ESTALIS ® 50/140
(estradiol hemihydrate, norethisterone acetate)

PL 00101/0690

UK Public Assessment Report

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Novartis Pharmaceuticals UK Limited a Marketing Authorisation (licence) for the medicinal product Estalis ® 50/140 (PL 00101/0690) on 25th April 2007. This is a prescription-only medicine (POM) used as hormone replacement therapy (HRT).

Estalis® contains the active ingredients estradiol (as estradiol hemihydrate) and norethisterone (as norethisterone acetate). Estradiol is a female sex hormone (or estrogen), which the ovaries produce in large amounts before the menopause. Norethisterone is also a female sex hormone and helps protect the lining of the womb in women who have not had a hysterectomy (surgical removal of the womb).

Estalis® is supplied as stick-on patches. When the patch is applied to your skin it releases small amounts of the active ingredients, which pass directly through your skin and into your bloodstream. Estalis ® 50/140 delivers 50 micrograms estradiol and 140 micrograms norethisterone acetate per 24 hours.

Estalis ® 50/140 is a type of treatment known as HRT. Estalis® delivers estradiol and norethisterone, and is therefore known as a continuous combined HRT product. Estalis® is used to help relieve the unpleasant symptoms of the menopause, such as hot face, neck and chest, ‘hot flushes’, sleep problems, irritability, and depression.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Estalis ® 50/140 outweigh the risk; hence a Marketing Authorisation has been granted.

ESTALIS ® 50/140
(estradiol hemihydrate, norethisterone acetate)

PL 00101/0690

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Novartis Pharmaceuticals UK Limited a Marketing Authorisation for the medicinal product Estalis ® 50/140 (PL 00101/0690) on 25th April 2007. The product is a prescription-only medicine used as HRT.

This is a standard abridged application for Estalis ® 50/140 transdermal patches, submitted under Article 8.3 of Directive 2001/83/EC, as amended. The application, a fundamental change in product strength to an existing MA, is a line extension of Estalis Sequi® transdermal patches, PL 00101 / 0590, granted to Novartis Pharmaceuticals UK Limited in November 2001. The original product, Estalis Sequi® consists of Phase 1 and Phase 2 patches: Each Phase 1 patch has a nominal release of 50 µg / 24 hours of estradiol. Each Phase 2 patch has a nominal release of 50 µg / 24 hours of estradiol and 250 µg / 24 hours of norethisterone acetate.

Estalis ® 50/140 contains the active ingredients estradiol (as estradiol hemihydrate (E2)) and norethisterone (as norethisterone acetate (NETA)), and is indicated as continuous-combined HRT for estrogen deficiency symptoms in non-hysterectomised postmenopausal women.

The active ingredient, synthetic 17β-estradiol is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women, and alleviates menopausal symptoms such as flushes and swelling. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. Norethisterone acetate (a progestogen) is given to greatly reduce the risk of estrogen-induced endometrial hyperplasia in non-hysterectomised women.

The application was referred to the Committee on Safety of Medicines (CSM) who met in May 2004 for consideration whether the safety, quality and efficacy of the product was demonstrated. At that time, the Commission advised that a Marketing Authorisation should not be approved. Following consideration of the applicant's response and further data that was submitted, the approval of the Marketing Authorisation was recommended.

This application for Estalis ® 50/140 was submitted and approved at the same time as the application for Estalis ® 25/125 (PL 00101/0689). A Public Assessment Report is also available for Estalis ® 25/125.

PHARMACEUTICAL ASSESSMENT

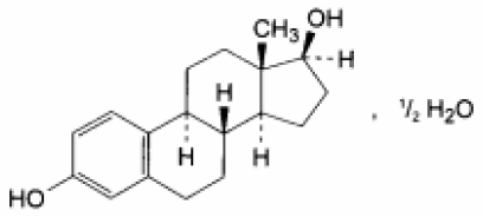
ACTIVE SUBSTANCE

Estradiol hemihydrate

Nomenclature:

INN:	Estradiol hemihydrate
Chemical name:	Estra-1,3,5(10)-triene-3,17β-diol hemihydrate

Structure:



Molecular formula:	$C_{18}H_{24}O_2,½H_2O$
Molecular weight:	281.4
CAS No:	50-28-2
Physical form:	White or almost white, crystalline powder or colourless crystals
Solubility:	Practically insoluble in water, soluble in acetone, sparingly soluble in alcohol, slightly soluble in methylene chloride

The active substance, estradiol hemihydrate, is the subject of a European Pharmacopeia (EP) monograph.

All aspects of the manufacture and control of estradiol hemihydrate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of estradiol hemihydrate for inclusion in this medicinal product.

Appropriate stability data have been generated for estradiol hemihydrate stored in the proposed packaging. These data demonstrate the stability of the active substance and a suitable retest period has been set based on the data.

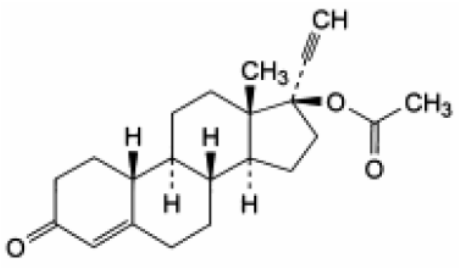
ACTIVE SUBSTANCE

Norethisterone acetate

Nomenclature:

INN:	Norethisterone acetate
Chemical name:	3-Oxo-19-nor-17α-pregn-4-en-20-yn-17-yl acetate

Structure:



Molecular formula:	$C_{22}H_{28}O_3$
Molecular weight:	340.5
CAS No:	51-98-9
Physical form:	White or yellowish-white, crystalline powder
Solubility:	Practically insoluble in water, freely soluble in methylene chloride, soluble in alcohol

The active substance, norethisterone acetate, is the subject of a EP monograph.

All aspects of the manufacture and control of norethisterone acetate are supported by an EDQM Certificate of Suitability. This certificate is accepted as confirmation of the suitability of norethisterone acetate for inclusion in this medicinal product.

Appropriate stability data have been generated for norethisterone acetate stored in the proposed packaging. These data demonstrate the stability of the active substance and a suitable retest period has been set based on the data.

DRUG PRODUCT

Description and Composition

The drug product is presented as off white, translucent circular patches. The patches are laminates containing a backing film, a pressure sensitive adhesive matrix containing the active substances and a peelable protective release liner.

Other ingredients consist of pharmaceutical excipients, namely povidone, toluene, isopropyl alcohol, silicone adhesive, acrylic adhesive, oleic acid, dipropylene glycol, polyester film and fluoropolymer. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of toluene, silicone adhesive, acrylic adhesive, dipropylene glycol, polyester film and fluoropolymer which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is oleic acid. A Certificate of Suitability has been provided by the supplier of oleic acid stating that the oleic acid they provide meets the criteria described in the current version of the monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’.

There were no novel excipients used and no overages.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specifications for both release and shelf life are acceptable, and provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification.

Container Closure System

The Estalis® transdermal patches are packed individually in heat-sealed pouches. The pouches are packaged, with the PIL (Patient Information Leaflet), into cardboard outer cartons. Estalis 50/140 are available as packs of 2, 8 and 24 transdermal patches.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with modified release transdermal dosage forms.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 30 months has been set: 24 months when refrigerated at 2°C-8°C, plus 6 months when stored up to 25°C. This is satisfactory. Special precautions for storage, as described in the SPC of the product, are “Do not freeze. Store between 2 and 8°C until dispensed to the patient. Then, Estalis® can be stored up to 25°C for a maximum period of 3 months. Do not store the transdermal patches unpouched.”.

Bioequivalence Study

Clinical studies were presented to demonstrate the efficacy, as well as the safety, of the product. The efficacy data remove the need for a bioequivalence study. Details of the clinical studies undertaken are found in the Clinical Assessment section.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory.

Conclusion

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted.

PRECLINICAL ASSESSMENT

I INTRODUCTION

This is a full national application for Estalis® 50/140 transdermal patches submitted by Novartis Pharmaceuticals UK Ltd. under article 8.3 of Council Directive 2001/83/EC, as amended.

Estalis® 50/140 are transdermal patches containing 17-β-estradiol as the hemihydrate (E2) and norethisterone acetate (NETA). The patches are circular, translucent laminates (9 cm^2) consisting of an impermeable backing film, the drug-containing adhesive matrix and a protective liner to be removed from the surface of the matrix before application to the skin. The patches are applied dermally twice weekly (every three or four days) and are indicated for the continuous combined treatment of oestrogen-deficiency symptoms in women with an intact uterus. The 50/140 patch delivers 50 µg E2 and 140 µg NETA per twenty-four hours. NETA has been selected because it is readily absorbed cutaneously and is a potent progestogen that provides endometrial protection.

Higher strength patches (Estalis® 50/250, delivering 50 µg E2 and 250 µg NETA) are available in all EU countries except the UK where only Estalis® sequi 50/250 has been approved. The latter consists of a combination pack including Estalis® 50/250 and an E2-only patch that delivers 50 µg E2, for continuous-sequential hormone replacement therapy (HRT).

The purpose of the 50/140 patches is to offer a lower strength therapy with an endometrial protective effect.

I.1 GOOD LABORATORY PRACTICE (GLP) ASPECTS

The non-clinical data on the two actives have been taken from the published literature; and data on the local tolerance and toxicity of the excipients have also been considered. Preclinical studies on local tolerance and special toxicity of the final dose form have been conducted, including phototoxicity and photoallergy investigations. All the new studies were conducted in accordance with GLP regulations.

II PHARMACODYNAMICS

The pharmacodynamics of both actives are well-established. The non-clinical overview contains a concise overview of the actions of E2 and NETA and how they interact relevant to the clinical indication, and notes that there is no preclinical model for the human menopause.

The absence of data on secondary pharmacodynamics, safety pharmacology and pharmacodynamic drug interactions was justified as these are well known from the development of other hormonal treatments.

III PHARMACOKINETICS

The absence of pharmacokinetic studies with Estalis® patches was justified because adequate human data are available. The absorption, distribution, metabolism and excretion of both actives are well known. Transdermally administered E2 is known to be absorbed through the skin unchanged and is detectable in the systemic circulation. NETA is a precursor hormone that is rapidly and completely hydrolysed by esterases to the active hormone norethisterone during its passage through the skin. The latter is detected in the circulation.

Clinical studies have shown that the bioavailability and pharmacokinetics of estrogens and norethisterone are unaffected by co-administration.

