AUSTRALIAN PRODUCT INFORMATION
ESTALIS® CONTINUOUS

(estradiol/norethisterone acetate)

WARNING

Estrogens 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 estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo (See Section 5.1 PHARMACODYNAMIC PROPERTIES Clinical Trials and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 estrogens (0.625 mg) relative to placebo (See Section 5.1 PHARMACODYNAMIC PROPERTIES Clinical Trials and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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 estrogens, with or without medroxyprogesterone acetate, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women (See Section 5.1 PHARMACODYNAMIC PROPERTIES Clinical Trials and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestogens were not studied in the WHI Section 5.1 PHARMACODYNAMIC PROPERTIES Clinical Trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens 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.

1 NAME OF THE MEDICINE

Estradiol and norethisterone acetate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Two strengths of Estalis Continuous transdermal matrix patches are available, providing the following release rates of estradiol and norethisterone acetate during 3.5 to 4 days.

Nominal Release rate (µg/day) **Estradiol/NETA****	**Estradiol content (µg)***	**NETA content (mg)**	**Surface area (cm^2)**	**Shape**
50/140	620	2.7	9	Round

50/250	512	4.8	16	Round

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

** NETA = norethisterone acetate

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Transdermal drug delivery system (patch)

Off-white translucent patch with a removable pre-cut liner.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- For the short-term treatment of symptoms of estrogen deficiency in menopausal women who have an intact uterus
- For prevention of postmenopausal bone mineral density loss in women with an increased risk of future osteoporotic fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of bone mineral density loss. When prescribed solely for the prevention of postmenopausal bone mineral density loss, therapy should only be prescribed for women who are at high risk of future fracture and who are intolerant of, or contraindicated for, non-estrogen products approved for prevention of bone mineral density loss. Lifestyle modifications and the risk-benefit profile of Estalis Continuous should be taken into careful consideration and discussed with the patient to allow the patient to make an informed decision prior to prescribing (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Initiation of therapy:

The treatment regimen may be initiated for women who are not currently on any estrogen/progestogen therapy. For those menopausal women, therapy may be commenced at any convenient time.

Women currently using sequential estrogen/progestogen therapy should complete the current cycle of therapeutic regimen before initiating Estalis Continuous. At the completion of a sequential cycle of therapy, women often experience bleeding. The first day of this bleeding would be an appropriate time to begin treatment with Estalis Continuous therapy.

Estalis Continuous and other hormonal combination patches cannot be considered to be bioequivalent.

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:

Therapy should be initiated with one Estalis Continuous 50/250 matrix patch applied to the skin (See "Method of application") every 3 or 4 days during a 28-day cycle. The dose of 50/250 µg/day may be decreased to 50/140 µg/day if progestogen-related side effects occur. Estalis Continuous 50/140 may be used as the starting dose, if it is considered more appropriate.

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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Women should be advised that irregular bleeding/spotting may occur in most patients, before amenorrhoea is established, in about half of the cases, by the end of one year of treatment.

Method of application:

Care should be exercised when applying Estalis Continuous. 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 Continuous 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 any 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 Continuous matrix patches should be folded (adhesive surfaces pressed together) and discarded.

4.3 CONTRAINDICATIONS

Estalis Continuous 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 estrogen-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 estrogens and progestogens or to any of the components of this product (see Section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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

When initiating estrogen/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.

Cardiovascular disorders

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

Estrogen/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.

Coronary heart disease and stroke

In the estrogen 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 Section 5.1 PHARMACODYNAMIC PROPERTIES Clinical Trials.)

In the same substudy of WHI, an increased risk of stroke was observed in women receiving estrogen/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 estrogen/ 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 estrogen/progestogen-treated group and the placebo group in HERS, HERS II, and overall.

Venous thromboembolism (VTE)

In the estrogen 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 estrogen/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.

If feasible, estrogens 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 Section 4.3 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 Continuous 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.

Malignant neoplasms

Breast cancer

The use of estrogens 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 estrogen plus progestogen (See Section 5.1 PHARMACODYNAMIC PROPERTIES 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 estrogen plus progestogen. Observational studies have also reported an increased risk for estrogen/progestogen combination therapy, and a smaller increased risk for estrogen 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 estrogen/progestogen combination therapy as compared to estrogen alone therapy. However, these studies have not found significant variation in the risk of breast cancer among different estrogens or among different estrogen/progestogen combinations, doses, or routes of administration.

In the WHI trial of estrogen plus progestogen, 26% of the women reported prior use of estrogen alone and/or estrogen/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 estrogen 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 estrogen 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 estrogen plus progestogen compared with placebo. In the WHI trial, invasive breast cancers were larger and diagnosed at a more advanced stage in the estrogen 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 estrogens alone or estrogens plus progestogens compared to never users, while the estrogen 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 estrogen 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.

Endometrial cancer

The reported endometrial cancer risk among unopposed estrogen users is about 2- to 12-fold greater than in nonusers, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens 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 estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/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 treatment should be re-evaluated. There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose.

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 estrogen-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 estrogen-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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in the elderly.)

Gallbladder disease

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

Hypercalcaemia

Estrogen 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.

