies
Alleviation of symptoms of oestrogen deficiency and bleeding profile.

Cyclic or sequential administration
Relief of symptoms of the menopause was achieved during the first few weeks of treatment.
Regular withdrawal bleeding occurred in 60-90% of women with an average duration of 3-4 days. The withdrawal bleeding usually started after the last pill of the progestogen phase. Breakthrough bleeding and/or spotting appeared in 10-20% of women during the first three months of therapy.
Combined-continuous administration
Amenorrhoea occurred in 90% of the women during the first three months of treatment.
Prevention of osteoporosis
Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogen on 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-analysis of trials show that current use of HRT, oestrogen 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.
In clinical studies conducted with Dermestril after two years of treatment, the increase in bone mineral density (BMD) in the lumbar spine was 6.57 ± 0.87.
Information on serum lipids
Considering that no benefit of HRT in the primary and secondary prevention of coronary artery disease has been demonstrated, the clinical relevance of changes in serum lipids is unknown and its relevance to product safety is therefore unclear.

5.2 Pharmacokinetic properties
The half-life of oestradiol in plasma is about 1 hour. Metabolism of oestradiol occurs mainly in the liver. The most important metabolites are estriol, estrone and their conjugates (glucuronates, sulphates), which are much less active than estradiol. Metabolites are largely eliminated in urine in the form of glucuronates and sulphates. Estradiol metabolites also pass through the enterohepatic cycle in the faeces.
After oral administration, most of the oestradiol is metabolised in the gut and liver into oestrone and its conjugates before reaching the bloodstream, causing non-physiological high concentrations of oestrone in plasma. The consequences of a chronic accumulation of oestrone in the body are still unclear. However, it has been established that prolonged oral administration of oestrogens induces an increase in protein synthesis in the liver, particularly of the renin substrate, resulting in an increase in blood pressure.
After cutaneous application of DERMESTRIL, oestradiol is released from the adhesive matrix containing the active ingredient directly to the skin and reaches the systemic circulation, without being metabolised in the liver, thus avoiding the stimulation of hepatic protein synthesis and an accumulation of oestradiol in the body. Consequently, the oestradiol/oestrogen ratio in plasma, which decreases to less than 1 after the menopause and is kept constant with oral oestrogen administration, returns to the premenopausal value of 1 with transdermal oestradiol administration.
The daily release of DERMESTRIL 25, 50, 100 in vivo is 25 µg, 50 µg and 100 µg of oestradiol respectively. The patch is active for 4 days.
After application, the doses released achieve physiological serum concentrations of oestradiol equal to those of the early premenopausal follicular phase, which remain constant throughout the treatment period. After a single application of DERMESTRIL with a daily release of 100 µg of oestradiol, physiological serum oestradiol levels are reached in postmenopausal women about 4 hours after application and average maximum levels of 70 pg/ml are reached. The serum oestradiol concentration remains within the physiological levels of women of childbearing age for 3-4 days of application and returns to baseline levels within 12 hours after the withdrawal of DERMESTRIL.
Serum oestradiol levels are proportional to the dose administered.
Following repeated applications of DERMESTRIL 25 at weekly intervals, a C_{max} value of oestradiol of 37 pg/ml was obtained at steady state.
The mean concentration of estradiol was 23 pg/ml at steady state.
The C_{min} value of oestradiol was 12 pg/ml at steady state.
Following repeated applications of DERMESTRIL 50 at weekly intervals, a C_{min} of oestradiol of 61 pg/ml was obtained at steady state.
The mean concentration of oestradiol was 40 pg/ml at steady state.
The C_{min} of oestradiol was 20 pg/ml at steady state.

Following repeated applications of DERMESTRIL 100 at weekly intervals, a C_{max} of oestradiol of 117 pg/ml was obtained at steady state.
The mean concentration of oestradiol was 79 pg/ml at steady state.
The C_{min} of oestradiol was 44 pg/ml at steady state.

5.3 Pre-clinical safety data

Since oestradiol is a physiological hormone, used for many years in the clinical setting in various pharmaceutical forms, well documented in the scientific literature, toxicity studies with DERMESTRIL have been limited to examining local tolerability.
Local tolerability studies in rabbits, with single and repeated application of DERMESTRIL, showed good system tolerability. A test animal sensitisation study with DERMESTRIL showed no sensitisation potential.
Primary irritation and sensitisation studies performed on the acrylic copolymers constituting, together with oestradiol, the adhesive matrix of the patch confirmed the safety of these components.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

Estradiol-containing adhesive matrix: acrylic copolymers.
Backing film: lacquered polyethylene terephthalate.
The transdermal systems are covered with a transparent polyester protective sheet that is peeled off before use.

6.2 Incompatibilities

There are no known pharmaceutical incompatibilities.

6.3 Shelf life

2 years.
The indicated expiry date refers to the product correctly stored in intact packaging.

6.4 Special precautions for storage

DERMESTRIL must be stored, in closed sachets, at temperatures below 25°C.

6.5 Nature and contents of the container

Cardboard box containing 8 transdermal therapeutic systems.
Each patch is packaged in a heat-sealed protective sachet with an aluminium lining.

6.6 Special precautions for disposal and other handling

No particular instructions.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations
in force.

7. MARKETING AUTHORISATION HOLDER

ROTTAPHARM S.p.A., Galleria Unione, 5 - 20122 Milan

8. MARKETING AUTHORISATION NUMBER

DERMESTRIL 25 microgram transdermal patches: MA No. 029001017
DERMESTRIL 50 microgram transdermal patches: MA No. 029001029
DERMESTRIL 100 microgram transdermal patches: MA No. 029001031

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

Date of first Authorisation: April 1995
Latest date of renewal: April 2010

10. DATE OF REVISION OF THE TEXT