III.1 TOXICOKINETICS

A study was conducted to investigate the dermal toxicity of and uptake from temperature-stressed patches (containing 3.4% estradiol degradants and 5.4% norethisterone degradants) in Crl:CDHAIRLESS rats. Patches were applied every three or four days for four weeks and the torso was wrapped, and the animals fitted with Elizabethan collars to prevent gnawing or removal of the patches. Mean plasma concentrations of both actives were slightly lower in the degraded patch groups but of sufficient level to indicate that absorption of the degradants capable of transdermal passage would occur.

Toxicokinetic data were also collected in a micronucleus study in Hairless Ico:OFA-hr rats with heat-degraded and refrigerated patches. Plasma samples were collected twenty-four hours after application of the patches. There was a trend for slightly lower plasma concentrations in animals receiving the degraded patches but the differences in systemic exposure were not significantly different for either active.

IV TOXICITY

The experimental toxicity of oestrogens and progestogens is well-known and E2 and NETA are the subjects of International Agency for Research on Cancer (IARC) monographs. However, the animal data are not considered representative of the effects in humans and clinical data are regarded as more relevant.

The nonclinical overview concentrates on the local tolerance of the transdermal patch, systemic and local toxicity and genotoxic potential of temperature-stressed patches (containing degradants), and of the excipients.

The absence of reproductive and genetic toxicity tests was justified as the effects of E2 and NETA in the former are well-known and there are no effects in the latter. The IARC considers that post-menopausal oral oestrogen-progestogen therapy is possibly carcinogenic in humans (group 2B).

IV.1 EXCIPIENTS

The excipients comprise povidone, toluene, isopropyl alcohol, silicone adhesive, acrylic adhesive, oleic acid, dipropylene glycol, polyester film and fluoropolymer. The non-clinical overview contains a clear and comprehensive review of their safety and suitability and there are no concerns suggested by the data.

IV.2 IMPURITIES AND DEGRADATION PRODUCTS

Chemical decomposition of the drug substances was found, the main route of degradation being oxidation with ester formation. The cause was considered to be the presence of oleic acid but because of its enhancement of absorption of the actives, it was retained in the formulation and appropriate production and supply controls instituted.

In order to qualify the impurities, single-dose acute and four-week repeat-dose topical toxicity studies were conducted with temperature-stressed patches. The levels of estradiol and norethisterone acetate degradants exceeded those found at the end of the proposed shelf-life. The tests revealed no effects indicative of any untoward toxicity and there was no evidence of contact hypersensitivity, photosensitisation or phototoxicity with the degraded patches.

In vitro genotoxicity testing of extracts from degraded patches and *in vivo* testing of degraded patches showed no evidence of genotoxicity.

IV.3 ENVIRONMENTAL RISK ASSESSMENT (ERA)

An ERA consisting of estimates of Predicted Environmental Concentrations (PECs) of E2 and NETA in surface water and soil and supporting published papers was provided. The PECs indicate that that material derived from Estalis® patches will be below the trigger levels stipulated in CPMP Note for Guidance III/5504/94 (now 4447/00) and further assessment is not required.

Assessor's comment:

Given that the application is for lower doses of a therapy well-established in other member states of the EU, and the rates of delivery of the estradiol and norethisterone are identical to those from existing patches, there is no need to re-evaluate the preclinical data here. The studies conducted specifically to investigate the potential for toxicity from degraded patches did not reveal any risks to human health.

V NONCLINICAL OVERVIEW

A preclinical expert report has been written by a suitably qualified person and is satisfactory. An appropriate CV has been provided for the expert.

VI SUMMARY OF PRODUCT CHARACTERISTICS

The final SmPC is satisfactory.

CONCLUSION

This application has not revealed any evidence of untoward toxicity with Estalis® 50/140. It is concluded that there is no objection to the grant of a licence for Estalis® 50/140 transdermal patches from a preclinical point of view.

CLINICAL ASSESSMENT

I INTRODUCTION

The rationale behind the development of the product is that it is envisaged that Estalis 50/140 would allow transdermal delivery of a low dose of oestrogen/progestogen, support the aim of dose individualisation/flexibility, and provide better patient acceptability. It is designed to provide plasma levels of E2 that are comparable to those in the early to mid-follicular phase in premenopausal women.

A licence application for Estalis 50/140 (as Aliatis 50/140) was previously considered but a MA was not granted. This application for Estalis 50/140 has been submitted with additional data.

I.1 GCP ASPECTS

The formulation of Estalis 50/140 intended for marketing was used in the clinical studies. All the clinical studies were conducted according to GCP.

II INDICATIONS

Estalis 50/140 are indicated as HRT for estrogen deficiency symptoms in non-hysterectomised postmenopausal women.

III CLINICAL PHARMACOLOGY

Pharmacokinetics

Estrogens and progestogens are well absorbed transdermally. E2 and NETA circulate in the blood, primarily bound to sex hormone binding globulin (SHBG) and, to a lesser extent, albumin. Transdermally absorbed E2 has a short t½ of 2-3h and there is little metabolism in the skin. NETA has a t½ of 6-8h and is hydrolysed to the active moiety NET, in most tissues, including skin and blood.

Both E2 and NET are metabolised primarily in the liver when administered orally, but when applied transdermally the hepatic first-pass effect, associated with the oral route, is avoided; thus the extensive conversion of E2 to estrone (E1) and its conjugates, seen with oral E2, is avoided. In contrast to oral preparations, therapeutic E2 levels can therefore be achieved with smaller doses and more closely approximate to premenopausal concentrations.

Drugs which induce hepatic enzymes e.g. barbiturates, anticonvulsants (e.g. phenobarbitone, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz) may impair activity of oestrogens/progestogens, resulting in breakthrough bleeding and/or reduced efficacy. Transdermal delivery, avoiding first-pass metabolism, may militate against this. Nevertheless, appropriate warnings are contained in the SmPC.

Justification for Dose/Site of Application

The previous application (Aliatis 50/140) discussed a clinical pharmacology package supporting dose selection and site of application. These studies have not been

resubmitted for Estalis 50/140 but they were evaluated and accepted during the previous submission, and are now summarised:

4 dose-finding studies were conducted to determine the final E2/NETA combination (Studies 101, 102, 103 and 105). The E2 dose was based on the finding that 50µg/day of transdermal (e.g. Estraderm TTS 50 or Menorest 50) was clinically equivalent to 0.625mg/day of conjugated equine estrogens (Premarin).

The NETA dose was based on data on Estragest TTS 50/250 which show that a transdermal dose of 250µg/day, given sequentially (with 50µg/day continuous transdermal E2), provided good cycle control, protection against endometrial hyperplasia and was well tolerated. A reduced dosage of 140µg/day, in this application, is being evaluated to provide further therapeutic options for women who do not tolerate higher dose combinations and to comply with global recommendations for the use of the lowest effective dose possible. The site of application (abdomen rather than buttock) was decided on the basis of a previously submitted bioavailability Study (122) which showed that drug delivery was superior from the abdominal site (serum levels 24% higher for E2 and 28% higher for NET when applied to the abdomen).

Pharmacodynamics

ATC Code: G 03 FAO1 Genito urinary system and sex hormones

The pharmacodynamics of E2 and NETA are well understood and no additional studies were undertaken.

The active ingredient, E2, is chemically and biologically identical to endogenous human estradiol and substitutes for the loss of oestrogen production in menopausal women, alleviating menopausal symptoms and protecting against postmenopausal osteoporosis.

The addition of a progestogen such as NETA reduces the oestrogen-induced risk of endometrial hyperplasia and cancer, though new evidence from the Women's Health Initiative (WHI) study indicates that this may be offset by a slightly increased risk of breast cancer.

Assessor's overall conclusions on pharmacodynamics

No new issues have arisen regarding the pharmacodynamics of these known actives, E2 and NETA, and no new data have been provided.

IV CLINICAL EFFICACY

Post-menopausal symptoms

Data from four clinical trials are presented. These have been previously submitted with the application for Aliatis 50/140. They consist of two pivotal controlled trials (Studies 302 and 304) and two long-term supportive trials, which included climacteric symptom evaluation as a secondary endpoint (Studies 202 and 305). The patients included in the studies were representative of the target postmenopausal population:

- 40-70 years of age.
- intact uterus.
- amenorrhoeic ≥ 1 year, FSH >40 IU/L; E2 <20 pg/ml
- satisfactory gynaecological examination, PAP smear, mammogram, no contraindications to estrogen therapy.
- All the studies, apart from 305, evaluated Estalis 50/140 itself. Study 305 compared Menorest 50 + a cyclic progestogen relative to placebo.
- The choice of comparators was based on the major HRT products available at the time of study initiation.
- Matching placebo patches or double-dummy technique, as appropriate, were used to maintain blinding.
- Standard measures of efficacy for post-menopausal symptoms were used, including the following variables:

  - Daily number of hot flushes
  - Severity of hot flushes (categorical scale: none, mild, moderate, severe)
  - Daily intensity of sweating (categorical scale: none, mild, moderate, severe)

- Criteria for efficacy

  Pivotal study 304: Efficacy was said to be demonstrated if a statistically significant change in symptoms, relative to baseline and compared to placebo ($p<0.05$), was shown.

  Pivotal study 302: Equivalence was considered to have been demonstrated if the upper limit of the 95% CI surrounding the difference between the E2/NETA group and Kliogest was ≤ 2.0.

  Study 202: No statistical tests were applied to post menopausal symptom data.

  No combined efficacy analyses were performed as the two pivotal. Phase III efficacy studies (Studies 304 and 302) examined different populations of patients, were of different lengths and had different objectives with regard to examining efficacy versus the control. The supportive study (Study 202) provided results for vasomotor symptoms in a small sub-population only.

- Safety was assessed on the incidence of AEs, laboratory safety results, vital signs, ECG, physical exam, genital bleeding pattern, endometrial safety, PAP smears and patch tolerability. The findings are discussed in detail in Section IV.

