ESTALIS® SEQUI

Transdermal Matrix Patch combination pack

WARNING

Oestrogens and progestogens should not be used for the prevention of cardiovascular disease or dementia.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with conjugated oestrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (See CLINICAL TRIALS and PRECAUTIONS).

The WHI study reported increased risks of stroke and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 6.8 years of treatment with conjugated oestrogens (0.625 mg) relative to placebo (See CLINICAL TRIALS and PRECAUTIONS).

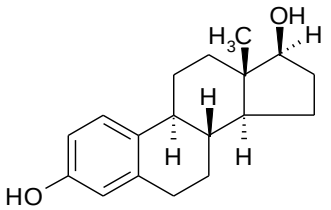
The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 to 5.2 years of treatment with conjugated oestrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (See CLINICAL TRIALS and PRECAUTIONS).

Other doses of conjugated oestrogens and medroxyprogesterone acetate, and other combinations and dosage forms of oestrogens and progestogens were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, oestrogens with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

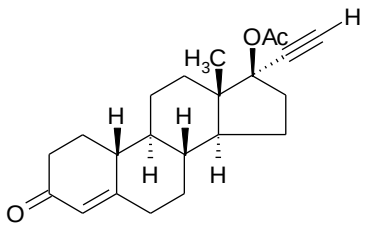
NAME OF THE MEDICINE

Estalis Sequi Week 1 and 2 (oestradiol)
Estalis Sequi Week 3 and 4 (oestradiol and norethisterone acetate)

Structural formulae:



Oestradiol
CAS : 50-28-2



Norethisterone Acetate
CAS : 51-98-9

DESCRIPTION

Estalis Sequi is a combination pack consisting of two matrix transdermal drug delivery systems (patches). Estalis Sequi Week 1 and 2 contains oestradiol and Estalis Sequi Week 3 and 4 contains oestradiol and norethisterone acetate (NETA).

Chemical name and properties:

The molecular weight of oestradiol is 272.4 and the molecular formula is $C_{18}H_{24}O_2$. The manufacturing source of the oestradiol is oestradiol hemihydrate, a white, or almost white crystalline powder. Oestradiol is chemically described as oestra-1,3,5(10)-triene-3,17β-diol.

NETA is a white to yellowish white odourless, crystalline powder, chemically described as 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one 17-acetate. The molecular weight of norethisterone acetate is 340.47 and the molecular formula is $C_{22}H_{28}O_3$.

Transdermal matrix patch:

Estalis Sequi matrix patches are designed to be applied to intact skin, providing continuous physiological levels of oestradiol (Estalis Sequi Week 1 and 2) or oestradiol and NETA (Estalis Sequi Week 3 and 4) for 3.5 to 4 days following application, thereby minimising the high doses of oestradiol and NETA normally required orally to compensate for the first-pass effect.

Estalis Sequi is an alcohol free, adhesive-based matrix patch comprising three layers: a backing, an adhesive layer and a protective liner. The adhesive matrix containing oestradiol (Estalis Sequi Week 1 and 2) or oestradiol and NETA (Estalis Sequi Week 3 and 4) is applied to a polyester/ethylene vinyl acetate laminate film on one side and is protected on the other side by a transparent fluoropolymer-coated release liner. The transparent release liner must be removed before the matrix patch can be used.

Excipients:

The remaining components of the matrix patch are pharmacologically inactive. The excipients in each of the matrix patches are as follows:

Estalis Sequi Week 1 and 2: Dipropylene glycol, povidone and oleyl alcohol. Proprietary ingredients: Gelva RA-788 acrylic adhesive, BIO-PSA 7-4502 silicone adhesive, Dow BLF 2050 non-removable backing layer and Scotchpak 1022 removable release liner.

Estalis Sequi Week 3 and 4: Silicone (BIO-PSA™ 131A-4603) and acrylic adhesives (Gelva 737), povidone, oleic acid and dipropylene glycol.

PHARMACOLOGY

The oestradiol matrix patch is an efficient systemic oestrogen replacement therapy which alleviates the symptoms of oestradiol deficiency in menopausal women, as oestradiol is largely responsible for the development and maintenance of the female urogenital system and of secondary sexual characteristics. Oestrogen replacement therapy promotes growth and development of the urogenital epithelium providing an efficient therapy to avoid vaginal discomfort, dyspareunia, urinary urgency and frequency. In particular, vaginal cytology is converted to a pattern similar to that found in premenopausal women. Oestrogens reduce post-menopausal bone loss and provide protection against osteoporotic fractures. When Estalis Sequi is used for the short-term relief of menopausal symptoms, it will provide a concomitant preventative effect in reducing bone mineral density loss.