Visual abnormalities

Retinal vascular thrombosis has been reported in patients receiving estrogens. 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, estrogens should be discontinued.

General precautions

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 estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen 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 estrogens compared with estrogen-alone regimens. These include a possible increased risk of breast cancer and impairment of glucose tolerance.

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

Elevated blood pressure

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

Hypertriglyceridaemia

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

Impaired liver function and past history of cholestatic jaundice

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

Hypothyroidism

Estrogen 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 estrogens 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.

Fluid retention

Because estrogens/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 estrogens are prescribed.

Hypocalcaemia

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

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 estrogen-only or combined estrogen-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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)."

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 (urticaria, pruritus, swelling of the face, throat, lips, tongue, skin and periorbital oedema) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) has been noted.

Angiodema

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

Exacerbation of endometriosis

Endometriosis may be exacerbated with administration of estrogen therapy.

Exacerbation of other conditions

Estrogen 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, hepatic disorders (e.g. liver adenoma), thromboembolic disorders, heart failure, hypertension, endometrial hyperplasia, renal disorders, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erythematosus, epilepsy, asthma, otosclerosis, gallbladder disease, estrogen-related jaundice and pruritus.

It should be taken into account that these conditions may recur or be aggravated during treatment with estrogens. 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 risk factors for estrogen-dependent 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 Section 4.3 CONTRAINDICATIONS develops.

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.

Patient monitoring

A complete medical and family history should be taken prior to the initiation or reinstatement of any estrogen or estrogen/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 hormone replacement therapy and the need for hormone replacement therapy should be 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 estrogens, 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.

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

Use in renal impairment

No studies were performed in patients with renal impairment.

All estrogen preparations are contraindicated in patients with severe hepatic impairment (see Section 4.3 CONTRAINDICATIONS).

Use in hepatic impairment

No studies were performed in patients with hepatic impairment.

All estrogen preparations are contraindicated in patients with severe hepatic impairment (see Section 4.3 CONTRAINDICATIONS).

Use in the elderly

Of the total number of subjects in the estrogen 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 Section 5.1 PHARMACODYNAMIC PROPERTIES 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 estrogens 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 estrogens (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 estrogen-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 estrogen-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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Dementia.)

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

Paediatric use

Estalis Continuous is not to be used in children.

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 estrogens and progestogens (irregular bleeding and recurrence of symptoms may occur). The extent of interference of transdermally administered estradiol and norethisterone acetate was not evaluated, although it may be limited by this route which avoids first pass hepatic metabolism.

Estradiol 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 estradiol 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 estrogens and progestogens.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

None known.

Use in pregnancy – pregnancy category D

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

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

Use in lactation

Estalis Continuous must not be used while breast feeding.

Estrogens or progestogens are excreted in breast milk and may reduce the production of breast milk**.** .

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None known. However, adverse effects of these medicines include dizziness which could affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS))

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 Section 5.1 PHARMACODYNAMIC PROPERTIES 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 (≥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 1:

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.
	Uncommon:	Vertigo.
	Rare:	Libido disorder.
Nervous system disorders		
	Very common:	Headache.
	Common:	Dizziness.
	Uncommon:	Migraine.

Rare:	Paraesthesia.
Cardiac disorders	
Uncommon:	Hypertension, varicose veins.
Rare:	Embolism venous.
Gastrointestinal disorders	
Common:	Diarrhoea, flatulence ,abdominal pain, abdominal distension, 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, papules/vesicles, redness and itching), rash, pruritus, dry skin.
Uncommon:	Skin discoloration.
Not known:	Alopecia, chloasma, contact dematitis
Musculoskeletal and connective tissue disorders	
Common:	Back pain, 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 localized bleeding, bruising, burning, discomfort, dryness, eczema, oedema, 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 estrogen-progestogen treatments: estrogen-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 estrogen-only or combined estrogen-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.

4.9 OVERDOSE

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

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The estradiol matrix patch is an efficient systemic estrogen replacement therapy which alleviates the symptoms of estradiol deficiency in menopausal women, as estradiol is largely responsible for the development and maintenance of the female urogenital system and of secondary sexual characteristics. Estrogen 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. Estrogens reduce post-menopausal bone loss and provide protection against osteoporotic fractures. When Estalis Continuous is used for the short-term relief of menopausal symptoms, it will provide a concomitant preventative effect in reducing bone mineral density loss.

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

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

Clinical Trials

<u>Trials with Estalis Continuous:</u>

Clinical data involving a total of 704 patients between three months to one year of therapy support the use of Estalis Continuous in menopausal women.

Estalis Continuous decreases rapidly the number and the intensity of hot flushes and sweating. Dimensions of Quality Of Life showed a beneficial effect of Estalis Continuous 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 Continuous 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, 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 Continuous 50/140 and 50/250 µg/day. Within one year of treatment, all markers decreased to normal premenopausal range (See Section 4.1 THERAPEUTIC 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 estrogen 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 2.

TABLE 2 RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN 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

TABLE 2 RELATIVE AND ABSOLUTE RISK SEEN IN THE ESTROGEN 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	
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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

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 estrogen/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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Dementia and Use in Geriatrics.)