The studies are summarised in Table 1:

Table 1: Summary of efficacy studies - post-menopausal symptoms

Study	Objectives Population	n	Treatment duration	Study Drug(s)	Efficacy endpoints
304 PIVOTAL PHASE III placebo-controlled	Change from baseline in mean daily hot flushes in target population	226	3 months (3 cycles*) 12 weeks	Estalis 50/140 Estalis 50/250 Estalis 50/400µg/d (contin.combined)	Number and severity of hot flushes @ 3 months
302 PIVOTAL PHASE III active-controlled	Change from baseline in mean daily hot flushes in target population	410	6 months (6 cycles*) 24 weeks	Estalis 50/140 Estalis 50/250µg/d (contin.combined) Kliogest (2mgE2:1mgNETA po)	Number and intensity of hot flushes @ 6 months
202 Supportive Active-controlled	1°:endometrial safety 2°:change in vasomotor symptoms in subsets of target population**	625	12 months (13 cycles*) 52 weeks	Estalis 50/140 Estalis 50/250 Estalis 50/400µg/d (Contin.combined) Noven 50 (E2 50µg/d)	1°Rate of endometrial hyperplasia 2°Number and intensity of hot flushes and sweating
305 Supportive Active-controlled	1°:change from baseline in lumbar spine BMD 2°:change from baseline in mean severity of hot flushes	277	24 months	E2: 25,50,75µg/d (+ Duphaston 10mg bd) Placebo	1°:BMD of L1-L4 AP at 24 months 2°: severity of hot flushes by VAS at 24 months

**each cycle=28days*
*** two subsets: ≥3 and ≥8 hot flushes a day at baseline*

Pivotal Studies

These were double-blind, randomised, controlled 3 or 4-armed studies, comparing the efficacy of Estalis with placebo for 3 months (Study 304) or with the active, albeit oral, comparator Kliogest for 6 months (Study 304) in postmenopausal women with moderate to severe postmenopausal symptoms. Baseline requirements ensured that symptomology was sufficiently severe to warrant HRT therapy and adequate washout of previous HRT therapy occurred before randomisation.

Baseline demographic characteristics and history of menopause were comparable across treatment groups. Discontinuations were fewer in the 3-month study (304) compared to the 6-month study (302) and were mostly for AEs. These differences in discontinuation rates were not considered to influence the conclusions drawn from the data.

The primary efficacy variable was the mean number of hot flushes compared to baseline, measured at study endpoint in the ITT population. Secondary efficacy variables included severity of hot flushes and sweating. Statistical analyses compared the effect of Estalis treatment with placebo or active control on mean changes, from baseline, in vasomotor symptoms.

Pivotal Phase III study

<u>Study 304</u> - A randomised, double-blind, multicentre, placebo-controlled, menopausal symptom study of three doses of E2/norethisterone acetate patches in a continuous-wear hormone replacement therapy regimen.

- **Study Participants**

Healthy post-menopausal women with an average of ≥ 8 hot flushes/day, of moderate to severe intensity, accompanied by sweating.

- **Treatments**

Patients were randomised to one of four treatment groups – E2/NETA 50/140, 50/250, 50/400 or placebo. Patches were applied to the lower abdomen every 3.5 days for 3 cycles, 12 weeks (1 cycle = 28 days).

- **Objectives**

1°: evaluation of the efficacy, relative to placebo, in terms of reduction in moderate to severe post-menopausal symptoms, of continuous transdermal E2 (50μg/day) combined with three different doses of NETA (140, 250 and 400μg/day).

2°: evaluation of the effect of transdermal E2/NETA, compared to placebo, on selected quality of Life (QOL) indices, patch adhesiveness, dermal patch tolerance, lipid profiles, genital bleeding, serum PK (E2 / E1 / E1 sulphate / NET) and laboratory and clinical safety parameters.

- **Endpoints**

1° Efficacy: In the ITT population, change, from baseline to endpoint, in the mean number of hot flushes per day.

2° Efficacy:

(a) in the Evaluable population, the change, from baseline to endpoint, in the mean *number* of hot flushes per day

(b) in the ITT and Evaluable population, the mean change from baseline for each cycle in the *number* of hot flushes per day

(c) in the ITT population, the mean change from baseline to endpoint and from baseline for each cycle in the *intensity* of hot flushes and sweating

(d) QOL in the ITT population, change in score from baseline to weeks 4, 8, 12 and to endpoint

(e) PK: Serum E2, E1, E1 sulphate and NET at each visit.

(f) Laboratory and clinical safety parameters.

Safety: In the ITT population, the following were summarised: genital bleeding/spotting patterns (mean number and intensity of bleeding/spotting days per cycle, and episodes of irregular bleeding/spotting and amenorrhoea during Cycles 1 through 3), dermal patch adhesiveness (percentage adherence), incidence of adverse skin reactions to patch, percentage of patients reporting redness and/or itching, incidence of adverse events, change in vital sign measurements, physical examination and PAP smear, abnormalities and changes from baseline laboratory safety data, mean percentage change from baseline to week 12 and to endpoint for lipid parameters.

- **Statistical methods**

The ITT population included all patients to whom at least one patch was applied. The Evaluable population included all patients who met the criteria regarding compliance with the protocol.

Efficacy analysis: changes in vasomotor symptoms, relative to baseline, using ANOVA with main effects of treatment and Investigator. Each E2/NETA group was compared to the placebo group using a one-sided test at the 0.05 significance level.

Safety analysis: changes from baseline in certain safety parameters using ANOVA. Each E2/NETA group was compared to the placebo group using a two-sided test at the 0.05% significance level.

Results

- **Efficacy**:

Primary endpoint: In all three E2/NETA groups there was a significant reduction in the mean number of daily hot flushes at endpoint relative to baseline - mean (± S.D) reduction in hot flushes per day 8.9 (± 0.6) to 9.3% (± 0.6) compared to placebo (mean reduction of 6.2 (± 0.6) hot flushes per day). Compared to placebo, reductions in the number of hot flushes occurred in all three E2/NETA groups as early as the second week of the first cycle and this was maintained throughout the study. In all three E2/NETA groups there was also a significant reduction in the mean intensity of hot flushes as early as the second week of Cycle 1 and continuing throughout the study.

Secondary endpoints:

Hot flushes / sweating: For placebo, the mean reduction was 6.2 ± 0.6. In all three groups there was also a significant reduction, compared to placebo, in the severity of the hot flushes and sweating.

Bleeding profile: The percentage of patients who were amenorrhoeic at cycle 3 decreased as the E2/NETA dose increased: 52% in the 50/140 group, 45% in the 50/250 group and 31% in the 40/400 group. Also, the percentage of patients with irregular bleeding at cycle 3 increased as the E2/NETA dose increased.

Safety and Tolerability: 89-95% of Investigator assessments stated that E2/NETA TDS remained fully adherent over the course of the study. Approximately 70% of patients indicated their patches never fell off, and 13-29% reported that their E2/NETA patches fell off on only one or two days. The incidence of application site reactions for active patches was 0-8%. The incidence of redness increased with increasing E2/NETA patch size (38-51%). The percentage of patients who reported itching was similar for the 9cm2 (31%) and 16cm2 (28%) patches but increased with the 26cm2 (51%) size.

QOL: QOL scores were generally improved in all treatment groups. Compared to placebo, the 50/140 group had significantly better sexual arousal scores and sleep index and the 50/250 had significantly better cognitive function and sleep index. For the other categories of QOL, those in the E2/NETA groups showed improvement over the course of the study, but the changes were not significantly different from those seen in the placebo-treated patients.

PK: The dose-normalised serum NET concentrations and predicted AUCs suggested that the 50/250 patch delivered approximately 20% less NET compared to the 50/400 patch, whereas the dose-normalised NET delivery from the 50/140 patch did not differ from the 50/250 or the 50/400 patches. The dose-normalised concentrations and predicted AUCs for NET did not vary across visits, suggesting that NET concentrations did not change following extended patch wear. Significant differences were seen in predicted AUCs for E2 when all three treatments were compared and indicated that the 50/140 patch delivered slightly less E2, whereas the 50/400 patch delivered more E2, when compared to the 50/250 patch. Statistically significant differences were not seen, however, when E2 serum concentrations and predicted AUCs were compared across visits, suggesting that E2 concentrations did not change with extended patch wear. E1 sulphate concentrations approximated to premenopausal follicular levels with no apparent accumulation in the circulation following treatment with any E2/NETA TDS.

- **Participant flow**

	E2/NETA				
	Placebo	**50/140**	**50/250**	**50/400**	**Total**
Randomised	54	58	53	61	226
Completed study	47	52	49	55	203
Discontinued	7	6	4	6	23

- **Conclusions**

The study showed that E2/NETA TDS at doses of 50/140, 50/250 and 50/400 µg/day, when administered in a continuous wear regimen over three cycles, and compared to placebo, was safe and effective for the treatment of moderate to severe vasomotor symptoms in post-menopausal women with an intact uterus.

Study 302 - A phase III, randomised, double-blind, double-dummy study of the twice –weekly 50/140 and 50/250 µg/day E2/NETA transdermal delivery systems versus daily Kliogest in the treatment of menopausal symptoms.

- **Study Participants**

Healthy post-menopausal women, with an average of ≥ 3 hot flushes/day.

- **Treatments**

Patients were randomised to one of three treatment groups – E2/NETA 50/140, 50/250 or Kliogest. Patches were applied to the lower abdomen every 3.5 days for 6 cycles, 24 weeks (1 cycle = 28 days).

- **Objectives**

1°: Efficacy - evaluation of the efficacy in the treatment of vasomotor symptoms (hot flushes) of a 6 cycle (24-week) regimen of transdermal 50µgE2 when administered continuously with NETA (140 or 250µg/day), compared to a positive control (daily Kliogest, an oral HRT preparation containing 2mg E2 and 1mg NETA).

- **Endpoints**

1° Efficacy: In the ITT population, mean change from baseline to endpoint in the *number* of hot flushes per day**.**

2° Efficacy:

- In the Evaluable population, mean change from baseline to endpoint in the *number* of hot flushes per day
- In the ITT population, mean change from baseline to endpoint in the daily *intensity* of both hot flushes and sweating

The following were summarised:

- In the ITT and Evaluable populations – mean change from baseline to each cycle in the *number* of hot flushes per day.

- In the ITT population – daily *intensity* of both hot flushes and sweating.

- QOL: In the ITT population, the change from baseline to week 12, 24 and endpoint.

Safety: In the ITT population, the following were summarised: genital bleeding patterns (incidence of amenorrhoea and irregular bleeding/spotting per cycle, number of episodes of bleeding, number of days of bleeding and spotting, intensity of bleeding), endometrial safety (endometrial ultrasound, incidence of endometrial hyperplasia from biopsy), patch-wear characteristics (percentage adherence, application site reactions), AEs, laboratory safety data, vital signs, PAP smear and physical exam. In addition, at selected centres, the mean percentage change from baseline to week 24 in lipid profile and clotting factors.