Oestrogen exerts a proliferative effect on endometrium which is prevented by concomitant progestogen administration. NETA induces secretory changes in an oestrogen-primed endometrium. It acts to inhibit the secretion of pituitary gonadotrophins which, in turn, prevent follicular maturation and ovulation.

Oestrogen replacement therapy increases skin thickness and collagen content, which are decreased after menopause.

Pharmacokinetics

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

Transdermally delivered oestradiol is metabolised only to a small extent by the skin and by-passes the first pass effect seen with orally administered oestrogen products. Therapeutic oestradiol serum 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.

Estalis Sequi Week 1 and 2:

In pharmacokinetic studies it was shown that, following the application of the Estalis Sequi Week 1 and 2 matrix patch, the average serum oestradiol concentrations and oestrone to oestradiol ratios were comparable with the physiological range reported for pre-menopausal women. These features are maintained for a 96-hour wear period. Following multiple applications of Estalis Sequi Week 1 and 2 matrix patch, the average oestradiol serum concentrations at steady state were 51 pg/mL. At the end of the application period, the average oestradiol serum concentrations were 41 pg/mL. Serum concentrations of oestradiol and oestrone declined to baseline levels within 12 - 22 hours after removal of the matrix patch.

Estalis Sequi Week 3 and 4:

In a pharmacokinetic study, it was shown that the Estalis Sequi Week 3 and 4 matrix patch achieves oestradiol serum levels and oestrone to oestradiol ratios in the range of those observed in premenopausal women at the early (oestradiol >40 pg/mL to mid-follicular phase. These features are maintained for an entire 84 to 96 hour wear period. Multiple applications of Estalis Sequi Week 3 and 4 (50/250 µg/day, 50/140 µg/day) matrix patches resulted in average oestradiol serum concentrations at steady-state of 50 and 45 pg/mL. At the end of the application periods, the average oestradiol serum concentrations were 37 and 27 pg/mL, respectively. Oestradiol has a short elimination half-life of approximately 2 to 3 hours.

Therefore, a rapid decline in serum levels is observed after the matrix patch is removed. After removal of the matrix patch, serum concentrations of oestradiol return to untreated postmenopausal levels (<20 pg/mL) within 4 - 8 hours.

Norethisterone

In a pharmacokinetic study, it was shown that multiple applications of Estalis Sequi Week 3 and 4 (50/250 µg/day, 50/140 µg/day) matrix patches resulted in average norethisterone serum concentrations at steady-state of 840 and 489 pg/mL, respectively. At the end of the application period, the average serum concentrations of norethisterone were 686 and 386 pg/mL, respectively. Serum norethisterone concentrations of Estalis Sequi Week 3 and 4 increased linearly with increasing doses of NETA. The elimination half-life of norethisterone is reported to be 6 to 8 hours. After removal of the Estalis Sequi Week 3 and 4 matrix patch, norethisterone serum concentrations diminish rapidly and are less than <50 pg/mL within 48 hours.

CLINICAL TRIALS

Trials with Estalis Sequi

Clinical data involving a total of 737 patients between three months to one year of therapy support the use of Estalis Sequi in menopausal women.

Estalis Sequi decreases rapidly the number and the intensity of hot flushes and sweating. Dimensions of Quality Of Life showed a beneficial effect of Estalis Sequi on sleep disturbance and sexual function arousal.

A favourable decrease of total cholesterol, LDL-cholesterol, Apoprotein B, Lp (a) and triglycerides from baseline was observed with both Estalis Sequi 50/140 and 50/250 µg/day, although there was also a decrease of 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. **However, these changes have been shown in robust studies not to be of clinical benefit (see PRECAUTIONS-Cardiovascular disorders).**

A clinically significant decrease in the percent change from baseline of the biochemical markers of bone resorption (C-telopeptide and N-telopeptide) and bone formation (bone phosphatase alkaline and osteocalcin) was observed in patients treated with Estalis Sequi 50/140 and 50/250 µg/day. Within one year of treatment, all markers decreased to normal premenopausal range. In patients treated with a continuous regimen of Estalis Sequi Week 1 and 2, bone markers from 6 months have been shown to be correlated with bone mineral density at two years (see INDICATIONS).

