

# NEW ZEALAND DATA SHEET

## ESTALIS<sup>®</sup> CONTINUOUS

### (oestradiol/norethisterone acetate)

#### Transdermal patch releasing

50 micrograms/24 hours of oestradiol and 140 micrograms/24 hours of norethisterone acetate  
50 micrograms/24 hours of oestradiol and 250 micrograms/24 hours of norethisterone acetate

#### Trade name(s)

ESTALIS<sup>®</sup> Continuous 50/140

ESTALIS<sup>®</sup> Continuous 50/250

#### Description and composition

##### Pharmaceutical form

Transdermal patch.

##### Active substance(s)

The active components of the Estalis<sup>®</sup> Continuous matrix transdermal patch are oestradiol hemihydrate and norethisterone acetate. The remaining components are pharmacologically inactive.

Two Estalis Continuous matrix transdermal patches are available. They release oestradiol and norethisterone acetate (NETA) in the following quantities and at the following rates over a period of 3.5 to 4 days:

Name	Nominal release rate (microgram/day) oestradiol/NETA	Oestradiol content (mg)*	NETA content (mg)	Surface area (cm <sup>2</sup> )	Shape
Estalis Continuous	50/140	0.620	2.70	9	Round
Estalis Continuous	50/250	0.512	4.80	16	Round

\* 1 mg oestradiol hemihydrate is equivalent to 0.968 mg oestradiol

##### List of excipients

Adhesive matrix: silicone adhesive, acrylic adhesive, povidone, oleic acid, dipropylene glycol,

Backing layer: polyester film laminate,

Protective (release liner): fluoropolymer coated polyester film.

## Indications

The Estalis Continuous regimen is indicated for the following:

- Treatment of symptoms of oestrogen deficiency in postmenopausal women with an intact uterus.
- Prevention of osteoporosis in postmenopausal women with an intact uterus. (see sections Dosage and Administration and Warnings and Precautions).

## Dosage and Administration

### Dosage

#### Adults and elderly

For all therapeutic indications, the lowest effective dose should be used.

Hormone replacement therapy (HRT) involving combined oestrogen-progestogen therapy should only be continued as long as the benefits outweigh the risks for the individual.

#### Initiation of therapy

Postmenopausal women who are not already receiving oestrogen-progestogen therapy may start using Estalis Continuous at any convenient time.

Women already receiving sequential oestrogen-progestogen therapy should complete the current cycle of therapy before starting on Estalis Continuous. 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 Continuous therapy.

#### Estalis Continuous regimen

Estalis Continuous exists in two dosage strengths: 50/140 and 50/250.

For initiation and maintenance of treatment, the lowest effective dose should always be used.

Estalis Continuous is used for continuous treatment (uninterrupted application twice weekly).

One patch is applied to the skin every 3 to 4 days during a 4-week cycle.

Women should be advised that irregular bleeding may occur during the first few months of treatment, usually before amenorrhoea is established.

#### Method of application

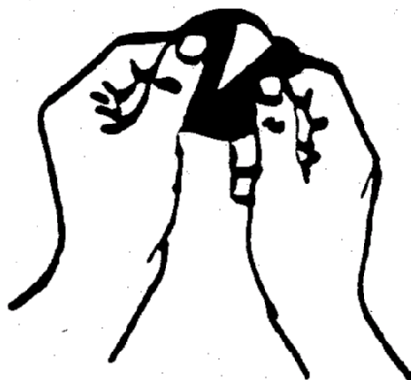
Care should be exercised when applying Estalis Continuous. The patch should be placed on an area of clean, dry skin which is free from irritation and abrasion and is not oily (do not use moisturising cream, lotion or oil).

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.

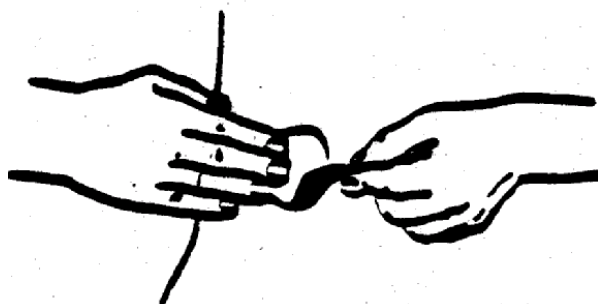
**Estalis Continuous must never be applied to, or near, the breasts.**

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 half of the protective liner, taking care not to touch the adhesive part of the patch.



Apply the 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 of the skin. 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.

