PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

PROPRIETARY NAMES (AND DOSAGE FORM)

Estalis® 50/140 (matrix transdermal patch)

Estalis® 50/250 (matrix transdermal patch)

COMPOSITION

ESTALIS matrix transdermal patches contain estradiol hemihydrate and norethisterone acetate, providing the following release rates of estradiol and norethisterone acetate over a period of 3,5 to 4 days.

Name	**Nominal release rate (microgram/day) Estradiol/NETA**	**Estradiol content (mg)***	**NETA** content (mg)**
ESTALIS 50/140	50/140	0,620	2,70
ESTALIS 50/250	50/250	0,512	4,80

* 1 mg estradiol hemihydrate Ph. Eur. is equivalent to 0,968 mg estradiol

** NETA = norethisterone acetate

List of excipients:

Silicone and acrylic adhesives, povidone, oleic acid and dipropylene glycol.

The backing layer consists of a polyester film laminate.

The protective (release) liner, which is removed before applying the patch to the skin, is a fluoropolymer coated polyester film.

PHARMACOLOGICAL CLASSIFICATION

A21.8.2 Progesterones with or without estrogens.

PHARMACOLOGICAL ACTION

Estradiol is an estrogen.

Norethisterone acetate:

NETA is a potent progestogen. It is hydrolysed in the skin to norethisterone (NET), which is the active hormone in the circulation.

NETA administered by the transdermal route, avoids first-pass metabolism.

Estradiol and NETA combination:

Unopposed estrogens increase the incidence of endometrial hyperplasia and the risk of endometrial carcinoma. The addition of a progestogen for 10 or more days of a cycle of estrogen administration greatly lowers the incidence of endometrial hyperplasia, and thereby irregular bleeding and endometrial carcinoma, compared to estrogen treatment alone. Whereas the use of these cyclic regimens results in the regular shedding of the estrogen-stimulated endometrium (monthly bleeds), the administration of ESTALIS, a continuous/combined estradiol/ progestogen, results in an atrophic endometrium and amenorrhoea.

Pharmacokinetics:

Absorption:

Estradiol:

Following the application of an ESTALIS matrix transdermal patch, serum estradiol levels and estrone-to-estradiol ratios lie in the same range as that found in premenopausal women at the early (estradiol > 40 pg/ml) to mid-follicular phase. These levels are maintained for an 84 to 96 hour application period. Repeated application of ESTALIS (50/250 µg/day, 50/140 µg/day) patches resulted in average serum estradiol concentrations of 51 and 46 pg/ml. At the end of the application periods, the mean serum estradiol concentrations were 46 and 30 pg/ml, respectively.

Norethisterone acetate:

Repeated application of ESTALIS (50/250 µg/day, 50/140 µg/day) patches resulted in average steady-state serum norethisterone concentrations of 832 and 492 pg/ml, respectively. At the end of the application periods, the mean serum concentrations of norethisterone were 681 and 393 pg/ml, respectively. Serum norethisterone concentrations increased linearly with increasing doses of NETA.

Distribution:

Serum estradiol and norethisterone concentrations demonstrate consistent deliveries over the application interval. There is no accumulation of estradiol or norethisterone in the circulation following multiple applications.

Metabolism and excretion:

Estradiol:

Transdermally delivered estradiol is metabolised only to a small extent by the skin and bypasses the first-pass effect seen with orally administered estrogen products.

Estradiol has a short elimination half-life of approximately 2 to 3 hours, and a rapid decline in serum levels is therefore observed after the patch is removed. Following removal, serum

concentrations of estradiol return to untreated postmenopausal levels (< 20 pg/ml) within 4 to 8 hours.

Norethisterone acetate:

The elimination half-life of norethisterone is reported to be 6 to 8 hours. After removal of the ESTALIS patch, serum norethisterone concentrations diminish rapidly and are less than 50 pg/ml within 48 hours.

INDICATIONS

ESTALIS 50/140 and 50/250 are indicated for:

The symptomatic treatment of post menopausal symptoms such as hot flushes and vaginal dryness in post-menopausal women with an intact uterus.

ESTALIS 50/140 and 50/250 are indicated to reduce the risk of postmenopausal bone loss in postmenopausal women with an intact uterus.