Women's Health Initiative (WHI) Studies

A substudy of the Women's Health Initiative (WHI) enrolled 16,608 predominantly healthy postmenopausal women (average age of 63 years, range 50 to 79; 83.9% White, 6.5% Black, 5.5% Hispanic) to assess the risks and benefits of the use of an oral continuous combined regimen of conjugated estrogens (CE) 0.625 mg/day plus medroxyprogesterone acetate (MPA) 2.5 mg/day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer, colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE + MPA on menopausal symptoms. The oestrogen plus progestogen substudy was stopped early because, according to the predefined stopping rule, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." Results are presented in Table 1.

TABLE 1 RELATIVE AND ABSOLUTE RISK SEEN IN THE OESTROGEN PLUS PROGESTOGEN SUBSTUDY OF WHI[a]

Event[c]	Relative Risk CE+MPA vs Placebo at 5.2 Years (Nominal 95% CI*)	Placebo n = 8102	CE+MPA n = 8506
		Absolute Risk per 10,000 Women-years	
CHD events	1.29 (1.02-1.63)	30	37
Non-fatal MI	*1.32 (1.02-1.72)*	*23*	*30*
CHD death	*1.18 (0.70-1.97)*	*6*	*7*
Invasive breast cancer[b]	1.26 (1.00-1.59)	30	38
Stroke	1.41 (1.07-1.85)	21	29
Pulmonary embolism	2.13 (1.39-3.25)	8	16
Colorectal cancer	0.63 (0.43-0.92)	16	10
Endometrial cancer	0.83 (0.47-1.47)	6	5
Hip fracture	0.66 (0.45-0.98)	15	10
Death due to causes other than the events above	0.92 (0.74-1.14)	40	37
Global Index[c]	1.15 (1.03-1.28)	151	170
Deep vein thrombosis[d]	2.07 (1.49-2.87)	13	26
Vertebral fractures[d]	0.66 (0.44-0.98)	15	9
Other osteoporotic fractures[d]	0.77 (0.69-0.86)	170	131

a: adapted from JAMA, 2002; 288:321-333
b: includes metastatic and non-metastatic breast cancer with the exception of in situ breast cancer
c: a subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, or death due to other causes
d: not included in Global Index
*: nominal confidence intervals unadjusted for multiple looks and multiple comparisons. Except for deep vein thrombosis and other osteoporotic fractures, based on adjusted confidence intervals, the relative risks were not statistically significant.

For those outcomes included in the "global index", the absolute excess risks per 10,000 women-years in the group treated with CE + MPA were 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures. The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (See BOXED WARNING and PRECAUTIONS.)

Women's Health Initiative Memory Study (WHIMS)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were age 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of oral CE + MPA (conjugated estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the oestrogen/progestogen group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21 to 3.48) compared to placebo. Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See BOXED WARNING and PRECAUTIONS, Dementia and Use in Geriatrics.)

INDICATIONS

For the short-term treatment of symptoms of oestrogen deficiency in menopausal women who have an intact uterus.

Combination HRT should not be used in hysterectomised women because it is not needed in these women and it may increase the risk of breast cancer.

CONTRAINDICATIONS

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

- Known or suspected pregnancy
- Breast-feeding
- Known, past or suspected cancer of the breast
- Known or suspected oestrogen-dependent neoplasia, including cancer of the endometrium
- Known or suspected pituitary or hypothalamic tumours
- Undiagnosed abnormal vaginal bleeding
- Severe hepatic impairment
- Endometriosis
- Connective tissue disease or otosclerosis

- Active venous thromboembolism [VTE] (e.g. deep venous thrombosis, pulmonary embolism), known thrombophilic or thromboembolic disorders (e.g. thrombophlebitis), arterial thromboembolic disease (e.g. coronary heart disease, stroke), or a documented history of these conditions
- Porphyria
- Hypersensitivity to oestrogens and progestogens or to any of the components of this product. (see "Excipients")

PRECAUTIONS

The benefits and risks of oestrogen / progestogen therapy must always be carefully weighed, including consideration of the emergence of risks as therapy continues.

When initiating oestrogen/progestogen therapy for the prevention of postmenopausal bone mineral density loss in women, 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.

1. Cardiovascular disorders

Estrogen/Progestogen therapy should not be used for the prevention of cardiovascular disease.