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. Interruption of treatment might increase the likelihood of recurrence of symptoms and breakthrough bleeding and spotting.

### **Children**

Estalis Continuous should not be used in children.

## Contraindications

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

- Known hypersensitivity to oestrogens, progestogens, or to any of the excipients
- Known, past or suspected cancer of the breast,
- Known or suspected oestrogen-dependent neoplasia, including cancer of the endometrium,
- Undiagnosed abnormal vaginal bleeding,
- Severe hepatic disease,
- History of, or current, venous thromboembolism (VTE) (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,
- Known or suspected pregnancy,
- Breast-feeding.

## Warnings and Precautions

### 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 of 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 for the prevention of cardiovascular disease.

Large clinical trials (Women's Health Initiative and Heart and Estrogen/Progestin Replacement study) evaluated the risk of cardiovascular events with the HRT products used in these studies.

The Women's Health Initiative (WHI) studies were a randomised clinical trials conducted with either continuous combined oral conjugated equine oestrogens (CEE) and medroxyprogesterone acetate (MPA) for an average follow-up of 5.2 years, or with oral CEE for an average follow-up of 6.8 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 the WHI oestrogen-only HRT trial, the use of CEE alone did not affect coronary heart disease incidence in postmenopausal women.

In addition, both WHI studies showed an increased incidence of stroke. The absolute excess risk in the trial of continuous combined oral CEE and medroxyprogesterone acetate (MPA) was 8 additional cases per 10,000 person-years (29 versus 21) in HRT-treated women, and the relative risk was 1.41. The absolute excess risk in the trial of continuous oral CEE was 12 additional cases per 10,000 person-years (44 versus 32) in HRT-treated women, and the relative risk was 1.39.

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

There have been no randomised controlled trials to date to assess the risk of cardiovascular morbidity or mortality, or stroke, with combined transdermal oestrogen-progestogen HRT products. Therefore there are no data to support the conclusion that the frequency of cardiovascular events and stroke is different with Estalis Continuous.

### **Venous thromboembolism**

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

Some randomised controlled trials (e.g. WHI oestrogen-alone, WHI combined HRT and HERS) and epidemiological studies have found a two- to three-fold increased risk for users compared with non-users.

The WHI continuous combined 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 during the first years of use than in 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 family history of thromboembolic disease (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), obesity (body mass index > 30 kg/m<sup>2</sup>) 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 abortions 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 by 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 immobilisation, consideration should be given to temporarily stopping HRT several weeks earlier, if possible. 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 develops after the start of therapy, treatment should be discontinued.

### **Breast cancer**

Randomised controlled trials and epidemiological studies have reported an increased risk of breast cancer in women taking HRT. Women using combined oestrogen-progestogen HRT had a possibly higher risk than women who used unopposed oestrogens. The excess risk of breast cancer increases with the duration of intake of combined oestrogen-progestogen HRT.

There is evidence arising from the WHI continuous combined 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.

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

The number of additional cases of breast cancer is broadly similar among women who start HRT between the ages of 45 and 65, regardless of their age at the start of treatment.

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

For transdermal oestrogen-progestogen combined HRT products, there are no large randomised clinical trials to date assessing 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 Continuous.

Women should be advised that changes in their breasts should be reported to their doctor or nurse. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices and adapted to the clinical needs of the individual woman.

### **Endometrial cancer**

The risk of endometrial cancer in users of unopposed oestrogens who have an intact uterus is greater than in non-users and appears to depend on the duration of treatment and the oestrogen 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.

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 treatment should be re-evaluated.

### **Ovarian cancer**

In some epidemiological studies, the long-term use of opposed and unopposed oestrogens in hysterectomised and non-hysterectomised women has been associated with an increased risk of being diagnosed with ovarian cancer. It is uncertain whether long-term use of combined HRT (oestrogens and progestogens) confers a different risk than oestrogen-only HRT products.

## **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 CEE 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 CEE/MPA treated women and the relative risk was 2.05.

In a randomised, placebo-controlled, oestrogen-alone ancillary study of the WHI (WHIMS), the absolute excess risk of probable dementia after an average follow-up of 5.2 years was 12 additional cases per 10,000 person-years (37 versus 25) in CEE-treated women (the relative risk was 1.49), which did not reach statistical significance ( $p = 0.18$ ) compared with placebo.

Since both sub-studies were conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women.

For transdermal oestrogen-progestogen combined products, 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 Continuous.

## **Angioedema**

Oestrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema.

