SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Estradot Conti 40/130 transdermal patch, 40 micrograms/24 hours and 130 micrograms/24 hours

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each patch of 27 cm^2 (matrix system) contains 4.32 mg estradiol (as hemihydrate) and 21.6 mg norethisterone acetate, releasing 40 micrograms estradiol and 130 micrograms norethisterone acetate per 24 hours.

Excipient(s) with known effect:

Each matrix patch contains Vitamin E preparation (contains d-α-tocopherol concentrate, partially hydrogenated vegetable oil (mainly soybean oil)).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Angular, transparent transdermal matrix patch with rounded corners located on an oversized removable protective liner.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

HRT for oestrogen deficiency in women at least 12 months since the last menstrual period.

Experience treating women older than 65 years is limited.

4.2 Posology and method of administration

Estradot Conti provides a continuous combined treatment with oestrogen and progestagen.

Posology

The oestrogen and the progestagen are given every day without interruption.

Estradot Conti should be applied twice weekly, every three to four days. Each patch should be applied to a different site.

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

For initiation and continuation of treatment of postmenopausal symptoms the lowest effective dose for the shortest duration should be used (see also section 4.4).

Thus, treatment should be started with the lower dose of Estradot Conti 30 µg/95 µg.

If satisfactory control of symptoms is not obtained after 3 months of treatment, the dose may be increased with application of Estradot Conti 40 µg /130 µg.

Pediatric population

There is no relevant use of Estradot Conti in the paediatric population.

Method of administration

Each patch should be applied to a different site. Recommended application sites are clean, free from any cream, dry and intact areas of skin on the dorsal region of the hip. The site selected should be one at which little wrinkling of the skin occurs during movement of the body. Estradot Conti must not be applied on or near the breasts.

The patch should not be exposed to the sun for long periods of time. Once in place, the patch should be covered by the clothing.

Immediately before use, the sachet is to be ripped open carefully at the incision close to the bag edge, and the patch is removed without damaging it (please note that the drying agent and oxygen absorber firmly attached to the inner surface of the sachet is for assuring product quality and not to be applied to the skin).

Caution should be exercised in bending the patch up and down at the perforation until the major part of the protective liner comes off the adhesive area. The free adhesive area is stuck to an intact, cleaned skin area on the back part of the hip. Slightly lift the smaller part of the transdermal patch, so that the remainder of the protective liner can be removed and the patch affixed completely. Once the patch has been put on completely, pressure should be exercised with the palm for about one minute.

Any touching of the adhesive area should be avoided.

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

Used patches should be discarded carefully in accordance with the instructions given in section 6.6.

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, stroke)
- Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal
- Porphyria
- Hypersensitivity to the active substances, soya, peanut or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the

risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk. Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women, however, the balance of benefits and risks for these women may be more favourable than in older women.

Medical examination/follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the Section 4.3, Contraindications and Section 4.4, Special warnings and precautions 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 Conti, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of therapy:

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure

- New onset of migraine-like 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.

Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy or continues after treatment has been discontinued, the reason should be investigated, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

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 of ovarian cancer (see section 4.8).

Venous thromboembolism

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

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

Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation obesity (body mass index > 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.

As in all postoperative patients, prophylactic measures need be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilised.

In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening). If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is ‘severe’ (e.g, antithrombin, protein S, or protein C deficiencies or a combination of defects) HRT is contraindicated.

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

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctor 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.

Hypothyroidism

Patients who require thyroid hormone replacement therapy should have their thyroid function monitored regularly while on HRT to ensure that thyroid hormone levels remain in an acceptable range.

Hepatitis C

During clinical trials with the hepatitis C virus (HCV) combination regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with and 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. 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 4.5.

Other conditions

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

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Women with pre-existing hypertriglyceridemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oral 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 a potential risk of 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.

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 telaprevir 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 effects and changes in the uterine bleeding profile.

Concomitant administration of cyclosporine may cause increased blood levels of cyclosporine, creatinine and transaminases due to decreased metabolism of cyclosporine in the liver.

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

Other 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Estradot Conti is not indicated during pregnancy. If pregnancy occurs during medication with Estradot Conti treatment should be withdrawn immediately.

Clinically, data on a limited number of exposed pregnancies indicate no adverse effects of norethisterone acetate on the foetus. At doses higher than normally used in oral contraceptives and HRT formulations masculinization of female foetuses was observed. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of oestrogens and progestagens indicate no teratogenic or foetotoxic effect.

Breast-feeding

Estradot Conti is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Estradiol/Norethisterone acetate has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequent reported undesirable effects during treatment with Estradiol/Norethisterone acetate were breast tenderness and pain, reactions at the application site, dysmenorrhoea, irregular bleeding, and headache.