Oestrogen/progestogen therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE). Should any of these occur or be suspected, estrogen/progestogen therapy should be discontinued immediately.

Risk factors for arterial vascular disease (e.g. hypertension, diabetes mellitus, tobacco use, hypercholesterolaemia,and obesity) and/or venous thromboembolism (e.g. personal history or family history of VTE, obesity and systemic lupus erythematosus) should be managed appropriately.

a. Coronary heart disease and stroke

In the oestrogen plus progestogen substudy of the Women's Health Initiative (WHI) study, an increased risk of coronary heart disease (CHD) events (defined as nonfatal myocardial infarction and CHD death) was observed in women receiving CE + MPA compared to women receiving placebo (37 vs 30 per 10,000 women-years). The increase in risk was observed in year one and persisted. (See CLINICAL TRIALS.)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving oestrogen/progestogen compared to women receiving placebo (29 vs 21 per 10,000 women-years). The increase in risk was observed after the first year and persisted.

In postmenopausal women with documented heart disease (n = 2,763, average age 66.7 years) a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/progestogen Replacement Study; HERS) treatment with CE + MPA demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE + MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the oestrogen/ progestogen-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand three hundred and twenty one women from the original HERS trial agreed to participate in an open label extension of HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events

were comparable among women in the oestrogen/progestogen-treated group and the placebo group in HERS, HERS II, and overall.

b. Venous thromboembolism (VTE)

In the oestrogen plus progestogen substudy of WHI, a 2-fold greater rate of VTE, including deep venous thrombosis and pulmonary embolism, was observed in women receiving CE + MPA compared to women receiving placebo. The rate of VTE was 34 per 10,000 women-years in the oestrogen/progestogen-treated group compared to 16 per 10,000 women-years in the placebo group. The increase in VTE risk was observed during the first year and persisted. (See CLINICAL TRIALS.)

If feasible, oestrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilisation.

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

A history of recurrent spontaneous abortions should be investigated to exclude thrombophilic predisposition. In patients in whom this diagnosis is confirmed, the use of Estalis Sequi is contraindicated.

Patients 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 VTE develops after initiating hormone replacement therapy (HRT), the drug should be discontinued.

2. Malignant neoplasms

a. Breast cancer

The use of oestrogens and progestogens by postmenopausal women has been reported to increase the risk of breast cancer. The most important randomised clinical trial providing information about this issue is the Women's Health Initiative (WHI) trial of oestrogen plus progestogen (See CLINICAL TRIALS). The results from observational studies are generally consistent with those of the WHI clinical trial.

After a mean follow-up of 5.6 years, the WHI trial reported an increased risk of breast cancer in women who took oestrogen plus progestogen. Observational studies have also reported an increased risk for oestrogen/progestogen combination therapy, and a smaller increased risk for oestrogen alone therapy, after several years of use. For both findings, the excess risk increased with duration of use, and appeared to return to baseline over about five years after stopping treatment (only the observational studies have substantial data on risk after stopping). In these studies, the risk of breast cancer was greater, and became apparent earlier, with oestrogen/progestogen combination therapy as compared to oestrogen alone therapy.

However, these studies have not found significant variation in the risk of breast cancer among different oestrogens or among different oestrogen/progestogen combinations, doses, or routes of administration.

In the WHI trial of oestrogen plus progestogen, 26% of the women reported prior use of oestrogen alone and/or oestrogen/progestogen combination hormone therapy. After a mean follow-up of 5.6 years during the clinical trial, the overall relative risk of invasive breast cancer was 1.24 (95% confidence interval 1.01-1.54), and the overall absolute risk was 41 vs. 33 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 vs. 25 cases per 10,000 women-years, for oestrogen plus progestogen compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 vs. 36 cases per 10,000 women-years for oestrogen plus progestogen compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the oestrogen plus progestogen group compared with the placebo group. Metastatic disease was rare with no apparent difference between the two groups. Other prognostic factors such as histologic subtype, grade and hormone receptor status did not differ between the groups.

The observational Million Women Study in Europe reported an increased risk of mortality due to breast cancer among current users of oestrogens alone or oestrogens plus progestogens compared to never users, while the oestrogen plus progestogen sub-study of WHI showed no effect on breast cancer mortality with a mean follow-up of 5.6 years.