CONTRAINDICATIONS

ESTALIS should not be used by women with any of the following conditions:

- Known hypersensitivity to estrogens or any other component of ESTALIS,
- Known or suspected pregnancy,
- Breast-feeding,
- Undiagnosed abnormal vaginal bleeding,
- Known or suspected breast cancer,
- History of breast cancer,
- Known or suspected cancer of the endometrium or other estrogen-dependent neoplasia,

- Existing or previous severe hepatic disease,
- History of or current venous thromboembolism (e.g. deep vein thrombosis, pulmonary embolism),
- Known thrombophilic disorders or thrombophlebitis,
- History of or current arterial thromboembolic disease (e.g. coronary heart disease, stroke),
- Porphyria.

WARNINGS

If any of the conditions/risk factors mentioned above is present, the use of ESTALIS should be carefully weighed against the possible risks for each individual woman. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should be told to contact her physician immediately. The physician should then decide on whether the use of ESTALIS should be discontinued.

Osteoporosis:

When initiating HRT for the prevention of osteoporosis, careful consideration should be given to the benefits versus the risks for the individual. Potential alternative therapies should be considered if the risks outweigh the benefits. Periodic re-evaluation for continuing treatment is recommended.

Contact sensitisation:

Contact sensitisation is known to occur with all topical applications. Although it is extremely rare, women who develop contact sensitisation to any of the components of the patch should be warned that a severe hypersensitivity reaction may occur with continuing exposure to the causative agent.

Cardiovascular disease:

HRT should not be used to prevent cardiovascular disease.

Large clinical trials (Women's Health Initiative and Heart and Estrogen/Progestin Replacement study) showed an increased risk of cardiovascular events with the combined HRT products used in these studies. The risk for estrogen-only HRT products is still under evaluation.

The Women's Health Initiative (WHI) is a randomised clinical trial conducted with continuous combined oral conjugated equine estrogens (CEO) and medroxyprogesterone acetate (MPA) for an average follow-up of 5,2 years. In the WHI trial, the absolute excess risk of coronary heart disease was 7 additional cases per 10 000 person-years (37 versus 30) in HRT-treated women and the relative risk was 1,29.

In addition, the WHI study showed an increased incidence of stroke. The absolute excess risk was 8 additional cases per 10 000 person-years (29 versus 21) in HRT-treated women and the relative risk was 1,41.

The Heart and Estrogen/Progestin Replacement Study (HERS), which is a controlled clinical trial of secondary prevention in postmenopausal women with documented heart disease conducted with CEO and MPA, showed an increased risk of cardiovascular events in the first year of use and no cardiovascular benefit thereafter.

For transdermal estrogen-only and estrogen-progestogen combined HRT products, there are no randomised controlled trials to date assessing the HRT-associated risk of cardiovascular morbidity or mortality, or stroke. Therefore there are no data to support the conclusion that the frequency of cardiovascular events and stroke is different with ESTALIS.

Breast cancer:

Randomised controlled trials and epidemiological studies have reported an increased risk of breast cancer in women taking HRT.

Women using estrogen-progestogen combined HRT had a possibly higher risk as compared with women who used unopposed estrogens. The excess risk of breast cancer increases with the duration of intake of estrogen-only and estrogen-progestogen combined HRT.

There is evidence arising from the WHI study (see subsection Cardiovascular disease) which shows an absolute excess risk of invasive breast cancer of 8 additional cases per 10 000 person-years (38 versus 30) in the HRT-treated women and a relative risk of 1,26.

A meta-analysis reanalysed 51 epidemiological studies conducted between the 1970s and the early 1990s. The cumulative incidence of breast cancer between the ages of 50 and 70 in non-users of HRT is about 45 per 1 000 women. The cumulative excess numbers of breast cancers diagnosed between these ages per 1 000 women who began use of HRT at age 50 to 70 and used it for 5, 10, and 15 years, are estimated to be 2, 6, and 12, respectively.

The number of additional cases of breast cancer is broadly similar for women who start HRT regardless of age at start of treatment (between ages of 45 and 65).

The excess risk seems to return to baseline in the course of about five years after stopping treatment.

For ESTALIS no large randomised clinical trials to date have assessed the HRT-associated risk of breast cancer. Therefore there are no data to support the conclusion that the frequency of breast cancer is different with ESTALIS.

Ovarian cancer:

In some epidemiological studies, the long-term use of unopposed estrogens in hysterectomised women has been associated with an increased risk of ovarian cancer.

Endometrial cancer:

The risk of endometrial cancer in users of unopposed estrogens who have an intact uterus is greater than in non-users and appears to depend on the duration of treatment and the estrogen dose. The greatest risk appears to be associated with prolonged use. It has been shown that adequate concomitant progestogen therapy lowers the incidence of endometrial hyperplasia and therefore the potential risk of endometrial carcinoma associated with prolonged use of estrogen therapy.