## **Precautions prior to initiation of Estalis Continuous therapy**

Before initiating or re-instituting HRT, a complete personal and family medical history, and appropriate physical (including pelvic and breast) examination should be performed (see Contraindications and Warnings and Precautions).

Consideration should be given to the lowest dose and shortest duration of use.

Hysterectomised women who require postmenopausal hormone therapy should receive oestrogen-only HRT unless otherwise indicated (e.g. endometriosis).

Caution is advised when risks factors for oestrogen-dependent tumours (e.g. first degree blood relatives who have ever had breast cancer) are present.

Women should be advised that Estalis Continuous is not a contraceptive nor will it restore fertility.

## **Monitoring during Estalis Continuous therapy**

During treatment, periodic check-ups of a nature and frequency adapted to the individual woman are recommended. A careful appraisal of the risks and benefits should be undertaken over time in women treated with HRT and the need for HRT re-evaluated periodically.

If any of the following conditions are present or have occurred previously (including during pregnancy or a previous hormone treatment), the woman should be closely monitored, in particular: leiomyoma (uterine fibroids) or endometriosis, thromboembolic disorders, heart failure, hypertension, hepatic disorders (e.g. liver adenoma), renal disorders, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erythematosus, endometrial hyperplasia, epilepsy, asthma, otosclerosis, gallbladder disease, oestrogen-related jaundice and pruritus.

It should be taken into account that these conditions may recur or be aggravated during treatment with oestrogens.

If worsening of any of the above-mentioned conditions is diagnosed or suspected during HRT, the benefits and risks of HRT should be reassessed on an individual basis.

Oestrogens may cause fluid retention and therefore women with cardiac or renal dysfunction should be carefully monitored.

Women with hypertriglyceridaemia should be followed closely during HRT, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oral oestrogen therapy in these women.

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

Thyroid function should be monitored regularly in patients who require thyroid hormone replacement therapy and who are also taking oestrogen to assure that thyroid hormone levels remain within an acceptable range.

### **Discontinuation of Estalis Continuous therapy**

Therapy should be discontinued in the following situations: jaundice or deterioration in liver function, a significant increase in blood pressure, new onset of migraine-type headache and pregnancy, or if a condition described under Contraindications develops.

### **Driving and using machines**

None known

## **Adverse drug reactions**

Approximately one-third of women treated with Estalis Continuous can be expected to experience adverse reactions. Most of these effects are mild and transient.

The table below presents the highest frequencies observed with the two Estalis Continuous dosage strengths Estalis Continuous 50/140 and Estalis Continuous 50/250.

Adverse drug reactions from clinical trials (Table 1) and post-marketing experience are listed according to the system organ class in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, the most frequent first. Within each frequency grouping, adverse drug reactions are presented in the order of decreasing seriousness. In addition the corresponding frequency using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1,000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), including isolated reports and not known.

**Table 1**

<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>	
Uncommon:	Breast cancer.
<b>Immune system disorders</b>	
Rare:	Hypersensitivity.
<b>Psychiatric disorders</b>	
Common:	Depression, insomnia*, nervousness*, affect lability.
Uncommon:	Vertigo.
Rare:	Libido disorder.
<b>Nervous system disorders</b>	
Very common:	Headache*.
Common:	Dizziness*.
Uncommon:	Migraine.
Rare:	Paraesthesia.
<b>Cardiac disorders</b>	
Uncommon:	Hypertension, varicose veins.
Rare:	Embolism venous.
<b>Gastrointestinal disorders</b>	
Common:	Diarrhoea*, abdominal pain, abdominal distension*, dyspepsia*, nausea.
Uncommon:	Vomiting, transaminases increased.
Rare:	Cholelithiasis, gallbladder disorder.
Very rare:	Jaundice cholestatic.
<b>Skin and subcutaneous tissue disorders</b>	
Common:	Acne*, rash, pruritus*, dry skin.
Uncommon:	Skin discoloration.
Not known**:	Alopecia, chloasma.
<b>Musculoskeletal and connective tissue disorders</b>	
Common:	Back pain*, pain in extremity*.
<b>Reproductive system and breast disorders</b>	
Very common:	Breast pain*, breast tenderness, menstrual disorder*, dysmenorrhoea*.
Common:	Endometrial hyperplasia, vaginal infection*, vaginal haemorrhage, menorrhagia*, genital discharge*, uterine spasms, breast enlargement*.
Rare:	Uterine leiomyomata, Fallopian tube cysts, endocervical polyps.
<b>General disorders and administration site conditions</b>	
Very common:	Application site reactions.
Common:	Pain, asthenia, oedema peripheral*, weight increased*.