Quality of Life: In the ITT population, the change from baseline to week 12, week 24 and endpoint in Quality of Life scores.

- **Statistical methods**

ITT Population: this included all patients to whom at least one patch was applied or who took at least one dose of oral study medication. The Evaluable population included all patients who met the criteria regarding compliance with the protocol.

Efficacy analysis: ANOVA on change from baseline to endpoint in mean number of hot flushes with main effects of treatment and country. Each E2/NETA group was compared to Kliogest using two-sided 95% CIs; equivalence was concluded if the upper limit of the CIs on (Active-control) was ≤ 2.0.

Safety analysis: ANOVA with main effects of treatment and country to analyse all percentage changes from baseline to week 24 and to end of study for lipid parameters.

Results

- **Participant flow**

	E2/NETA			
	Kliogest	**50/140**	**50/250**	**Total**
Randomised	129	142	139	410
Completed study	99	117	98	314
Discontinued	30	25	41	96

- **Efficacy**: All analyses showed equivalence between both doses of E2/NETA and Kliogest.

Primary endpoint: See Table 2:

Table 2: ITT population - mean change in the number of hot flushes per day at the end of the study compared to baseline

Treatment	Mean change in # of hot flushes/day	95% CI active-control	Conclusion
Kliogest	-7.2 ± 0.43		
50/140	-7.8 ± 0.40	-1.69 to 0.55	Equivalent
50/250	-6.9 ± 0.40	-0.79 to 1.46	Equivalent

These results were confirmed in secondary analysis of the Evaluable population.

Secondary endpoints: See Tables 3 and 4:

Table 3: ITT population - mean change in the severity of the hot flushes from baseline to end of study

Treatment	Mean change in # of hot flushes/day	95% CI active-control	Conclusion
Kliogest	-1.4 ± 0.06		
50/140	-1.4 ± 0.06	-0.17 to 0.14	Equivalent
50/250	-1.3 ± 0.06	-0.07 to 0.25	Equivalent

Table 4: ITT population – mean change in intensity of sweating from baseline to endpoint

Treatment	Mean change in intensity of sweating from baseline to endpoint (ITT)	95% CI active-control	Conclusion
Kliogest	-1.4 ± 0.08		
50/140	-1.4 ± 0.07	-0.17 to 0.23	Equivalent
50/250	-1.4 ± 0.07	-0.18 to 10.23	Equivalent

Safety:

Patch tolerability: application site reactions were reported slightly more frequently with the larger 50/250 patch (26%) compared to the 50/140 patch (20%). The reactions were mostly mild erythema. Similarly, patient-reported redness and itching at the application site tended to increase with the size of the patch. Skin adherence of both patches was excellent (>80% of patch assessments were considered completely adherent).

Transvaginal biopsy: mean endometrial thickness increased slightly from baseline to week 24 and endpoint in all groups, as expected. There was one case of endometrial hyperplasia, in the 50/140 group.

Bleeding profile: the incidence of amenorrhoea tended to be higher in the Kliogest group at each cycle compared to both the E2/NETA groups. Irregular bleeding/spotting episodes appeared to be longer in the Kliogest group. In all groups, the bleeding episodes were classified as spotting or light.

Coagulation parameters and lipid profile: no clinically relevant findings.

- **Conclusions**

Both transdermal treatments were equivalent to oral Kliogest in their ability to reduce the number and severity of hot flushes and sweating over a 24 week treatment period. This relief in vasomotor symptoms was associated with improvements in patient QOL in all groups. The treatments also appeared to be safe and well tolerated with only a few reports of minor skin reactions, and patch adherence was excellent.

Supportive Studies

<u>Study 202</u> - A randomised, double-blind, multicentre, progestin efficacy study of three doses of estradiol/norethisterone acetate (NETA) patches in a continuous wear HRT regimen compared to an estradiol 50 patch.

This study was conducted in healthy non-hysterectomised postmenopausal women (aged 40-70 yrs; amenorrhoeic ≥ 1 year; [FSH] >40mIU/mL). The primary objective was to assess the efficacy of three doses of NETA when administered continuously with E2 for 1 year (13 cycles), compared to E2 alone, on the incidence of estrogen-induced endometrial hyperplasia. The E2-only comparator was Noven ETDS 50. Secondary objectives included the evaluation of three doses of NETA when administered continuously with E2, compared to E2 alone, on genital bleeding, vasomotor symptoms, lipid profiles, metabolic and coagulation parameters, bone biochemical markers, patch tolerance/adherence, laboratory and clinical safety parameters, selected Quality of Life (QOL) indices, and serum concentrations of E1, E2 and NET (at baseline and weeks 12, 24 and 52).

Table 5 – participant flow

	E2 50	E2/NETA			
		50/140	50/250	50/400	Total
Enrolled	**155**	**163**	**149**	**158**	**625**
Completed study	**76**	**123**	**99**	**93**	**391**
Discontinues	**79**	**40**	**50**	**65**	**234**

With regard to postmenopausal symptoms, two subsets of women were evaluated for change in hot flushes after 12 months:

- Women with ≥ 3 hot flushes per day at baseline
- Women with ≥ 8 hot flushes per day at baseline

The primary efficacy variable was the incidence of hyperplasia, determined by endometrial biopsy, in the ITT population at 1 year (patients who either had a biopsy after cycle 12 or developed endometrial hyperplasia at any time before cycle 12). Secondary efficacy variables included the reduction in the number and intensity of hot flushes and sweating, and assessment of other parameters, on the ITT population. They also included the incidence of endometrial hyperplasia in the 'Evaluable at 1 year' population. The incidence of endometrial hyperplasia in the ITT at 1 year population was analysed using Fisher's exact test. No distinction was made between the types of hyperplasia. Each E2/NETA combination was compared to the E2-only group using a one-sided test at the 0.05 significance level, with an adjustment for

multiple comparisons. There was good inter-observer variability (94% concordance) and among patients in the E2 50 group, 38 (37%) developed hyperplasia compared to 1 (≤ 1%) in both the 50/140 and 50/400 groups. No patient in the 50/250 group developed hyperplasia. Thus, the combinations were all significantly better than E2 50 alone ($p<0.001$). Results seen in the 'Evaluable at 1 year population' were similar to those in the primary, ITT, population. In women who had ≥ 8 hot flushes a day, there was a reduction in the number per day from baseline to cycles 3, 6, 12 and endpoint. The percentage of women who were amenorrhoeic during cycles 10 through 12 decreased to 35% in the E2 50 group and increased to 53%, 39% and 44% in the 50/140, 50/250 and 50/400 E2/NETA groups, respectively, compared to 78% in the E2 group. Although the number of days of bleeding/spotting per episode was very variable, bleeding occurred on average for 4-6 days in the E2/NETA groups and for 7 days in the E2 50 group. Most bleeding was spotting or light bleeding only. Patch tolerability was good; 86-90% of patients reported that the E2/NETA patches "fell-off" < 1% of the total number of days worn and 74% experienced no application site reaction. QOL: sexual arousal improved in all groups and all E2/NETA groups showed a statistically significant decline in sleep disturbance between baseline and endpoint compared to E2 alone. The 50/400 group showed a statistically significant improvement in cognitive function and urinary incontinence compared to E2 50 at endpoint. There was no evidence of accumulation of E2 or NET based on the PK analysis. It was concluded, from this study, that transdermal delivery of three doses of NETA (140, 250 and 400μg/day), when administered in a continuous treatment regimen with 50μg/day of E2 is safe and effective in reducing estrogen-induced endometrial hyperplasia in non-hysterectomised post-menopausal women.

<u>Study 305</u> - A phase II/III, randomised, double-blind, placebo-controlled, multicentre study of continuous, twice-weekly Menorest (25μg/day, 50μg/day and 75μg/day) combined with a cyclic progestin for the prevention of bone loss in early post-menopausal women.

This study was designed to examine the efficacy of a two-year treatment with Menorest at three different doses compared to placebo in the prevention of bone loss in early post-menopausal women. It included women aged 40-60 years who had undergone either a natural or surgical (bilateral oophorectomy) menopause for between 1 and 6 years (FSH >34.4mIU/ml and serum E2 <30pg/ml). Secondary endpoints included changes in post-menopausal symptoms in the 277 women studied. No inclusion criteria regarding post-menopausal symptoms were specified other than that patients were not included if they had severe post-menopausal symptoms (≥ 10 hot flushes a day at baseline or other symptoms considered severe or disabling). The severity of hot flushes was determined using a visual analogue scale (VAS) in the ITT population. Each active treatment group was statistically significantly superior to placebo for reduction in severity of hot flushes with a mean reduction of 20.1mm, 29.3mm and 24.5mm in the E2 25, 50 and 75 μg/day groups, respectively compared to 9.4mm in the placebo group.

<u>Assessor's comment:</u> Estalis 50/140 was not shown to be bioequivalent to Menorest 50, so data cannot be extrapolated directly from study 305 to Estalis 50/140. Nevertheless, as superiority over placebo was demonstrated even with Menorest 25

(providing 25µg E2 day), this study provides some confidence of long-term efficacy, in the treatment of post-menopausal symptoms, to be expected with Estalis 50/140.

Published Data

There are published data demonstrating the efficacy, in the treatment of postmenopausal symptoms, of 50µg/day transdermal E2 either alone or in combination with 140-400µg/d transdermal NETA.

Assessor's overall conclusions on clinical efficacy

Postmenopausal symptoms

The population examined in the controlled studies 304, 302 and 202 was the target patient population of postmenopausal women with vasomotor symptoms. There were no important demographic differences in the patient populations within the studies (mean age 52-55 with average time from the menopause 5-7 years). There was some variability in terms of baseline characteristics (years since menopause, prior HRT use, i.e. 44-57% in 304; 62-71% in 302; 28-42% in 202). At baseline, patients included in 304 were more severely affected by hot flushes than those in 302 (≥8 vs ≥ 3/day, respectively). In 202 patients for entry into this study were not required to be experiencing hot flushes and the baseline number was therefore low (2.3-2.8 per group).

- **Number of hot flushes**

From the two pivotal phase III studies (304 and 302), the reduction in the mean number of daily hot flushes was statistically superior to placebo for all doses of Estalis (50/140, 50/250 and 50/400). This was demonstrated from baseline to study endpoint at 3 months (Study 304) and 6 months (Study 302). Efficacy was equivalent to Kliogest from baseline to study endpoint at 6 months (study 302). See Table 6.