The use of oestrogen plus progestogen has been reported to result in an increase in abnormal mammograms requiring further evaluation. All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. Women should be advised that changes in the breasts should be reported to their doctor and in addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

b. Endometrial cancer

The reported endometrial cancer risk among unopposed oestrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on oestrogen dose. Most studies show no significant increased risk associated with the use of oestrogens for less than one year. The greatest risk appears associated with prolonged use, with increased risks of 15- to 24-fold for five to ten years or more, and this risk has been shown to persist for at least 8 to 15 years after oestrogen therapy is discontinued.

Clinical surveillance of all women taking oestrogen/progestogen combinations is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding or spotting and the treatment should be re-evaluated. There is no evidence that the use of natural oestrogens results in a different endometrial risk profile than synthetic oestrogens of equivalent oestrogen dose.

3. Dementia

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 women aged 65 to 79 years was randomised to CE + MPA or placebo. A population of 2,947 hysterectomised women, aged 65 to 79 years, was randomised to CE (0.625 mg) alone or placebo. In the planned analysis, pooling the events in women receiving CE alone or CE + MPA in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60). In the oestrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia

was observed compared to placebo. In the oestrogen-plus-progestogen group, after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See PRECAUTIONS, Use in Geriatrics.)

4. Gallbladder disease

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving oestrogens has been reported.

5. Hypercalcaemia

Oestrogen administration may lead to severe hypercalcaemia in patients with breast cancer and bone metastases. If hypercalcaemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

6. Visual abnormalities

Retinal vascular thrombosis has been reported in patients receiving oestrogens. Discontinue medication pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, oestrogens should be discontinued.

7. General precautions

a. ***Addition of a progestogen when a woman has not had a hysterectomy.***

Studies of the addition of a progestogen for 10 or more days of a cycle of oestrogen administration, or daily with oestrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by oestrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer.

There are, however, possible risks that may be associated with the use of progestogens with oestrogens compared with oestrogen-alone regimens. These include a possible increased risk of breast cancer and impairment of glucose tolerance.

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

b. ***Elevated blood pressure***

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to oestrogens. In a large, randomised, placebo-controlled clinical trial, a generalised effect of oestrogen therapy on blood pressure was not seen. Blood pressure should be monitored at regular intervals with oestrogen use.

c. ***Hypertriglyceridaemia***

In patients with pre-existing hypertriglyceridaemia, oestrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications. These patients should be monitored closely.

d. ***Impaired liver function and past history of cholestatic jaundice***

Although transdermally administered oestrogen therapy avoids first-pass metabolism, oestrogens may be poorly metabolised in patients with impaired liver function. For patients with a history of cholestatic jaundice associated with past oestrogen use or with pregnancy, caution should be exercised and in the case of recurrence, medication should be discontinued.

e. ***Hypothyroidism***

Oestrogen administration leads to increased thyroid-binding globulin (TBG) levels. Patients with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T_4 and T_3 serum concentrations in the normal range. Patients dependent on thyroid hormone replacement therapy who are also receiving oestrogens may require increased doses of their thyroid replacement therapy. These patients should have their thyroid function monitored in order to maintain their free thyroid hormone levels in an acceptable range.

f. ***Fluid retention***

Because oestrogens/progestogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as cardiac or renal dysfunction, warrant careful observation when oestrogens are prescribed.

g. ***Hypocalcaemia***

Oestrogens should be used with caution in individuals with severe hypocalcaemia.

h. ***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-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see 'ADVERSE EFFECTS')."

i. ***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. Involvement of skin (utricaria, pruritus, swelling of the faces throat, lips, tongue, skin and periorbital edema) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) has been noted.

j. ***Angioderma***

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

k. ***Exacerbation of endometriosis***

Endometriosis may be exacerbated with administration of oestrogen therapy.

l. ***Exacerbation of other conditions***

Oestrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or severe headache, porphyria, systemic lupus erythematosus and hepatic haemangiomas and should be used with caution in women with these conditions.

The patient should also be closely monitored if any of the following conditions are present or have occurred previously (including during pregnancy or a previous hormone treatment): leiomyomas (uterine fibroids) or endometriosis, thromboemolic disorders, hepatic disorders (e.g. liver adenoma), heart failure, hypertension, renal disorders, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erthematosus, past endometriosis, 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 conditions is diagnosed or suspected during HRT, the benefits and risks of continuing HRT should be reassessed.