Dementia:

In a randomised placebo-controlled ancillary study of the WHI, the Women's Health Initiative Memory Study (WHIMS), women aged 65 and older (average age 71) treated with oral CEO and MPA for an average follow-up of 4 years were reported to have a two-fold increase in the risk of developing probable dementia. The absolute excess risk of probable dementia was 23 additional cases per 10 000 person-years (45 versus 22) in CEO/MPA treated women and the relative risk was 2,05.

Since only women aged 65 and older were included in this study, it is unknown whether these findings apply to younger postmenopausal women.

For ESTALIS no large randomised clinical trials have assessed the HRT-associated risk of probable dementia to date. Therefore there are no data to support the conclusion that the frequency of probable dementia is different with ESTALIS.

Venous thromboembolism:

Estrogen-only and estrogen-progestogen combined HRT are associated with a higher risk of developing venous thromboembolism (VTE), e.g. deep vein thrombosis or pulmonary embolism.

Two randomised controlled trials (WHI and HERS) and epidemiological studies have found a two- to threefold higher risk for users compared with non-users.

The WHI study (see subsection Cardiovascular disease) showed an increased incidence of pulmonary embolism. The absolute excess risk was 8 additional cases per 10 000 person-years (15 versus 7) in HRT-treated women and the relative risk was 2,13.

The increase in risk was found only in current users and did not persist in former users. The risk appeared to be higher in the first years of use compared to later years.

For non-users, it is estimated that the number of cases of VTE that would occur over a 5-year period is about 3 per 1 000 women aged 50 to 59 years and 8 per 1 000 women aged 60 to 69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE would be between 2 and 6 per 1 000 women aged 50 to 59 years and between 5 and 15 per 1 000 women aged 60 to 69 years.

Risk/benefit should therefore be carefully weighed in consultation with the individual when prescribing HRT to women with a risk factor for the occurrence of VTE that is not already mentioned under Contraindications.

Generally recognised risk factors for VTE include a personal history or positive family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition) of thromboembolic disease, severe obesity (Body Mass Index > 30 kg/m^2) and systemic lupus erythematosus (SLE). The risk of VTE also increases with age. There is no consensus about the possible role of varicose veins in VTE.

A history of recurrent spontaneous abortion should be investigated to exclude thrombophilic predisposition. In women in whom this diagnosis is confirmed, the use of HRT is viewed as contraindicated.

The risk of VTE may be temporarily increased with prolonged immobilisation, major elective or posttraumatic surgery, or major trauma. In women on HRT, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Depending on the nature of the event and the duration of the immobilisation, consideration should be given to temporarily stopping HRT several weeks (four to six weeks) earlier, if possible. The treatment should not be restarted until the woman is completely mobile.

Women should be told to contact their doctor immediately if they become aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

If venous thromboembolism (VTE) develops after initiating therapy, the drug should be discontinued.

INTERACTIONS

Preparations that induce microsomal liver enzymes, e.g. barbiturates, anticonvulsants (including hydantoins and carbamazepine), meprobamate, phenylbutazone and antibiotics (including rifampicin), may impair the activity of estrogens and progestogens (irregular bleeding and recurrence of symptoms may occur). The extent of interference with transdermally administered estradiol and norethisterone acetate is not known but is thought to be limited by this route which avoids any first-pass hepatic metabolism.

PREGNANCY AND LACTATION

Both estrogens and progestogens may cause foetal harm when administered to a pregnant woman. Estrogens or progestogens must not be used during pregnancy.

Estrogens or progestogens are excreted in breast milk and may reduce the production of breast milk. Estrogens or progestogens must not be used while breast feeding.

DOSAGE AND DIRECTIONS FOR USE

Initiation of therapy:

Menopausal women who are not already receiving estrogen/progestogen therapy may start using ESTALIS patches at any convenient time.

Women already receiving sequential estrogen/progestogen therapy should complete the current cycle of therapy before starting on ESTALIS. Bleeding usually occurs at the end of a cycle of sequential therapy, and the first day of this bleeding would be an appropriate time to begin ESTALIS therapy.

Continuous combined regimen:

For all therapeutic indications, the lowest effective dose should be used. Hormone replacement therapy (HRT) involving estrogen-progestogen therapy should only be continued as long as the benefits outweigh the risks for the individual.