Adverse events are listed below by system organ class and frequency.

The following undesirable effects may occur during treatment with Estradiol/Norethisterone acetate:

Organ system class	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)
Immune system disorders				Hypersensitivity		anaphylactic reaction
Psychiatric disorders		depression*, nervousness*, affect lability, mood changes		libido disorder		
Nervous System disorders	headache*	dizziness*, insomnia*	migraine, vertigo	paresthesia		
Vascular disorders			hypertension, varicose veins	venous thromboembolism		
Gastro-intestinal disorders		nausea, abdominal distension*, diarrhoea*, dyspepsia*, flatulence, abdominal pain	vomiting			
Hepatobiliary disorders				gallbladder disorder, cholelithiasis	jaundice cholestatic	
Skin and subcu-taneous tissue disorders	application site reactions	acne*, rash, pruritus*, dry skin, erythema	skin discoloration			Alopecia
Musculo-skeletal and connective tissue disorders		back pain*, pain in extremity*		myastenia		
Reproductive system and breast disorders	breast pain*, breast tenderness, dysmenorrhoea*, menstrual disorder*	breast enlargement*, menorrhagia*, genital discharge*, irregular vaginal bleeding, uterine spasms,	breast cancer	uterine leiomyoma, fallopian tube cysts, endocervical polyps		

		vaginal infection, endometrial hyperplasia				
General Disorders and administration site conditions		pain, asthenia, oedema peripheral*, weight increased*				
Investigations			transaminases increased			

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

(**) Reported in post-marketing experience

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 1000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio	Additional cases per 1000 HRT users after 5 years
		Oestrogen only HRT	
50	13.3	1.2	2.7
		Combined oestrogen-progestagen	
50	13.3	1.6	8.0
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.			

*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)

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 1000 never-users of HRT over a 10 year period (50-59 years)*	Risk ratio	Additional cases per 1000 HRT users after 10 years
		Oestrogen only HRT	
50	26.6	1.3	7.1
		Combined oestrogen-progestagen	
50	26.6	1.8	20.8

* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/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 (yrs)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95% CI	Additional cases per 1000 HRT users over 5 years (95% CI)
		CEE oestrogen-only	
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
		CEE+MPA oestrogen & progestagen‡	
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

‡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 1000 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 1000 women between the ages of 50 and 65.

Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of

combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

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

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 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 1000 women in placebo arm over 5 years	Risk ratio and 95% CI	Additional cases per 1000 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 disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
- Probable dementia over the age of 65 (see section 4.4)
- Dry eyes
- Tear film composition changes

Partially hydrogenated soya oil may very rarely cause allergic reactions.

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: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App store.

4.9 Overdose

The mode of administration makes significant overdose unlikely. If signs of overdose appear the transdermal patch should be removed. Overdose symptoms are generally breast tenderness, metrorrhagia, nausea, vomiting, abdominal or pelvic swelling, anxiety, irritability or fluid retention. Flatulence, depressive mood, fatigue, acne and hirsutism may also occur as a symptom of overdose. These symptoms disappear when the transdermal patch is removed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and oestrogens, fixed combination

ATC Code: G03 FA01

Estradiol

The active ingredient, synthetic 17ß-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.

Norethisterone acetate

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestagen greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical efficacy and safety

Relief of oestrogen-deficiency symptoms and bleeding patterns

In clinical studies with Estradiol/Norethisterone acetate, relief of menopausal symptoms was achieved during the first few weeks of treatment.

Amenorrhoea (no bleeding or spotting) was seen in 33.9 % of the women (about 90% treatment naive, median 2.4 years postmenopausal) during months 10-12 of treatment whereas the cumulative amenorrhoea rate increased from 33.9 % in cycle 10 to 40.2% in cycle 12. Breakthrough bleeding and/or spotting appeared in 63.4 % of the women during the first three months of treatment and in 66.1 % during months 10-12 of treatment.

5.2 Pharmacokinetic properties

The labelled release rates of estradiol and norethisterone over 24 hours for Estradot Conti 30/95 transdermal patch and Estradot Conti 40/130 transdermal patch are theoretical values and do not reflect the systemic bioavailabilities of either estradiol or norethisterone. The labelled quantity of estradiol (as the hemihydrate) and norethisterone acetate is also different. However, comparable estradiol and norethisterone bioavailabilities over a 96 hour dosing interval were demonstrated in a pivotal comparative pharmacokinetic study in post-menopausal women comparing Estradot Conti (30/95) versus Evorel Conti (50/170).

Estradiol

Absorption

Transdermally administered estradiol circumvents the first pass metabolism as it is observed with oral oestrogen products.