Table 6 - Change in daily hot flushes (mean ± SE) – controlled studies 304 and 302 (ITT population)

Study 304		**Placebo n=54**	**Estalis 50/140 n=58**	**Estalis 50/250 n=53**	**Estalis 50/400 n=61**
n		51	57	52	61
Baseline[3]		10.56 ± 0.56	11.45 ± 0.53	10.37 ± 0.38	9.81 ± 0.29
Endpoint (3 mths)		4.80 ± 0.66	2.63 ± 0.65	1.78 ± 0.52	1.33 ± 0.43
Adjusted change[1]		-6.20 ± 0.58	-9.29 ± 0.57	-8.86 ± 0.57	-8.98 ± 0.54
p-value[2]			<0.001	<0.001	<0.001
Study 302	**Kliogest n=129**		**Estalis 50/140 n=142**	**Estalis 50/250 n=139**	
n	126		142	139	
Baseline	1.67 ± 0.06		1.61 ± 0.07	1.64 ± 0.07	
Endpoint (6 mths)	0.23 ± 0.05		0.20 ± 0.04	0.24 ± 0.05	
Endpoint-Baseline[2]	-1.4 ± 0.08		-1.4 ± 0.07	-1.4 ± 0.07	
Delta [(Estalis)-(Kliogest)][4]			0.0 [-0.17; 0.23][5]	0.0 [-0.18; 0.23][5]	

n = patients who had both baseline and endpoint observations

[1] means were adjusted for imbalances among treatment groups and investigators (least squares means from ANOVA)

[2] p-value (comparison to placebo) is from one-sided ANOVA with main effects of treatment and investigator, using a pairwise step-down procedure to adjust for multiple comparisons

[3] baseline mean was defined for patients who had data at both baseline and endpoint

[4] means were adjusted for imbalances among treatment groups and countries (least squares means from ANOVA)
[5] Delta is calculated as (active-control) thus a negative difference is favourable to the Estalis group. Two-sided 95% CI is calculated on Delta. For equivalence upper limit of 95% CI should be ≤ =2.
In Study 304, the reduction in the mean number of daily hot flushes from baseline was statistically significantly greater than placebo as early as cycle 1 (p=0.007) and continued to decrease in cycles 2 and 3. In the ITT population the mean number of hot flushes was reduced by 8.9 ± 0.6 and 9.3 ± 0.6 per day with the three Estalis treatments, and did not appear to be related to the NETA dose, compared to a reduction of 6.2 ± 0.6 with placebo.

In Study 302, equivalence of both Estalis 50/140 and 50/250 with Kliogest, in both the ITT and Evaluable populations, was shown. The 95% CIs for the treatment differences, Estalis vs. Kliogest were [-1.69, 0.55] and [-0.79,1.46] for the ITT population and [-0.87, 1.56] for the Evaluable population. These met the pre-defined equivalence criteria which required the upper limit of the 95% CI for the difference in the change from baseline in the mean number of daily hot flushes to be ≤ 2. Analysis of the Evaluable population gave similar results: 95% CI for Estalis 50/140 vs Kliogest [-1.89; 0.53]. Onset of action was rapid and the number of hot flushes decreased by approximately 50% of baseline after 2 weeks of treatment and continued to decrease in subsequent cycles. From baseline to cycle 1, the mean number of daily hot flushes was reduced by 6 per day in the two Estalis groups, compared to 6.5 in the Kliogest group.

The supportive study (202) indicates that the effect is maintained for 12 months. The supportive study (305) shows that a sustained effect to at least 24 months would be expected (although as Study 305 did not use Estalis 50/140 directly, the validity of the data is limited). However, efficacy in this indication has been adequately demonstrated by the pivotal studies, conducted in line with the CPMP Guideline.

- **Intensity of hot flushes**

For this secondary efficacy variable (see Table 7):

Pivotal Study 304: each strength of Estalis was statistically superior to placebo in the reduction of the mean daily intensity of hot flushes at all three cycles and at study endpoint.

Pivotal Study 302: mean change from baseline showed a similar response for Estalis and Kliogest. Although no criterion for equivalence was pre-specified, both Estalis patches were considered equivalent to Kliogest in the mean decrease from baseline in the hot flush intensity because of the tight two-sided 95% CIs which included zero.

Table 7 - Change in daily intensity of hot flushes (mean ± SE) – controlled studies 304 and 302 (ITT population)

Study 304		**Placebo n=54**	**Estalis 50/140 n=58**	**Estalis 50/250 n=53**	**Estalis 50/400 n=61**
n		50	56	52	61
Baseline[3]		5.48 ± 0.17	6.02 ± 0.22	5.98 ± 0.21	5.59 ± 0.17
Endpoint (3 mths)		2.63 ± 0.33	1.44 ± 0.31	1.03 ± 0.27	0.79 ± 0.24
Adjusted change[1]		-2.79 ± 0.535	-4.58 ± 0.33	-4.96 ± 0.34	-4.79 ± 0.32
p-value[2]			<0.001	<0.001	<0.001

Study 302	Kliogest n=129		Estalis 50/140 n=142	Estalis 50/250 n=139	
n	128		142	139	
Baseline	1.61 ± 0.05		1.66 ± 0.04	1.55 ± 0.05	
Endpoint (6 mths)	0.18 ± 0.04		0.22 ± 0.04	0.22 ± 0.04	
Endpoint-Baseline[2]	-1.4 ± 0.06		-1.4 ± 0.06	-1.3 ± 0.06	
Delta [(Estalis)-(Kliogest)][4]			0.0 [-0.17; 0.14][5]	0.0 [-0.07; 0.25][5]	

n = patients who had both baseline and endpoint observations
[1] means were adjusted for imbalances among treatment groups and investigators (least squares means from ANOVA)
[2] p-value (comparison to placebo) is from one-sided ANOVA with main effects of treatment and investigator, using a pairwise step-down procedure to adjust for multiple comparisons
[3] baseline mean was defined for patients who had data at both baseline and endpoint
[4] means were adjusted for imbalances among treatment groups and countries (least squares means from ANOVA)
[5] Delta is calculated as (active-control) thus a negative difference is favourable to the Estalis group. Two-sided 95% CI is calculated on Delta. For equivalence upper limit of 95% CI should be ≤ =2.

- **Intensity of sweating:**

In the pivotal studies 304 and 302, Estalis (all treatment groups) showed superiority over placebo in the reduction in the mean intensity of sweating from baseline to each cycle and study endpoint. In Study 302, the two-sided 95% CIs comparing Estalis and Kliogest were tight and included zero for both Estalis groups, indicating equivalence for these two treatments.

Statistical assessment of efficacy

Studies 302, 304 and 202 have been submitted to support the efficacy of Estalis 50/140 in terms of reduction in vasomotor symptoms. These studies provide clear evidence of a beneficial effect of Estalis 50/140 on the frequency of hot flushes.

A new study (Study 301 – see 'Clinical safety' section) has been submitted to provide sufficient evidence of endometrial safety. Both study 301 on its own and the pooled analysis of studies 301 and 202 provide an acceptably small estimate of the incidence of endometrial hyperplasia, which has been estimated with sufficient precision. The estimate of the incidence of endometrial hyperplasia from the pooled analysis is 0.32% with an upper limit of a one-sided 95% confidence interval of 1.53%. This is the appropriate analysis as recommended in the CPMP Points to consider on HRT and the estimate is both sufficiently small and estimated with sufficient precision to fulfil the criteria laid down in this guideline. The estimated incidence of hyperplasia for Study 301 was 0/185 (0%) with the upper limit of the one-sided 95% confidence interval of 1.61%.

Statistical Conclusion

The efficacy of Estalis 50/140 in the treatment of vasomotor symptoms has been established, as has the endometrial safety of the product. A positive risk-benefit for Estalis 50/140 for the treatment of vasomotor symptoms has been demonstrated.

V CLINICAL SAFETY

The Applicant has conducted an additional study, 0301, to demonstrate the endometrial safety of the product. The key studies, providing the main safety data, are summarised in Table 8. These studies include all the larger studies examining relevant doses and longer duration of therapy in the claimed indication. They consist of 4 trials (one placebo and three reference therapy) in a total of 1666 patients in the target population.

Table 8 - Studies providing safety data

Study #	Objectives	Number of patients randomised	Treatment duration	Medication dose/day	Type of Control
Controlled, pivotal phase III studies					
302	Change in mean daily hot flushes, safety & tolerability	410	**6 mths (6 cycles, 24 weeks)**	**E2/NETAμg/day (Estalis)** 50/140 50/250 **E2/NETA (Kliogest)** 2mg/1mg (po,od)	Active
304	Change in mean daily hot flushes safety & tolerability	226	3 mths (3 cycles, 12 weeks)	**E2/NETAμg/day (Estalis)** 50/140 50/250 50/400	Placebo
Controlled, endometrial safety studies					
202	**1°**: Endometrial safety **2°:** Change in vasomotor symptoms, other safety & tolerability	625	12 nths (13 cycles, 52 weeks)	**E2/NETAμg/day (Estalis)** 50/140 50/250 50/400 E2 (Menorest) 50μg/day	Active
0301 New Study	Endometrial safety, other safety & tolerability	406	48 weeks (12 cycles)	**E2/NETAμg/day (Estalis)** 50/140 **E2/NETA (Kliogest)** 2mg/1mg (po,od)	Active

Main Safety Populations

The following population groupings were employed for safety analyses:

- *Main safety population*, consisting of all patients from studies 302, 304, 202 and 301 (pooled data) – the relevant patient population receiving Estalis 50/140 in controlled Phase III studies.
    - *Endometrial safety population,* consisting of patients from studies 202 and 0301 (pooled data), a subset of the main safety population providing biopsy-based, histological data on the incidence of endometrial adverse events or hyperplasia after long-term treatment with Estalis 50/140.

Safety evaluation

Safety was assessed for the main safety population and is based on all reported AEs, SAEs, deaths, laboratory safety data and vital signs/exam. Other safety data were the assessment of endometrial hyperplasia/cancer, lipid profiles and bleeding patterns. Further data on the findings of pelvic examinations, cervical smears and

mammography are given in the study reports. No formal statistical methods were applied to the safety data other than that on endometrial safety.

Additional evaluation of the tolerability, including application site reactions, and adhesiveness of the patch was made.

Demographic data show that, overall, the treatment groups were comparable at baseline and the patient populations were representative of the target population.