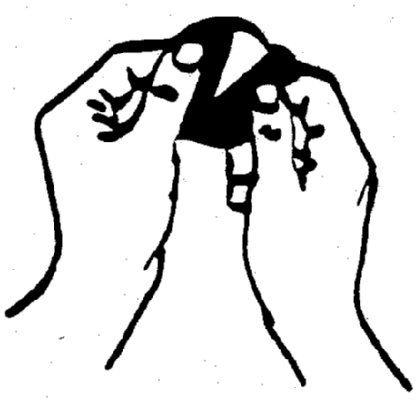
One ESTALIS patch is applied to the skin every 3 to 4 days during a 28-day cycle. Women should be advised that irregular bleeding may occur in the first few months of treatment, usually before amenorrhoea is established.

Method of application:

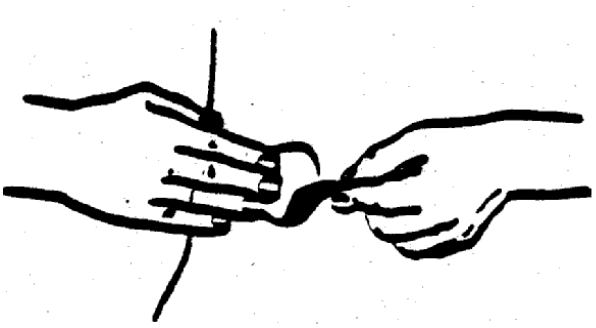
Care should be exercised when applying ESTALIS patches. The patch should be placed on an area of clean, dry skin which is free from irritation and abrasion and is not oily (do not use moisturising cream, lotion or oil).

The patch should be applied to a smooth (fold-free) area of the skin on the abdomen whenever possible. The waistline should be avoided, since tight clothing may rub the patch off. **ESTALIS must never be applied to or near the breasts.** The patch should be replaced every 3 to 4 days. The sites of application should be rotated, with an interval of at least one week allowed between applications to a particular site.

After opening the pouch, remove one half of the protective liner, taking care not to touch the adhesive part of the patch.



Apply patch to the skin immediately. Remove the second half of the protective liner.



Press the patch firmly to the skin with the palm of the hand for at least 10 seconds, carefully smoothing down the edges.

Care should be taken during bathing and other activities to ensure that the patch does not become dislodged.

If the patch falls off (e.g. as a result of strenuous physical activity, excessive sweating or friction from tight clothing), it may be reapplied to another area. If necessary, a new patch may be applied, in which case the original treatment schedule should be followed. Once in place, the patch should not be exposed to the sun for prolonged periods of time.

The patch should be removed slowly and carefully to avoid irritation of the skin. Should any adhesive remain on the skin after removal of the patch, allow the area to dry for 15 minutes. The residue can then be removed by gently rubbing the area with an oil-based cream or lotion.
After use, ESTALIS patches should be folded (adhesive surfaces pressed together) and discarded.

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Frequency estimate: very common ≥ 10 %, common ≥ 1 % to < 10 %, uncommon ≥ 0,1 % to < 1 %, rare ≥ 0,01 % to < 0,1 %, very rare < 0,01 %.

Psychiatric or nervous system disorders	
Very common	Headache*.
Common	Dizziness*, depression*, nervousness*, insomnia*, emotional lability. Migraine, vertigo.

Uncommon	
Cardiovascular disorders	
Uncommon Rare	Hypertension, varicose veins. Venous thromboembolism.
Gastrointestinal disorders	
Common Uncommon Rare Very rare	Nausea, bloating*, diarrhoea*, dyspepsia*, abdominal pain. Vomiting, elevated transaminases. Gallstones, gallbladder disease. Cholestatic jaundice.
Skin and subcutaneous tissue disorders	
Very common Common Uncommon	Application site reactions. Acne*, rash, pruritus*, dry skin. Skin discoloration.
Musculoskeletal, connective tissue and bone disorders	
Common	Back pain*, pain in extremity*.
Reproductive system and breast disorders	
Very common Common Uncommon Rare	Breast pain*, breast tenderness, dysmenorrhoea*, menstrual disorder*. Breast enlargement*, menorrhagia*, leukorrhoea*, vaginal haemorrhage, uterine spasms, vaginitis, endometrial hyperplasia. Breast cancer. Uterine leiomyomata, paratubular cysts, endocervical polyps.

General disorders and administration site conditions	
Common Rare	Pain, asthenia, weight gain*, peripheral oedema*. Allergic reactions, libido changes, paraesthesia.