The application of Estradiol/Norethisterone acetate induces estradiol serum levels and estrone-estradiol-ratios in postmenopausal women comparable to premenopausal values observed in early to middle proliferation phase. These levels maintain constant during the whole 3.5 days of application time.

Distribution

Estradiol widely distributes in body tissues and is bound to albumin (about 60-65%) and sex-hormone-binding globulin (about 35-45%) in serum. Serum protein fractions remain unaltered following transdermal delivery of estradiol. Estradiol is promptly eliminated from the systemic circulation. The elimination half-life is about 1 hour following intravenous administration.

Biotransformation and elimination

Estradiol is metabolised principally into the less pharmacologically active estrone and its conjugates. Estradiol, estrone and estrone sulphate are interconverted and excreted in urine as glucuronides and sulphates. The skin metabolises estradiol only to a small extent.

Linearity/non-linearity

In a multiple application study in postmenopausal women, average steady-state estradiol concentrations in serum of 21.2 pg/ml were reached by application of the estradiol and norethisterone patch. At the end of application period, average estradiol concentrations in serum were about 15.8 pg/ml.

During steady state after multiple application, C_{max} and C_{min} concentrations of estradiol in serum were 32.7 pg/ml and 11.1 pg/ml.

The mean serum estradiol to estrone ratio was 0.86 for Estradiol/Norethisterone acetate after multiple application. These values are comparable to women with intact ovaries prior to menopause.

Norethisterone acetate

Absorption

Norethisterone acetate is rapidly hydrolysed to the active progestagen, norethisterone. After oral administration, norethisterone is subject to pronounced first-pass metabolism which reduces the bioavailability. Transdermal delivery of norethisterone acetate produces a sustained and effective level of norethisterone in the systemic circulation.

Distribution

Norethisterone widely distributes in body tissues and is bound to albumin (about 61%) and sex-hormone-binding globuline (about 36%) in serum. The elimination half-life is about 6 to 12 hours following oral administration which is not altered following long-term therapy.

Biotransformation

Norethisterone is primarily metabolised in the liver by reduction of the α-, β-unsaturated ketone structure in ring A of the molecule. Among the four possible

tetrahydrosteroids, the 5-β-, 3-α-hydroxy-derivative appears to be the predominant metabolite.

Elimination

These compounds are primarily excreted in urine and faeces as sulphate and glucuronide conjugates.

Linearity/non-linearity

In a multiple application study in postmenopausal women, average steady-state norethisterone concentrations in serum of 261.8 pg/ml were reached by application of the estradiol and norethisterone patch. These levels maintain constant during the whole 3.5 days of application time. At the end of the application period, average norethisterone concentrations in serum were about 211 pg/ml.

During steady state after multiple application, C_{max} and C_{min} concentrations of norethisterone in serum were 341 pg/ml and 162 pg/ml.

Minimal variations in serum concentrations of estradiol and norethisterone acetate prove the constant delivery of estradiol and norethisterone. After multiple application, no accumulation of estradiol and norethisterone acetate was observed in circulation.

5.3 Preclinical safety data

The toxicity profiles of oestradiol and norethisterone have 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, liver and pituitary and lymphoid tumours. Long-term, continuous administration of norethisterone in certain animal species increases the frequency of tumours of the hypophysis and ovary in females, and of liver and breast in males. Both compounds induced adverse effects in non-clinical reproductive toxicity studies, in particular embryotoxic effects and anomalies in urogenital tract development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Release liner: Polyester foil, siliconized

Matrix layer: Vitamin E preparation (contains: d-α-tocopherol concentrate, partially hydrogenated vegetable oil (mainly soybean oil)), acrylic copolymer

Backing foil: Polyester foil, not siliconized

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package.

6.5 Nature and contents of container

The patches are packed in sachets which are inserted into a carton.

The patch is covered on the side of the drug containing adhesive matrix with a siliconized polyester foil.

The sachet consists of (from the outer to the inner layer): paper, polyethylene foil, aluminium foil, polyethylene foil, and an attached polypropylene layer with moisture- and oxygen-absorbing properties.

The following sizes of original packages are available:

8, 16, 24 patches

6.6 Special precautions for disposal

Disposal of used and unused patches:

Dispose of used patches with care. After use the patch still contains considerable quantities of ingredients. Remaining hormonal active ingredients of the patch may have harmful effects if reaching the aquatic environment. Therefore be sure to fold the used patch in half, adhesive side inwards, so that the sticky side is not exposed. Any used or unused patches should be discarded away from the sight and reach of children and according to local requirements or returned to pharmacy. To help protect the environment, do not flush used patches down the toilet or place in liquid disposal systems.

7 MARKETING AUTHORISATION HOLDER

Sandoz Limited

Park View, Riverside Way

Watchmoor Park

Camberley, Surrey

GU15 3YL

United Kingdom

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