Main safety population

Exposure by treatment and duration is shown in Table 9:

Table 9 -Exposure by treatment and duration – main safety population (1 month ≡ 28 days)

	Estalis 50/140 N=669 n(%)	Estalis 50/250 N=341 n(%)	Estalis 50/400 N=219 n(%)	Menorest 50 N=155 n(%)	Kliogest N=228 n(%)	Placebo N=54 n(%)
0-4 weeks	23 (3.4)	17 (5.0)	9 (4.1)	10 (6.5)	14 (6.1)	4 (7.4)
4-12 weeks	91 (13.6)	68 (30.1)	66 (30.1)	12 (7.7)	19 (8.3)	40 (74.1)
3-6 months	144 (21.5)	114 (33.4)	40 (18.3)	19 (12.3)	83 (36.4)	10 (18.5)
6-9 months	49 (7.3)	41 (12.0)	6 (2.7)	19 (12.3)	35 (15.40	0 (0.0)
9-12 months	96 (14.3)	2 (0.6)	6 (2.7)	16 910.3)	32 (14.00	0 (0.0)
>12 months	266 (39.8)	99 (29.0)	92 (42.0)	79 (51.0)	45 (19.7)	0 (0.00
Patient years	444.1	181.4	126.6	111.7	129.0	11.4

Endometrial safety population

As this makes up >50% of the main safety population, the overall exposure and demographics are similar. Exposure to treatment is summarised in Table 10, which shows that approximately 50% of the patients for each treatment were exposed for >12 months. Again, demographic data show that, overall, the treatment groups were comparable at baseline and the patient populations were representative of the target population.

Table 10 - Exposure by treatment and duration – endometrial safety population (1 month ≡ 28 days)

	Estalis 50/140 N=469 n(%)	Estalis 50/250 N=149 n(%)	Estalis 50/400 N=2158 n(%)	Menorest 50 N=155 n(%)	Kliogest N=99 n(%)
0-4 weeks	14 (3.0)	5 (3.4)	7 (4.4)	10 (6.5)	4 (4.0)
4-12 weeks	42 (9.0)	16 (10.7)	24 (15.2)	12 (7.7)	5 (5.1)
3-6 months	32 (6.8)	14 (9.4)	23 (14.6)	19 (12.3)	9 (9.1)
6-9 months	19 (4.1)	13 (8.7)	6 (3.8)	19 (12.3)	4 (4.0)
9-12 months	96 (20.5)	2 (1.3)	6 (3.8)	16 (10.3)	32 (32.3)
>12 months	266 (56.7)	99 (66.4))	92 (58.2)	79 (51.0)	45 (45.5)
Patient years	372.7	115.9	113.1	111.7	77.7

Endometrial Safety

Determining the incidence of endometrial hyperplasia/cancer was the primary objective of studies 0301 and 202. The aim was to show that Estalis 50/140 meets the endometrial safety requirements specified in the current 1997 CPMP guideline "Points to consider on hormone replacement therapy" i.e. an incidence rate estimate for endometrial hyperplasia/cancer that is ≤ 2% after 1 year and a precision of the estimate within 2% (i.e. the upper limit of the one-sided 95% CI ≤2% above the point

estimate). The histological definition of endometrial hyperplasia/cancer included simple and complex endometrial hyperplasia or atypical endometrial hyperplasia and endometrial carcinoma, but excluded endometrial polyps or other malignancies. There were no incidences of hyperplasia/cancer in study 0301 and only one case in study 202. The incidence rates and 95% CI calculated using the exact binomial CI based upon the F-distribution (Collett 1991) are shown in Table 11. The incidence rates and precision of the estimates meet the CPMP requirements for 0301 and for the combined data from both studies.

Table 11 - Summary of Results

	Estalis 50/140 n(%)	Estalis 50/250 n(%)	Estalis 50/400 n(%)	Menorest 50 n(%)	Kliogest n(%)
Study 0301 (ITT)					
total # studied	185	-	-	-	57
hyperplasia/Ca	0 (0.0)	-	-	-	0 (0.0)
Upper limit one-sided 95% CI	1.61%	-	-	-	5.12%
Study 202 (ITT)					
total # studied	123	97	89	102	-
hyperplasia/Ca	1 (0.81)	0 (0.0)	0 (0.0)	38 (37.25)	-
Upper limit one-sided 95% CI*	3.80%	3.04%	5.22%	45.83%	
Pooled data from 0301 and 202 (ITT)					
total # studied	308	-	-	-	-
hyperplasia/cancer	1 (0.32)	-	-	-	-
Upper limit one-sided 95% CI	1.53%	-	-	-	-

**calculated post-hoc using an exact binomial CI as for 301*

Pivotal Studies

<u>Study 202</u> (also discussed in Clinical Efficacy section) - A randomised, double-blind, multicentre, progestin efficacy study of three doses of estradiol/norethisterone acetate (NETA) patches in a continuous wear HRT regimen compared to an estradiol 50 patch.

- **Objectives:**

1° Safety: Evaluation of the effect of three doses of NETA when administered continuously with E2, compared to E2 alone, on the incidence of estrogen-induced hyperplasia.

2° Safety: Evaluation of the effect of three doses of NETA when administered continuously with E2, compared to E2 alone, on: genital bleeding, vasomotor symptoms, lipid profiles, selected parameters of metabolism and coagulation, dermal patch tolerance, patch adherence, laboratory and clinical safety parameters and selected Quality of Life (QOL) indices

PK: Serum E1, E2 and NET

- **Subjects:** healthy post-menopausal women aged 40-70years. Intact uterus, amenorrhoea ≥ 1 year, FSH >40mlU/ml, satisfactory pelvic exam, PAP smear and mammogram.

- **Treatments:** Subjects were randomised to receive one of the following treatments: E2/NETA: 50/140, 50/250, 50/400 µg/day TDS or E2 50µg/day, TDS (Noven ETDS 50) - applied to lower abdomen every 3.5 days

- **Endpoints:**

1° Safety: in the "ITT at 1 year population": incidence of hyperplasia by endometrial biopsy.
2° Safety: in the "Evaluable at 1 year population": incidence of hyperplasia by endometrial biopsy; determination of inter-observer variability for pathologists A, B and C (ITT at one year population).The following were summarised: genital bleeding/spotting patterns, dermal patch adhesiveness, incidence of application site reactions and patient-reported redness and/or itching. AEs, changes in vital signs, physical exam, mammogram, PAP smear findings, endometrial thickness measured by TVS at baseline, week 24, 52 and at endpoint, changes from baseline in laboratory safety tests. Changes from baseline to weeks 24, 52 and endpoint for lipid parameters.

Efficacy: In the ITT population:

Postmenopausal symptoms: Reduction in the number and intensity of hot flushes and sweating from baseline to cycles 3, 6, 12 and at endpoint.

Quality of Life: Changes from baseline to weeks 12, 24, 52 and endpoint in QOL scores.

PK: Serum levels of E2, E1 and NET at baseline and weeks 12, 24 and 52.

Statistical methods:

Populations analysed: The ITT population included all patients who wore at least one patch.

The "ITT at 1 year" population used for primary analysis of hyperplasia was limited to patients who either had a biopsy after cycle 12 of treatment or who developed endometrial hyperplasia at any time before cycle 12.

The "Evaluable" population was based on patients who adhered to protocol requirements regarding entry criteria, treatment compliance and other protocol-specified conditions.

The "Evaluable at 1 year" population used in the secondary analysis of hyperplasia included evaluable patients with a biopsy after cycle 12 or a biopsy which diagnosed hyperplasia at any time before cycle 12.

Efficacy Analysis: The incidence of endometrial hyperplasia (ITT at one year population) was analysed using Fisher's exact test. No distinction was made between the types of hyperplasia; each patient was classified using a yes/no dichotomy. Each E2/NETA combination patch treatment group was compared to the E2 only group using a one-sided test at the 0.05 significance level, with an adjustment for multiple comparisons.

Safety Analysis: Changes from baseline in selected safety parameters were analysed using ANOVA with the main effects of treatment and investigator. Each E2/NETA group was compared to the E2 only group using a two-sided test at the 0.05 significance level.

Results

Primary efficacy: In the "ITT at one year population": 38 (37%) of patients in the E2 50 group developed hyperplasia compared to 1 (≤1%) in both the 50/140 and 50/400 groups. No patients in the 50/250 group developed hyperplasia. All three E2/NETA groups were significantly better than E2 50 ($p<0.001$).

Secondary efficacy:

Hyperplasia: In the "Evaluable at 1 year population", results were similar to those seen in the "ITT at one year population". The inter-observer variability was low between Pathologist A and B. Pathologists A and B agreed on the presence or absence of hyperplasia in 94% of the biopsies read.

Vasomotor symptoms: there was a reduction in the number of hot flushes per day from baseline to cycles 3, 6, 12 and endpoint, for women with ≥ 8 hot flushes per day at baseline.

Conclusion

It was concluded, from this study, that transdermal delivery of three doses of NETA (140, 250 and 400μg/day), when administered in a continuous treatment regimen with 50μg/day of E2 is safe and effective in reducing estrogen-induced endometrial hyperplasia in non-hysterectomised post-menopausal women.

Study 0301 - An open, multicentre, randomised, one-year trial to assess endometrial safety (incidence of endometrial hyperplasia/cancer) and systemic tolerability of Estalis 50/140, a 9cm2 adhesive-based matrix transdermal patch (nominal daily delivery rate of estradiol 50 μg plus 140μg norethisterone acetate) and Kliogest (estradiol 2mg plus 1mg norethisterone acetate) in a continuous combined hormone replacement therapy in postmenopausal women.

- **Objectives**

1°: Evaluation of endometrial protection with Estalis 50/140 in terms of post-treatment incidence of endometrial hyperplasia/cancer after 12 cycles of treatment.

2°: Evaluation of the effects of Estalis 50/140 and Kliogest on vaginal bleeding pattern and assessment of safety and tolerability in terms of breast tenderness, AEs, laboratory safety tests (including lipid profile) and other parameters.

- **Subjects**

Healthy, postmenopausal (≥ 1 year) women aged 45 to 70 years with an intact uterus, endometrial thickness of < 5mm and satisfactory baseline endometrial biopsy. Exclusion criteria included undiagnosed vaginal bleeding, abnormal cervical smear, uterine pathology (including polyps and clinically significant leiomyomas).

A total of 547 subjects were screened; 407 were randomised (306 to Estalis 50/140 and 100 to Kliogest). 294 women completed the study.

- **Treatments**

Patients were randomised to receive, over a 48 week (12 cycle) period either; Estalis 50/140 applied twice a week to the lower abdomen and worn continuously; or Kliogest (Novo Nordisk) tablets containing 2mg E2 plus 1mg NETA, once daily.