(\*) Adverse reactions associated with oestrogen and progestogen have been found to be relatively less frequent at the lower dosage strength.

(\*\*) Reported in post-marketing experience.

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

- Oestrogen-dependent neoplasms, benign and malignant, e.g. endometrial cancer,
- Cerebrovascular accident,
- Myocardial infarction,
- Dementia,
- Dry eyes,
- Tear film composition changes.

## Interactions

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

Caution should be used if the woman is receiving protease inhibitors (e.g. ritonavir and nelfinavir), which are known as strong inhibitors of cytochrome P450 enzymes, and 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 progestogens.

Clinically, increased metabolism of oestrogens and progestogens may lead to decreased effects, and changes in the uterine bleeding profile.

With transdermal HRT administration, the first-pass effect in the liver is avoided and thus transdermally applied oestrogens and progestogens may be less affected by enzyme inducers than are oral hormones.

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

## Pregnancy and Breast-feeding

### Pregnancy

Estalis Continuous must not be used during pregnancy. Both oestrogens and progestogens may cause foetal harm when administered to a pregnant woman.

### Breast-feeding

Estalis Continuous must not be used while breastfeeding. Oestrogens or progestogens are excreted in breast milk and may reduce the production of breast milk.

## Overdosage

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

## Clinical pharmacology

Pharmacotherapeutic group: Progestogens and oestrogens, fixed combinations (ATC code G03F A01)

### Pharmacodynamic properties (PD)

#### Oestradiol

Like all steroid hormones, oestrogens exert their metabolic effects intracellularly. In the cells of target organs, oestrogens interact with a specific receptor to form a complex which modulates gene transcription and subsequent protein synthesis. Such receptors have been identified in various organs, e.g. hypothalamus, pituitary, vagina, urethra, uterus, breast and liver, and in osteoblasts.

Oestradiol, which from the menarche to the menopause is produced mainly by the ovarian follicles, is the most active oestrogen. It is largely responsible for the development and maintenance of the female urogenital system and of secondary sexual characteristics. After

the menopause, when the ovaries have ceased to function, only small amounts of oestradiol are still produced, from aromatisation of androstenedione and, to a lesser extent, testosterone by the aromatase enzyme, yielding oestrone and oestradiol, respectively. Oestrone is further transformed to oestradiol by the enzyme 17beta-hydroxysteroid-dehydrogenase. Both enzymes occur in fat, liver and muscle tissue.

In many women, the cessation of ovarian oestradiol production results in vasomotor symptoms (hot flushes), sleep disturbances, and progressive atrophy of the urogenital system. These disorders can be largely eliminated by means of oestrogen replacement therapy. It has also been shown that HRT or oestrogens are effective in preventing the decline in skin thickness seen after the menopause.

It is well established that oestrogen replacement therapy prevents postmenopausal bone loss, especially when initiated early in the menopause.

### **Norethisterone acetate**

NETA is a potent progestogen which essentially mimics the biological effects of endogenous progesterone. It is hydrolysed in the skin to norethisterone (NET), which is the active hormone in the circulation.

Progesterone reduces the number of oestradiol receptors in target organs and induces the enzyme 17 beta-hydroxysteroid-dehydrogenase, which locally oxidises oestradiol to its weaker oestrogenic metabolite, oestrone.

One of the major target organs of progestogens is the uterus. In premenopausal women and in postmenopausal women receiving cyclic HRT, progestogens induce secretory transformation of the oestrogen-primed endometrium, which is then shed.

In the majority of women, NETA administered by the transdermal route is effective at doses lower than those used orally owing to the absence of first-pass metabolism.

### **Oestradiol and NETA combination**

Unopposed oestrogens increase the incidence of endometrial hyperplasia and the risk of endometrial carcinoma. Studies have reported that the addition of a progestogen for 10 or more days of a cycle of oestrogen administration greatly lowers the incidence of endometrial hyperplasia, and thereby also of irregular bleeding and endometrial carcinoma, compared with oestrogen treatment alone. Whereas the use of these cyclic regimens results in the regular shedding of the oestrogen-stimulated endometrium (monthly bleeds), the administration of Estalis Continuous, a continuous/combined oestradiol/ progestogen, results in an atrophic endometrium and amenorrhoea.