Caution is advised when rist factors or oetrogen-dependant tumours (e.g. first degree blood relatives who have ever had breast cancer) are present.

Treatment with HRT should be stopped in the following situations: an increase in epileptic seizures, jaundice or deterioration in liver function, a significant increase in blood pressure, new onset of migraine type headache, pregnancy or if a condition described under CONTRAINDICATIONS develops.

m. ***Contact sensitisation***

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

n. ***Patient monitoring***

A complete medical and family history should be taken prior to the initiation or reinstatement of any oestrogen or oestrogen/progestogen therapy. The pretreatment and periodic physical examinations should include special reference to breasts and pelvic organs and should include a Papanicolaou smear. As a general rule, HRT should not be prescribed for longer than 1 year without another physical examination being performed.

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

Regular examination of the breasts is desirable. 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.

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

Although observations to date suggest that oestrogens, including transdermal oestradiol 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.

Patients should be advised that Estalis Sequi is not a contraceptive, neither will it restore fertility.

Use in patients with renal and / or hepatic impairment

No studies were performed in patients with renal and hepatic impairment.

All oestrogen preparations are contraindicated in patients with severe hepatic impairment (see CONTRAINDICATIONS).

Use in Pregnancy (Category D)

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

In animal studies, maternal administration of high doses of oestrogens has produced urogenital malformations in the offspring. However, the relevance of this finding for the clinical use of oestradiol is not certain. Animal studies have also shown that high doses of progestogens can cause masculinisation of the female foetus.

Use in breast feeding

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

Paediatric use

Estalis Sequi is not to be used in children.

Use in the elderly

Of the total number of subjects in the oestrogen plus progestogen substudy of the Women's Health Initiative study, 44% (n = 7320) were 65 years and over, while 6.6% (n = 1,095) were 75 years and over (See CLINICAL TRIALS). There was a higher incidence of stroke and invasive breast cancer in women 75 and over compared to women less than 75 years of age.

In the Women's Health Initiative Memory Study (WHIMS), an ancillary study of WHI, a population of 4,532 women aged 65 to 79 years was randomised to conjugated oestrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day (CE + MPA) or placebo. A population of 2,947 hysterectomised women, aged 65 to 79 years, was randomised to conjugated oestrogens (CE 0.625 mg) or placebo. In the planned analysis, pooling the events in women receiving CE or CE + MPA in comparison to those in women on placebo, the overall relative risk (RR) for probable dementia was 1.76 (95% CI 1.19-2.60).

In the oestrogen-alone group, after an average follow-up of 5.2 years a RR of 1.49 (95% CI 0.83-2.66) for probable dementia was observed compared to placebo. In the oestrogen-plus-progestogen group, after an average follow-up of 4 years, a RR of 2.05 (95% CI 1.21-3.48) for probable dementia was observed compared to placebo. Since this study was conducted in women aged 65 to 79 years, it is unknown whether these findings apply to younger postmenopausal women. (See PRECAUTIONS, Dementia.)

With respect to efficacy in the approved indications, there have not been sufficient numbers of geriatric patients involved in studies utilising oestrogens and progestogens to determine whether those over 65 years of age differ from younger subjects in their response to oestrogens and progestogens.

Carcinogenicity and mutagenicity:

In humans, unopposed estrogen therapy is associated with an increased risk of endometrial hyperplasia and endometrial carcinoma (see "PRECAUTIONS" section).

There is limited evidence available in the literature suggesting that oestradiol may be weakly genotoxic at high doses. No evidence could be found for an increase in the rate of gene mutation in bacterial or mammalian cells, but there was some evidence for the induction of chromosomal aberrations and aneuploidy in mammalian cells, and two groups reported an increase in the incidence of sister chromatid exchanges, indicative of DNA damage. Neither of these latter effects were induced by oestradiol in human lymphocyte cultures. Importantly, there was no evidence for micronuclei formation in well controlled rodent bone marrow assays.

Effect on driving and operating machinery

None known.

INTERACTIONS WITH OTHER MEDICINES

Preparations inducing microsomal liver enzymes, e.g. barbiturates, anticonvulsants (including hydantoins and carbamazepine), meprobamate, phenylbutazone, antibiotics (including rifampicin, rifabutin, nevirapine, efavirenz), may impair the activity of oestrogens and progestogens (irregular bleeding and recurrence of symptoms may occur). The extent of interference with transdermally administered oestradiol and norethisterone acetate was not evaluated, although it may be limited by this route which avoids any first pass hepatic metabolism.