(*) Adverse reactions associated to estrogen and progestogen has been found to be relatively less frequent with the lowest dosage strength.

Other adverse reactions have been reported in association with some estrogen-progestogen treatments:

- Estrogen-dependent neoplasms, benign and malignant, e.g. endometrial cancer,
- Stroke,
- Myocardial infarction,
- Dementia.

Precautions:

ESTALIS should only be prescribed after a general medical and gynaecological examination to rule out endometrial abnormalities and breast cancer. Patients receiving prolonged treatment should have regular follow-ups, including monitoring of the endometrium if this is thought necessary.

In all cases of undiagnosed persistent vaginal bleeding or spotting, adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out abnormality and the treatment should be re-evaluated.

Findings reported from available data in a meta-analysis of 51 epidemiological studies, referring predominantly to the use of estrogens without progesterone, suggest that there is an increase in the risk of developing breast cancer in women aged 50 to 70 years who have used HRT for more than five years. Similar findings have been reported by several other published meta-analyses.

The risk increases with duration of treatment and is comparable to the increased risk of breast cancer observed in women, with every year of delay of the natural menopause. The increased risk disappears during the first five years after stopping HRT.

The available data for the estrogen/progesterone combination products are sparse and it is therefore not possible to evaluate fully the effects of these products on breast cancer. The above meta-analysis of 51 epidemiological studies showed no evidence of marked differences between the results obtained so far.

Breast cancers found in women using HRT are more likely to be localised to the breast than those found in non-users. It is important that the increased risk of being diagnosed with breast cancer is discussed with the patient and weighed against the known benefits of HRT.

Women with known risk factors associated with the development of breast cancer, such as a family history of the disease in first-degree relatives or a breast condition associated with an increased risk, should be instructed in self-examination of the breasts. It is recommended that such women deemed to be at high risk should undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

Pre-existing uterine leiomyomas or fibroids may become enlarged during estrogen therapy. Women with endometriosis should be carefully monitored.

The following conditions may deteriorate on HRT:

Hypertension, asthma, heart failure, disorders of renal or hepatic function, migraine, epilepsy. It is essential that affected patients be kept under surveillance and HRT be stopped if there is an increase in epileptic seizures. If worsening of any of the above conditions is diagnosed or suspected during HRT, the benefits and risks of HRT should be reassessed based on the individual case.

Caution is advised in patients with a history of estrogen-related jaundice and pruritus. If cholestatic jaundice develops, the treatment should be stopped, and appropriate investigations carried out.

Patients with gall-bladder disease require careful observation.

Women with familial hypertriglyceridaemia need special surveillance. Lipid-lowering measures are recommended additionally, before HRT is started.

Although observations to date suggest that estrogens, including transdermal estradiol taken in combination with low doses of transdermal progestogen, do not impair carbohydrate metabolism, diabetic patients should be monitored during initiation of therapy until further information is available.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Given the mode of administration, overdose of estradiol or norethisterone acetate is unlikely to occur, but can if necessary be rapidly reversed by removing the patch.

IDENTIFICATION

A patch consisting of an off-white, translucent adhesive with a translucent polymeric backing on one side and a release liner on the other, containing no visible crystals. The patch is contained in a heat sealed pouch.

PRESENTATION

ESTALIS matrix transdermal patches are individually heat-sealed in foil laminate pouches of a paper/ LDPE polyethylene/ aluminium foil/ polyethylene composite.

One pack contains 8 or 24 ESTALIS 50/140 or ESTALIS 50/250 matrix transdermal patches.

STORAGE INSTRUCTIONS

Store ESTALIS matrix transdermal patches between 2 °C and 8 °C (Refrigerate. Do not freeze).
After dispensing to the patient, the patches may be stored unrefrigerated at temperatures below 25 °C **for a period of 1 month only**. Prior to use, the patches must be allowed to reach ambient temperature before application to ensure that they stick satisfactorily.
The patches must remain in their pouch during storage.

BOTH USED AND UNUSED ESTALIS PATCHES SHOULD ALWAYS BE KEPT OUT OF THE REACH OF CHILDREN.

REGISTRATION NUMBERS

ESTALIS 50/140: 37/21.8.2/0456

ESTALIS 50/250: 37/21.8.2/0457

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION

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DATE OF PUBLICATION OF THIS PROFESSIONAL INFORMATION

Date of registration: 11 February 2005

Date of most recent approval of professional information: 18 June 2025

® Registered trademark

[1]Company Reg. No.: 1990/001979/07