SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Estradot 25 microgram/24 hours, transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

3

2.5 cm^2 patch containing 0,39 mg estradiol (as hemihydrate) with a release rate of 25 micrograms estradiol per 24 hours.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

Rectangular patch with rounded corners, comprising a pressure-sensitive adhesive layer containing estradiol, with a translucent polymeric backing on one side and a protective liner on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women.

The experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Dosage

The transdermal patch is applied twice weekly, i.e. every three to four days.

Oestrogen deficiency symptoms:

Estradot is available in five strengths: 25, 37.5, 50, 75 and 100. 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. Depending on the clinical response the dose can then be adjusted to the patient's individual needs. If, after three months, there is insufficient response in the form of alleviated symptoms, the dose can be increased. If symptoms of overdose arise (e.g. tender breasts) the dose must be decreased.

General instructions

Estradot is administered as continuous therapy (uninterrupted application twice weekly).

In women with an intact uterus, Estradot should be combined with a progestagen approved for addition to oestrogen treatment in a continuous sequential dosing scheme: the oestrogen is dosed continuously. The progestagen is added for at least 12 to 14 days of every 28-day cycle, in a sequential manner.

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

In women who are not taking HRT or women transferring from a continuous combined HRT product, treatment may be started on any convenient day. In women transferring from a sequential HRT regimen, treatment should begin the day following completion of the prior regimen.

Method of administration

The adhesive side of Estradot should be placed on a clean, dry area of the abdomen. ***Estradot should not be applied to the breasts.***

Estradot should be replaced twice weekly. The site of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged, or irritated. The waistline should be avoided, since tight clothing may dislodge the patch. The patch should be applied immediately after opening the sachet and removing the protective liner. The patch should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges.

In the event that a patch should fall off, the same patch may be reapplied. If necessary, a new patch may be applied. In either case, the original treatment schedule should be continued. The patch may be worn during bathing.

If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The subsequent patch should be applied according to the original treatment

schedule. The interruption of treatment might increase the likelihood of irregular bleeding and spotting.

4.3 Contraindications

- Known, past or suspected breast cancer;
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer);
- Undiagnosed genital bleeding;
- Untreated endometrial hyperplasia;
- Previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism);
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction);
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal;
- Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- 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.

Estradot 25 and Estradot 37.5 are not indicated for osteoporosis.

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 Estradot, 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 (SLE)
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contraindication 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 Estradot 75 or 100 µg/day the endometrial safety of added progestagens has not been studied.

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 the use of combined HRTs may be associated with a similar or slightly smaller risk (see Section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3- 3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).

- Generally recognised risk factors for VTE include use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE) and cancer. There is no consensus about the possible role of varicose veins in VTE.

- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3).

- Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

- 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.

- 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).

Severe anaphylactic/anaphylactoid reactions

- Cases of anaphylactic/anaphylactoid reactions, which developed anytime during the course of estradiol treatment and required emergency medical management, have been reported in the post marketing setting.

Angioedema
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Patients who develop angioedema after treatment with estradiol should not receive Estradot again.

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

- Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.

- Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-I-antitrypsin, ceruloplasmin).

- 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.

- 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.

ALT elevations
During clinical trials with patients treated for hepatitis C virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as combined hormonal contraception (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

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Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin 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 following combination drug regimens: ombitasvir/paritaprevir/ritonavir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/ voxilaprevir (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. Herbal preparations containing St. John's wort (*Hypericum perforatum*) may induce the metabolism of oestrogens (and progestagens).

Estradiol is predominantly metabolized by CYP3A4, hence concomitant administration of inhibitors of CYP3A4 such as ketoconazole, erythromycin, may result in increase in the exposure of estradiol.

At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens (and progestagens) might be less affected than oral hormones by enzyme inducers.

Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

Some laboratory tests may be influenced by oestrogen therapy, such as tests for glucose tolerance or thyroid function.

Pharmacodynamic interactions
Direct acting antiviral agents (DAAs) and ethinylestradiol-containing medicinal products such as CHCs

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, 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 or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs.

Direct acting antiviral agents (DAAs) and medicinal products containing oestrogens other than ethinylestradiol, such as estradiol

Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, and ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin 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 following combination drug regimens: ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin; glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

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

4.7 Effects on ability to drive and use machines

Estradot has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Mild erythema at the patch application site was the most reported undesirable effect (16.6%). The erythema was observed after removing the patch by peeling from the skin at the application site. Mild pruritus and rash were also reported around the application site.

Adverse drug reactions (Table 1) are ranked under headings of frequency, the most frequent first, using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following adverse drug reactions have been reported from clinical trials and from post-marketing experience with either Estradot or oestrogen therapy in general:

Table 1

Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Not known*:	Breast cancer.
Immune system disorders	
Rare:	Hypersensitivity.
Very rare:	Urticaria, anaphylactic reaction.
Not known*:	Anaphylactoid reaction.
Metabolism and nutrition disorders	
Very rare:	Decreased carbohydrate tolerance.
Psychiatric disorders	
Common:	Depression, nervousness, affect liability.
Rare:	Libido disorder.
Nervous system disorders	
Very common:	Headache.
Common:	Insomnia.
Uncommon:	Migraine, dizziness.
Rare:	Paraesthesia.
Very rare:	Chorea.
Eye disorders	
Very rare:	Contact lens intolerance.
Vascular disorders	
Uncommon:	Hypertension.
Rare:	Embolism venous.
Not known*:	Embolism.
Gastrointestinal disorders	
Common:	Nausea, dyspepsia, diarrhoea, abdominal pain, abdominal