Oestradiol is predominantly metabolized by CYP3A4; concomitant administration of inhibitors of CYP3A4 such as ketoconazole, erythromycin or ritonavir may therefore result in an increase of approximately 50% in oestradiol exposure

Caution should be used if the patient 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.

Effect on laboratory tests

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

ADVERSE EFFECTS

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

Adverse drug reactions from multiple sources including clinical trials (Table 2) 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 (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports and not known.

Table 2

Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Uncommon:	Breast cancer.
Immune system disorders	
Rare:	Hypersensitivity.
Not known:	Anaphylactic reaction, anaphylactoid reaction
Psychiatric disorders	
Common:	Depression, insomnia, nervousness, affect lability.
Rare:	Libido disorder.
Nervous system disorders	
Very common:	Headache.
Common:	Dizziness.
Uncommon:	Migraine.
Rare:	Paraesthesia.
Cardiac disorders	
Uncommon:	Hypertension.
Rare:	Embolism venous.
Gastrointestinal disorders	
Common:	Diarrhoea, abdominal pain, flatulence, dyspepsia, nausea.
Uncommon:	Vomiting, asymptomatic impaired hepatic function (transaminases increased).
Rare:	Cholelithiasis, gallbladder disorder.
Very rare:	Jaundice cholestatic.
Skin and subcutaneous tissue disorders	
Common:	Acne, application site reactions (including temporary erythema, scaling/glazing, rash, pruritus, dry skin.
Uncommon:	Skin discoloration.
Not known*:	Alopecia, chloasma, contact dermatitis.
Musculoskeletal and connective tissue disorders	
Common:	Back pain.
Not known:	Pain in extremity .
Reproductive system and breast disorders	
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.
General disorders and administration site conditions	
Very common:	Application site reactions[1].
Common:	Pain, asthenia, oedema peripheral , weight increased.

[1]Application site reactions include localised bleeding, bruising, burning, discomfort, dryness, eczema, edema, erythema, inflammation, irritation, pain, papules, paraesthesia, pruritus, rash, skin discolouration, skin pigmentation, swelling, urticaria, and vesicles

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 (stroke), myocardial infarction, dementia, dry eyes, tear film composition changes.

Published literature has reported an increased risk of inflammatory bowel disease (ulcerative colitis and Crohn's disease) in association with HRT use.

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed.

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.

DOSAGE AND ADMINISTRATION

One treatment cycle of Estalis Sequi consists of 4 matrix patches of Estalis Sequi Week 1 and 2 followed by 4 matrix patches of Estalis Sequi Week 3 and 4. Therapy is started with Estalis Sequi Week 1 and 2 (50 µg/day) matrix patch. The next treatment cycle should be started immediately after the removal of the last Estalis Sequi Week 3 and 4 (50/250 or 50/140 µg/day) matrix patch.

Initiation of therapy:

The treatment cycle may be initiated for women who are not currently on any oestrogen therapy. For most menopausal women, therapy may be commenced at any convenient time.

Women currently using oestrogen or oestrogen/progestogen therapy should complete the current cycle of therapeutic regimen before initiating Estalis Sequi (Estalis Sequi Week 1 and 2 and Estalis Sequi Week 3 and 4). At the completion of a cycle of therapy, women often experience withdrawal bleeding. The first day of this bleeding would be an appropriate time to begin a new treatment cycle with Estalis Sequi therapy.

Estalis Sequi 50/140 and 50/250 can not be considered to be bioequivalent to other combination hormone patches.

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacological therapy. Postmenopausal women require an adequate daily intake of elemental calcium. Therefore when not contraindicated, calcium supplementation may be helpful for women with sub-optimal dietary intake. Vitamin D supplementation may also be required to ensure adequate daily intake in postmenopausal women.

Therapeutic regimen:

Estalis Sequi Week 1 and 2 matrix patch is applied to the skin (see "Method of application") every 3 to 4 days for the first 14 days of a 28-day cycle, followed by the application of Estalis Sequi Week 3 and 4 50/250 µg/day matrix patch to the skin every 3 to 4 days for the remaining 14 days of the 28-day cycle. The Estalis Sequi Week 3 and 4 dose may be decreased to 50/140 µg/day if progestogen-related side effects occur.