## **Pharmacokinetic properties (PK)**

### **Absorption**

#### **Oestradiol**

Following application of an Estalis Continuous matrix transdermal patch, serum oestradiol levels and oestrone-to-oestradiol ratios lie in the same range as those found in premenopausal women at the early (oestradiol > 40 pg/mL) to mid-follicular phase. These levels are maintained for an entire 84 to 96 hour application period.

Repeated application of Estalis Continuous patches (50/250 micrograms/day, 50/140 micrograms/day) resulted in steady-state maximum oestradiol serum concentrations (C<sub>max</sub>) of 71 and 73 pg/mL, respectively. The average serum oestradiol concentrations were 52 and 46 pg/mL. At the end of the application periods, the mean serum oestradiol concentrations were 46 and 30 pg/mL, respectively.

### **Norethisterone acetate**

Repeated application of Estalis Continuous patches (50/250 micrograms/day, 50/140 micrograms/day) resulted in steady-state maximum norethisterone serum concentrations (C<sub>max</sub>) of 1,060 and 638 pg/mL, respectively. The average steady-state serum norethisterone concentrations were 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**

Minimal fluctuations in serum oestradiol and norethisterone concentrations demonstrate consistent deliveries over the application interval. There is no accumulation of oestradiol or norethisterone in the circulation following multiple applications.

Oestradiol circulates in the blood largely bound to sex hormone binding globulin (SHBG) and albumin. In plasma, norethindrone is bound approximately 90% to SHBG and albumin.

### **Biotransformation/Metabolism**

#### **Oestradiol**

Transdermally delivered oestradiol is metabolised only to a small extent by the skin and bypasses the first-pass effect seen with orally administered oestrogen products. Therapeutic serum oestradiol levels with lower circulating levels of oestrone and oestrone conjugates are achieved with smaller transdermal doses (daily and total) as compared to oral therapy and more closely approximate premenopausal concentrations.

Transdermally applied oestradiol is metabolised in the same way as the endogenous hormone. Oestradiol is metabolised to oestrone, then later – primarily in the liver – to oestriol, epioestriol and catechol oestrogens, which are then conjugated to sulphates and glucuronides.

#### **Norethisterone acetate**

Norethindrone undergoes extensive ring A reduction, forming dihydro- and tetrahydro-norethindrone metabolites, which undergo conjugation.

### **Elimination**

#### **Oestradiol**

Oestradiol 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 oestradiol 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 Continuous patch, serum norethisterone concentrations diminish rapidly and are less than 50 pg/mL within 48 hours.

## **Clinical studies**

In clinical studies in postmenopausal women lasting between three months and one year, Estalis Continuous rapidly reduced the frequency and intensity of hot flushes and sweating. It also had a positive effect on other quality-of-life indicators, such as sleep disturbances and sexual function. No adverse effects on blood pressure or coagulation tests were observed.

Decreases in total cholesterol, LDL-cholesterol, apoprotein B, Lp-(a) and triglycerides, as compared with baseline, were observed with Estalis 50/140 and 50/250. There was also a

decrease in HDL-cholesterol. All plasma lipoproteins remained within the clinically desirable range. Moreover, total cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol ratios remained unchanged from baseline to one year.

### **Non-clinical safety data**

The toxicity profiles of oestradiol and norethindrone 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, and liver. 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.

## **Pharmaceutical information**

### **Incompatibilities**

Not applicable.

### **Special precautions for storage**

Store Estalis Continuous matrix transdermal patches between 2°C and 8°C prior to dispensing (Refrigerate. Do not freeze).

After dispensing, the patches may be stored without refrigeration below 25°C, in which case they should be used either within 6 months (for Estalis Continuous 50/140 and Estalis Continuous 50/250) or before the expiry date, whichever comes first. If the patches are refrigerated, they must be allowed to reach ambient temperature before application in order to ensure proper adhesion.

The patches must remain in their pouches during storage.

Information might differ in some countries.

Estalis Continuous patches must be kept out of the reach and sight of children.

### **Instructions for use and handling**

See section Dosage and Administration.

After use, Estalis Continuous patches should be folded (adhesive surfaces pressed together) and discarded in such a way as to keep them out of the reach and sight of children.

### **Special precautions for disposal**

Disposal should be performed according to local regulations.

Each Estalis Continuous transdermal patch is packed individually in a heat-sealed paper/polyethylene/aluminium/polyethylene sachet.

One Estalis pack contains 2, 8 or 24 Estalis transdermal patches.

### **Medicine classification**

Prescription Medicine

### **Name and address**

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***Date of preparation***

21 October 2011