	distension.
Uncommon:	Vomiting.
Hepatobiliary disorders	
Rare:	Cholelithiasis.
Skin and subcutaneous tissue disorders	
Very common:	Application site reactions**, erythema.
Common:	Acne, rash, dry skin, pruritus.
Uncommon:	Skin discoloration.
Rare:	Alopecia.
Very rare:	Skin necrosis, hirsutism.
Not known*:	Angioedema, contact dermatitis, chloasma.
Musculoskeletal and connective tissue disorders	
Common:	Back pain.
Rare:	Myasthenia.
Not known*:	Pain in extremity.
Reproductive system and breast disorders	
Very common:	Breast tension and pain, dysmenorrhoea, menstrual disorder.
Common:	Breast enlargement, menorrhagia, genital discharge, irregular vaginal bleeding, uterine spasms, vaginal infection, endometrial hyperplasia.
Rare:	Uterine leiomyoma, fallopian tube cysts, cervical polyps.
Not known*:	Fibrocystic breast disease.
General disorders and administration site conditions	
Common:	Pain, asthenia, oedema peripheral, weight fluctuation.
Investigations	
Uncommon:	Transaminases increased.
Not known*:	Liver function test abnormal.

(*) Reported in post-marketing experience
(**) Application site reactions includes localized bleeding, bruising, burning, discomfort, dryness, eczema, edema, erythema, inflammation, irritation, pain, papules, paraesthesia, pruritus, rash, skin discolouration, skin pigmentation, swelling, urticaria, and vesicles.

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/m^2)

Age at start HRT (years)	Incidence per 1,000 never-users of HRT 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-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/m^2)

Age at start HRT (years)	Incidence per 1,000 never-users of HRT over a 10 year period (50-59 years)*	Risk ratio	Additional cases per 1,000 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 1,000 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)

‡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.

* WHI study in women with no uterus, which did not show an increase in risk of breast cancer.

Endometrial cancer risk

Postmenopausal women with a uterus

The endometrial cancer risk is about 5 in every 1,000 women with a uterus not using HRT.

In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1,000 women between the ages of 50 and 65.

Adding a 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 HRT (see section 4.4). Results of the WHI studies are presented:

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

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

* Study in women with no uterus.

Risk of coronary artery disease

- The risk of coronary artery disease is slightly increased in users of combined oestrogen-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* over 5 years' use

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

* No differentiation was made between ischaemic and haemorrhagic stroke.

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:
- Gallbladder disease.
- Skin and subcutaneous tissue disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Acute overdose is unlikely due to the method of administration. The most common symptoms of overdose in clinical use are breast tenderness and/or vaginal bleeding. If such symptoms occur, a reduction in dosage should be considered. The effects of overdose can be rapidly reversed by removal of the patch.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Oestrogens, ATC code: G03CA03

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

- Relief of oestrogen-deficiency symptoms

- Relief of menopausal symptoms was achieved during the first few weeks of treatment.

5.2 Pharmacokinetic properties

Absorption

Transdermal administration of estradiol achieves therapeutic plasma concentrations using a lower total dose of estradiol than required with oral administration, whereas plasma levels of estrone and estrone conjugates are lower with the transdermal route.

In studies in postmenopausal women with application of Estradot 25, 37.5, 50, and 100 µg/24 hours patches, average peak estradiol serum levels (C_{max}) were approximately 25 pg/ml, 35 pg/ml, 50-55 pg/ml and 95-105 pg/ml, respectively. Linear pharmacokinetics have been demonstrated for estradiol following transdermal administration.

At steady state, after repeated applications of Estradot 50 µg/24 hours patches, C_{max} and C_{min} values were 57 and 28 pg/ml for estradiol and 42 and 31 pg/ml for estrone, respectively.

Distribution

Estradiol is more than 50% bound to plasma proteins such as sex hormone binding globulin and albumin. Only 2% is free and biologically active.

Biotransformation/Metabolism

Transdermally applied estradiol is metabolised in the same way as the endogenous hormone. Estradiol is metabolised primarily in the liver to estrone, then later to estriol, epioestriol and catechol estrogens, which are then conjugated to sulphates and glucuronides. Cytochrome 450 isoforms CYP1A2 and CYP3A4 catalyze the hydroxylation of estradiol forming estriol. Estriol is glucuronidated by UGT1A1 and UGT2B7 in humans. Estradiol metabolites are subject to enterohepatic circulation.

Elimination

The sulphate and glucuronide esters along with a small proportion of estradiol and several other metabolites are excreted in the urine. Only a small amount is excreted in faeces. Since estradiol has a short half-life (approximately one hour), serum concentrations of estradiol and estrone returned to baseline values within 24 hours following removal of the patch.

5.3 Preclinical safety data

The toxicity profile of estradiol has been well established. Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases

the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver as well as the frequency of lymphoid and pituitary tumours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adhesive matrix:

- acrylic adhesive,
- silicone adhesive,
- oleyl alcohol,
- dipropylene glycol,
- povidone (E1201).

Backing layer:

- Ethylene vinyl acetate
- Vinylidene chloride
- Methyl acrylate

Release liner:

- fluoropolymer-coated polyester film.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.3 Shelf life

3 years

6.5 Nature and contents of container

Each Estradot patch is individually sealed in an aluminium laminate sachet.

Sachets may be provided in cartons of 2, 8, 24 and 26.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Used transdermal patches should be folded in half with the adhesive side inwards, and discarded safely and out of the reach and sight of children. Any used or unused transdermal patches should be disposed of in accordance with local requirements or returned to the pharmacy, preferably in the original packaging.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

Park View, Riverside Way

Watchmoor Park

Camberley, Surrey

GU15 3YL

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1646

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/09/2004 / 31/07/2006

10 DATE OF REVISION OF THE TEXT

10 DATE OF REVISION OF THE TEXT

20/05/2025