- **Endpoints**

1° Efficacy: Incidence of endometrial hyperplasia/cancer after 48 weeks of treatment based on the assessment of pre- and post-treatment endometrial biopsies.

2°: Safety: Vaginal bleeding/spotting (diaries), skin tolerability, breast tenderness, endometrial thickness, pelvic exam, mammography, vital signs, physical exam, monitoring of AEs and laboratory safety data.

- **Statistical methods:**

Descriptive statistics were used for the incidence of endometrial hyperplasia / carcinoma. The upper limit of a one-sided 95% CI in the ITT population was also presented (the exact one-sided 95% CI was calculated using the binomial distribution). Demographic and baseline characteristics, efficacy observations (including bleeding data) and measurements, and safety observations and measurements, were analysed using standard descriptive statistics. Changes in lipid parameters from baseline to the last visit were additionally evaluated by using an analysis of covariance model and treatment differences in the occurrence of breast tenderness were tested by applying Fisher's exact test. No interim analyses were performed.

Results

- **Primary - Efficacy:**

Following treatment with Estalis 25/125 or Kliogest, the incidence of endometrial hyperplasia/carcinoma was 0% with a 95% CI, one-sided, upper limit of 1.61% (Estalis) and 5.12% (Kliogest) for the ITT1 population and for the PP population, respectively. This result is in accordance with the CPMP requirement for endometrial safety, except that the duration analysed was 12 treatment cycles, equivalent to 48 weeks, rather than 13 cycles.

- **Secondary - Safety:**

In both treatment groups, spotting/bleeding days occurred with a similar frequency in Cycle 1 (Estalis 2.5 and Kliogest 2.2) and Cycle 2 (Estalis 4.0, Kliogest 4.2). In the subsequent cycles the mean number of spotting/bleeding days decreased in women in either group, though the decrease was greater in the Kliogest group. During cycles 7 to 12 the mean number of spotting/bleeding days was about 2 days higher in the Estalis group compared to the Kliogest group (ITT2 population) – see Table 12.

Table 12:

	Estalis				Kliogest			
Cycle No.	**n**	**Mean No.**	**Mean %age of days**	**Amenorrhoeic n (%)**	**n**	**Mean No.**	**Mean %age of days**	**Amenorrhoeic n (%)**
1-3 (Q1)	**299**	10.0	12.8	101 (33.8)	99	9.4	12.2	43 (43.4)
4-6 (Q2)	**261**	7.9	11.6	119 (45.6)	88	6.6	9.3	55 (62.5)
7-9 (Q3)	**236**	6.9	8.7	121 (51.3)	79	2.9	3.6	58 (73.4)
10-12 (Q4)	**219**	7.0	8.8	115 952.5)	75	1.4	1.7	55 (73.3)
Overall	**300**	27.4	12.1	70 (23.3)	99	18.7	9.3	31 (31.3)

On-Going study

Study 0301E1 (Extension to Study 0301)

This extension to Study 0301 is summarised in Table 13:

Table 13: Summary of Design of Study 0301E1

Study No	Study Objective Population	No of patients planned	Treatment duration	Medication dose/day	Type of control
0301E1	Endometrial safety in target population, other safety and tolerability parameters	238	48 weeks (12 cycles)	Estalis 50/140 Kliogest	active

Adverse Events

The most frequently affected body system was the reproductive system and breast disorders, which was related to NETA dose and is consistent with the known pharmacology in this target population. There were no unexpected findings.
The most frequently observed AEs with Estalis 50/140 were breast tenderness or pain, headache, application site reaction and dysmenorrhoea. Breast pain and tenderness correlates with dose of NETA and was lowest with placebo and Estalis 50/140. Certain events were higher in the Menorest 50 group (vaginal haemorrhage, aesthenia and endometrial hyperplasia). A dose relationship to [NETA] was evident for some events, including dysmenorrhoea, abdominal pain, back pain, dizziness and genital discharge. The percentage of women reporting these events was lower with Estalis 50/140 than with Menorest but higher than with Kliogest. All other data showed comparable incidence rates of AEs for all treatments and did not indicate any trend or dose-relationship.

Serious Adverse Events (SAEs) and Deaths

There were no deaths. SAEs (Table 14) were few in number and comparable across treatment groups. SAEs were examined, by body system, to detect rare and potentially serious events known or suspected for this class of drug (e.g. myocardial infarction, thrombosis, breast/ovarian cancer). There was an apparent small increase in the overall incidence of neoplasia with Estalis 50/140 but exposure was 2-4 x greater in patient years in this group. There were no reported incidences of stroke or DVT with Estalis 50/140.

Table 14:

	Estalis 50/140 n(%)	Estalis 50/250 n(%)	Estalis 50/400 n(%)	Menorest 50 n(%)	Kliogest n(%)	Placebo n(%)
Patients studied	669	341	219	155	228	54
SAEs	20 (3.0)	7.21)	9 (2.6)	6 (2.6)	1 (1.9)	40 (74.1)
Any AEs	528 (78.9)	293 (85.9)	201 (91.8)	145 (93.5)	186 (81.6)	36 (66.7)
Discontinuation due to SAE	6 (0.9)	2 (0.6)	2 (0.9)	1 (0.6)	2 (0.9)	0
Discontinuation due to any AEs	119 (17.8)	74 (21.7)	48 (21.90	59 (38.10	40 (17.5)	2 (3.7)

Discontinuation due to AEs / SAEs

Discontinuations due to SAEs (Tables 14 & 15) were most frequent in the Menorest 50 group but were otherwise similar for all active treatments, being lowest with Estalis 50/140 and Kliogest. SAEs were seldom the reason for discontinuation. The discontinuation rates with Estalis 50/140 for AEs or SAEs were lower or similar to other active treatments despite the 2-4 x greater exposure in terms of patient years.

Of the AEs leading to discontinuation, the most frequently affected body systems were the reproductive system and breast disorders and the most frequent causes were vaginal haemorrhage, followed by breast pain/tenderness. There was no evidence of increased discontinuations due to thrombosis or malignancy (possible drug class effects) in any group.

On active treatments, the number of patients with bleeding related AEs was highest with Menorest 50 and lowest with Kliogest and there was a positive association with increasing NETA dose. The most common bleeding related AE reported was dysmenorrhoea. The frequency of vaginal haemorrhage and menorrhagia was higher in the Menorest group compared to other groups.

Table 15 - Discontinuation for SAEs by body system – main safety population

	Estalis 50/140 n (%)	Estalis 50/250 n (%)	Estalis 50/400 n (%)	Menorest 50 n (%)	Kliogest n (%)	Placebo n (%)
Patients studied						
Total #	669	341	219	155	228	54
Total # with SAE	6 (0.9)	2 (0.6)	2 (0.9)	1 (0.6)	2 (0.9)	0
AE (MedDRA body system)	3 (0.4)	0	1(0.5)	0	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)						
Breast Ca female	1 (0.1)	0	0	0	0	0
Ovarian Ca NOS	1 (0.1)	0	0	0	0	0
Uterine fibroids	1 (0.1)	0	0	0	0	0
Neoplasm NOS	0	0	1 (0.5)	0	0	0
Cardiac disorders	2 (0.3)	0	0	0	0	0
Myocardial infarction	2 (0.3)	0	0	0	0	0
Atrial fibrillation	1 (0.1)	0	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.1)	0	0	0	0	0
Pain in limb						
Skin and subcutaneous tissue disorders						
Erythema induratum	1 (0.1)	0	0	0	0	0
Vascular disorders	1 (0.1)	1 (0.3)	0	0	1 (0.4)	0
Thrombosis	1 (0.1)	0	0	0	0	0
DVT	0	1 (0.3)	0	0	1 (0.4)	0
Infections and infestations	0	1 (0.3)	0	0	0	0
Salpingitis NOS	0	1 (0.3)	0	0	0	0
Psychiatric disordes	0	0	1 (0.5)	0	1 (0.4)	0
Agitation	0	0	0	0	1 (0.4)	0
depression	0	0	1 (0.5)	0	0	0
Reproductive system and breast disorders						
Endometrial hyperplasia	0	0	0	1 (0.6)	0	0
menorrhagia	0	0	0	1 (0.6)	0	0

Neoplasia

See Table 16. There is a slightly higher incidence of neoplasia in the Estalis 50/140 population.

Assessor's comment: This excess of neoplasia in the Estalis50/140 treated population is of no clinical concern given that the rates are still very low and patient exposure was 2-4 x greater with Estalis50/140, relative to the other, treatment regimens studied.

Table 16 - Neoplasms reported as SAEs – main safety population (studies 0301, 202, 302, 304).

	Estalis 50/140 n (%)	Estalis 50/250 n (%)	Estalis 50/400 n (%)	Menorest 50 n (%)	Kliogest n (%)	Placebo n (%)
Patients studied						
Total # studied	669	341	219	155	228	54
Total # with SAE	20 (3.0)	7 (2.1)	9 (4.1)	4 (2.6)	6 (2.6)	1 (1.90)
Neoplasms benign, malignant & unspecified (including cysts/polyps)						
Overall total	9 (1.3)	1 (0.3)	2 (0.9)	0	1 (0.4)	0
Breast Ca NOS	3 (0.4)	0	1 (0.5)	0	0	0
Benign lung neoplasm	1 (0.1)	0	0	0	0	0
Breast Cancer female	1 (0.1)	0	0	0	0	0
Carcinoma NOS	1 (0.1)	0	0	0	0	0
Ovarian Ca NOS	1 (0.1)	0	0	0	0	0
Uterine fibroids	1 (0.1)	0	0	0	0	0
Vulvar Ca	1 (0.1)	0	0	0	0	0
Neoplasm NOS	0	0	1 (0.5)	0	1 (0.4)	0
Skin Ca NOS	0	0	0	0	0	0

Bleeding Profile

Bleeding patterns were generally more favourable with Kliogest than with Estalis 50/140 or other active treatments. Bleeding was correlated with increasing dose of NETA but was worst with Menorest (E2 alone). During cycles 1 to 3 the amenorrhoea rates were very similar with Estalis 50/140 and Kliogest at around 40%. During cycles 10-12, Kliogest was associated with an approx 72% amenorrhoea rate; that for Estalis 50/140 was around 53%. Over 12 cycles, the Kliogest group had the highest proportion of completely amenorrhoeic patients followed by the Estalis 50/140 group. The Estalis 50/250 and 50/400 groups had low rates of amenorrhoea over cycles 1-12. In the last quarter (cycles 10-12), over 50% of patients on Estalis 50/140 had complete amenorrhoea. This was higher than the other Estalis groups but lower than for Kliogest.