5.2 PHARMACOKINETIC PROPERTIES

Estalis Continuous is designed to be applied to intact skin, providing continuous physiological levels of estradiol and NETA for 3.5 to 4 days following application, thereby minimising the high doses of estradiol and NETA normally required orally to compensate for the first-pass effect'

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

Estradiol

Absorption:

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

Distribution:

Estradiol distributes widely in body tissues and is bound to albumin (about 60-65 %) and sex hormone-binding globulin (about 35-45 %) in serum. Serum protein-binding fractions remain unaltered following transdermal delivery of estradiol.

Metabolism:

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

Excretion:

Estradiol 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 estradiol return to untreated postmenopausal levels

(< 20 pg/mL) within 4 - 8 hours.

Norethisterone

Absorption:

In a pharmacokinetic study it was shown that multiple applications of Estalis Continuous (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 Continuous increased linearly with increasing doses of NETA.

Distribution:

Norethisterone distributes widely in body tissues and is bound to albumin (about 61 %) and sex hormone-binding globulin (about 36 %) in serum.

Metabolism:

Norethisterone acetate is rapidly hydrolysed to the active norethisterone. Norethisterone is primarily metabolised in the liver.

Excretion:

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There is limited evidence available in the literature suggesting that estradiol 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 estradiol in human lymphocyte cultures. Importantly, there was no evidence for micronuclei formation in well-controlled rodent bone marrow assays.

Carcinogenicity:

In humans, unopposed estrogen therapy is associated with an increased risk of endometrial hyperplasia and endometrial carcinoma (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Silicone (BIO-PSA™ N131A-4603) and acrylic (Gelva 737) adhesives, povidone, oleic acid and dipropylene glycol.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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

After dispensing to the patient, Estalis Continuous 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.

Instructions for pharmacist:

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

6.5 NATURE AND CONTENTS OF CONTAINER

Estalis Continuous is an alcohol free, adhesive-based matrix patch comprising three layers: a backing, an adhesive layer and a protective liner. The adhesive matrix containing estradiol and NETA 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'

The Estalis Continuous matrix patches are individually heat sealed in foil laminate sachets.

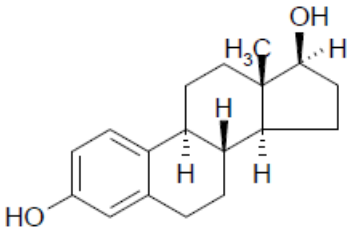
The sachets are packed into cartons of 2 (starter pack) and 8 matrix patches.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

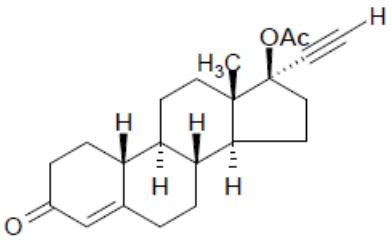
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Estradiol
CAS : 50-28-2



Norethisterone Acetate
CAS : 51-98-9

Estradiol

The molecular weight of estradiol is 272.4 and the molecular formula is $C_{18}H_{24}O_2$.

The manufacturing source of the estradiol is estradiol hemihydrate, a white, or almost white crystalline powder. estradiol is chemically described as estra-1,3,5(10)-triene-3,17β-diol.

Norethisterone acetate

Norethisterone acetate 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 $C_{22}H_{28}O_3$.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine.

8 SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

Macquarie Park NSW 2113

® = Registered Trademark

9 DATE OF FIRST APPROVAL

11 October 1999

10 DATE OF REVISION

8 May 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Reformatted in line with the revised Australian form for providing product information Revise oestrogen to estrogen and oestradiol to estradiol to comply with TGA Approved Names for Ingredients.
2	Revise amount of estradiol to 512 micrograms, to reflect registration details of Estalis Continuous 50/250.
3	Amended as follows: '~~Estalis Continuous is a matrix t~~Transdermal drug delivery system (patch) ~~containing oestradiolestradiol and norethisterone acetate (NETA)~~.' Added: 'Off-white translucent patch with a removable pre-cut liner'

4.7	Added: However, adverse effects of these medicines include dizziness which could affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS))
5.2	Deleted the subheading 'PHARMACOKINETIS'. Added: Estalis Continuous is designed to be applied to intact skin, providing continuous physiological levels of estradiolestradiol and NETA for 3.5 to 4 days following application, thereby minimising the high doses of estradiolestradiol and NETA normally required orally to compensate for the first-pass effect
6.1	Amended as follows: '~~The pharmacologically inactive components of the matrix patch are: are s~~Silicone (BIO-PSA™N131A-4603) and acrylic (Gelva 737) adhesives, povidone, oleic acid and dipropylene glycol.'
6.5	Added: Estalis Continuous is an alcohol free, adhesive-based matrix patch comprising three layers: a backing, an adhesive layer and a protective liner. The adhesive matrix containing estradiolestradiol and NETA 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'
6.7	Deleted the subheading 'Transdermal matrix patch' and the two associated paragraphs.

For internal use only

(els080520i_V2.doc) based on CDS dated 8 August 2016