For all therapeutic indications, the lowest effective dose should be used and consideration should be given to the shortest duration of use. A careful appraisal of the risks and benefits

should be undertaken over time in women treated with HRT and the need for treatment re-evaluated periodically. Treatment should only be continued for as long as the benefits outweigh the risks for the individual (see "PRECAUTIONS").

Women should be advised that monthly bleeding will usually occur.

Method of application:

Care should be exercised when applying Estalis Sequi Week 1 and 2 or Estalis Sequi Week 3 and 4. The matrix patch should be placed on an area of clean, dry skin which is not irritated, abraded or oily (i.e. should not be used with any moisturising cream, lotion or oil).

Site of application:

The matrix patch should be applied to a smooth (fold-free) hair free area of the skin on the buttocks or abdomen. The waistline should be avoided, since tight clothing may rub the matrix patch off. **Estalis Sequi Week 1 and 2 or Estalis Sequi Week 3 and 4 must never be applied to or near the breasts.** The matrix 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.

Application:

After opening the sachet, remove one half of the protective liner, taking care not to touch the adhesive part of the sachet with the fingers. Apply the matrix patch to the skin immediately. Remove the second half of the protective liner and press the matrix patch firmly to the skin with the palm of the hand for at least 10 seconds, carefully smoothing down the edges. Once in place, the matrix patch should not be exposed to the sun for prolonged periods of time.

Dislodged patches:

Care should be taken during bathing or other activities so that the matrix patch does not become dislodged. If the matrix patch falls off (after strenuous physical activity, excessive sweating or friction from tight clothing), the same matrix patch may be reapplied to another area. If necessary, a new matrix patch may be applied, in which case the original treatment schedule should be followed.

Removal and disposal:

The removal of the matrix patch should be done carefully and slowly to avoid irritation of the skin. Should any adhesive remain on the skin after removal of the matrix patch, allow the area to dry for 15 minutes, then gently rubbing the area with an oil-based cream or lotion should remove any adhesive residue. Once used, Estalis Sequi matrix patches should be folded (adhesive surfaces pressed together) and discarded.

OVERDOSAGE

Due to the mode of administration, overdose of oestradiol or norethisterone acetate is unlikely to occur. The effects of overdose with oral oestrogens are breast tenderness, nausea, vomiting and/or metrorrhagia. Oral overdose effects for norethisterone are nausea and vomiting.

If signs of overdose appear, the Estalis Sequi matrix patch should be removed.

PRESENTATION AND STORAGE CONDITIONS

One strength of Estalis Sequi Week 1 and 2 matrix patches and two strengths of Estalis Sequi Week 3 and 4 matrix patches are available, providing the following release rates of oestradiol and norethisterone acetate during 3.5 to 4 days.

Nominal Release rate (µg/day) Oestradiol/NETA**	Oestradiol content (mg)*	NETA content (mg)	Surface area (cm^2)	Shape
Estalis Sequi Week 1 and 2 50/0	0.78	-	5	Rounded Rectangle
Estalis Sequi Week 3 and 4 50/140	0.62	2.7	9	Round
Estalis Sequi Week 3 and 4 50/250	0.51	4.8	16	Round

* 1 mg oestradiol hemihydrate Ph. Eur. is equivalent to 0.968 mg of oestradiol.

** NETA = norethisterone acetate

Both Estalis Sequi Week 1 and 2 and Estalis Sequi Week 3 and 4 matrix patches are individually heat sealed in foil laminate sachets. Each Estalis Sequi pack contains four sachets of Estalis Sequi Week 1 and 2 and four sachets of Estalis Sequi Week 3 and 4.

Storage conditions:

Prior to dispensing to patients, store at 2 - 8° C (Refrigerate. Do not freeze).

After dispensing to the patient, Estalis Sequi can be stored below 25° C for up to 6 months or until the expiry date, whichever comes first. Do not store the matrix patches out of the sachet. Protect from light.

Instructions for pharmacist:

When Estalis Sequi is dispensed to the patient, if the expiry date is more than 6 months away, place a new expiry date of 6 months from the date of dispensing on the label.

Children:

Estalis Sequi, either new or used, should always be kept out of the reach of children.

Shelf life:

The shelf life of Estalis Sequi is 24 months, including up to 6 months stored below 25° C after dispensing to the patient (refer "Storage Conditions").

NAME AND ADDRESS OF THE SPONSOR

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