Application site AEs

- **Skin Tolerability**

This was formally assessed in studies 302, 304 and 202. Pooled data showed no application site reaction in 80%. Erythema was the most often reported AE (17%) compared to other reactions (≤ 6%). Application site reactions were an uncommon reason for discontinuation (5%). The findings in study 0301 were consistent with the above.

Table 17 - Summary of application site reactions to active patches (pooled studies 302, 304, 202)

	Estalis groups combined n (%)	Monorest 50 n (%)
Patients studied		
Total # studied	923	155
Patients with any skin AE (%)	188 (200	18 912)
Application Site Reaction		
Depigmentation	6 (1)	0 (0)
Edema	29 93)	2 (1)
Erythema	155 (17)	16 (10)
Exudate/crusting	14 (2)	0 (0)
Fissuring	8 (1)	0 (0)
Papules/Vesicles	33 (4)	3 (2)
Scaling/Glazing	56 (6)	3 (2)
Other	21 (2)	3 (2)

- **Potential for contact dermatitis & patch adhesion**

Contact allergy was evaluated in a study which maximised the potential for skin irritation and sensitisation (modified Draize method) in a double-blind study of Estalis 50/250 vs placebo, in 54 postmenopausal women. There was a 28 day induction phase, a 14 day washout and a 6-day challenge (3 day wear with a 3 day assessment). Only one woman developed contact dermatitis at the application site of an active patch. Reported skin reactions occurred mostly in the induction phase rather than the challenge phase (16 vs 2 skin AEs, respectively) and consisted of mild irritation (mainly papules and erythema).

Patch adhesion was assessed in studies 302, 304 and 202, based on the total number of patch applications reviewed by the investigator. Overall, 88% of the applied patches adhered to >90% (completely adherent), 70% adhered to 75-90% (minor lifting of edges) and only 4% of the patches had come off the skin on the date of assessment.

The results of the investigator's assessment of the Estalis patch adhesion in study 0301 revealed that patch adhesion was maximal (>90%) in over 90% of the women treated. Overall, the number of patches which fell off was very low (1.9 ± 3.8 per cycle among all patients over 12 cycles) with no patch falling off in 50% of the Estalis group during the 12 month treatment period.

Other Safety Parameters

There were no clinically relevant findings in terms of laboratory safety samples, ECGs, vital signs, body weight or physical examination. The changes from baseline, in lipid profile for the main safety population showed a general decrease in lipids. For Estalis 50/140 the fall in total cholesterol, LDL and triglycerides in all studies, and a small fall in HDL in study 0301 provide evidence of a favourable or neutral effect on lipids.

Post marketing experience

Estalis 50/140 has been licensed since August 1998 in the USA and is also approved in Canada, Australia and some non-EU countries. The post-marketing safety of Estalis 50/140 (in both continuous combined and continuous sequential regimens) is documented in PSURs and in Line-Listings. The patient exposure during the period of the PSURs and in Line-Listings is estimated at 200,360 patient treatment years (20.8

million patches). No new major safety issues have been revealed and the safety profile from the above is consistent with that provided in the approved Estalis 50/140 SmPC.

Assessor's overall conclusions on clinical safety

Estalis 50/140 appears to be safe and well tolerated and the type and frequency of AEs, or other safety related effects seen in the large, target population of post-menopausal women studied, are consistent with similar HRT products.

There were no safety concerns regarding possible drug class effects (e.g. breast or ovarian cancer, endometrial hyperplasia/cancer, venous thromboembolism) and no emergence of new safety problems with long-term use. There was no noticeable difference in safety between patients treated for 1 year and those treated for 2 years and no development of new AEs. The small risk of developing breast or ovarian cancer is known to increase with duration of therapy but no such effect would be expected in studies of this size or duration.

Breast tenderness or pain, headache, application site reaction and dysmenorrhoea were the most common AEs and the incidence of breast tenderness and breast pain (also dysmenorrhoea, abdominal pain, back pain, dizziness, and genital discharge) increased with increasing doses of NETA and was least common with Estalis 50/140.

The pooled analysis for endometrial safety satisfied the point estimate and precision requirements of the CPMP guideline, as the overall rate of endometrial hyperplasia/cancer was 0.3% and the upper limit of the one-sided 95% CI was 1.5% in pooled data on patients treated with Estalis 50/140 for 1 year.

The majority of women did not report skin irritation and few discontinued because of local skin reactions to the patch or experienced any skin sensitisation. Patch adhesion was good (>90% in >90% of the women treated).

VI EXPERT REPORT

A satisfactory expert report is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

VII PRODUCT INFORMATION:

Summary of Product Characteristics

The approved SmPC is satisfactory.

Patient Information Leaflet

The approved PIL is in line with the final SmPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

CONCLUSIONS

With the efficacy and safety data provided in this application, the overall risk-benefit analysis of Estalis 50/140 for the treatment of postmenopausal symptoms is considered to be favourable provided the product is used according to the recommendations. There are no new safety concerns with this product and the safety profile and tolerability is considered to be consistent with that of other HRT products.

All issues have been adequately addressed by the applicant. Sufficient clinical information has been submitted to support this application. When used as indicated, Estalis 50/140 has a favourable benefit-to-risk ratio. A Marketing Authorisation is, therefore, recommended on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Estalis ® 50/140 are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

A pre-clinical expert report has been provided by an appropriately qualified consultant. This application has not revealed any evidence of untoward toxicity for Estalis ® 50/140.

EFFICACY

The clinical studies have demonstrated the efficacy of Estalis ® 50/140 in the indication of HRT for estrogen deficiency symptoms in non-hysterectomised postmenopausal women.

The clinical studies identify no new safety issues or concerns.

PRODUCT LITERATURE

The approved SmPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with estradiol hemihydrate and norethisterone acetate, as a combination transdermal patch product, is considered to have demonstrated the therapeutic value of the drug product. The risk: benefit is, therefore, considered to be positive.

ESTALIS ® 50/140

(estradiol hemihydrate, norethisterone acetate)

PL 00101/0690

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation application on 12th September 2003

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 31st October 2003

3 Following assessment of the application, the MHRA sought advice from the Committee on Safety of Medicines with regards to issues raised during assessment. The Committee met in May 2004 and issued their advice

4 The applicant responded to the CSM advice, providing further information on 30th April 2006

5 Following review of the application, the MHRA requested further information relating to the quality sections on 18th August 2006

6 The applicant responded to the MHRA's request, providing further information for the quality sections on 8th January 2007

7 The application was determined on 25th April 2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Estalis ® 50/140 is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Estalis 50/140

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One 9 cm^2 patch contains 0.62 mg estradiol (as hemihydrate) and 2.70 mg norethisterone acetate, and delivers a nominal 50 micrograms estradiol and 140 micrograms norethisterone acetate per 24 hours.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

Translucent to off white round patches with printed backing on one side and a release liner on the other, no crystals should be visible. The unit is packed individually in heat-sealed pouches.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Estalis 50/140 is indicated for:

Hormone replacement therapy for estrogen deficiency symptoms in postmenopausal women.

Treatment is to be used by women more than one year post menopause.

Experience of treating women older than 65 years is limited.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Adults and elderly

Estalis 50/140 is a continuous combined hormone replacement therapy.

Estalis exists in two doses: Estalis 50/140 and Estalis 25/125. For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also section 4.4) should be used.

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

Initiation of therapy

The treatment regimen may be initiated at any convenient time for menopausal women who are not currently on any oestrogen/progestogen therapy.

Women who are already using continuous combined oestrogen/progestogen therapy may be switched to Estalis 50/140 directly.

Women currently using cyclic or sequential oestrogen/progestogen therapy should complete the on-going treatment cycle before treatment with Estalis 50/140 is initiated. The appropriate time to begin treatment with Estalis 50/140 would be the first day of a withdrawal bleeding or seven days after finishing the previous treatment cycle.

Estalis regimen

Estalis 50/140 is used as a continuous treatment (uninterrupted application twice weekly). One patch is applied to the skin every 3 to 4 days during a 4-week cycle.

The transdermal patch is applied to the abdomen every 3 or 4 days.

Estalis 50/140 is less suitable to women who are close to menopause as the risk for withdrawal bleedings is then increased.

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

Administration

Estalis 50/140 transdermal patch should be placed on the abdomen. It must never be placed on or near the breasts.

For further information see section 6.6.

If a woman has forgotten to apply a patch, she should apply a new patch as soon as possible. The subsequent patch should be applied according to the original treatment schedule. The interruption of treatment might increase the likelihood of recurrence of symptoms and irregular bleeding and spotting.

Children

Estalis 50/140 should not be used in children.

4.3 CONTRAINDICATIONS

Estalis 50/140 should not be used by women with any of the following conditions:

Known, past or suspected breast cancer

Known or suspected estrogen-dependent malignant tumours (e.g. endometrial cancer)

Undiagnosed genital bleeding

Untreated endometrial hyperplasia

Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)

Known thrombophilic disorders or thrombophlebitis

Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)

Acute liver disease, or a history of liver disease as long as liver function tests have failed to return to normal

Hypersensitivity to estrogens, progestogens, or any other components of Estalis 50/140

Porphyria.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Medical Examination / Follow-up

Before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.

Conditions which need supervision

If any of the following conditions are present, have occurred previously and/or have aggravated during pregnancy or a previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may, in rare cases, recur or be aggravated during treatment with Estalis 50/140:

Leiomyoma (uterine fibroids) or endometriosis

Fibrocystic disease of the breast

A history of or risk factors for thromboembolic disorders

Risks factors for oestrogen dependent tumours, e.g. 1st degree blood relatives who have ever had breast cancer

Hypertension

Liver disorders (e.g. liver adenoma)

Diabetes mellitus with or without vascular involvement

Cholelithiasis

Migraine or severe headache

Systemic lupus erythematosus

A history of endometrial hyperplasia

Epilepsy

Asthma

Otosclerosis

Oestrogen-related jaundice

Pruritus

Gallbladder disease

Reasons for Immediate Withdrawal

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:

- Jaundice or deterioration in liver function

- Significant increase in blood pressure

- New onset of migraine-type headache

- Pregnancy

- Endometrial hyperplasia

The risk of endometrial hyperplasia and carcinoma is increased when estrogens are administered alone for prolonged periods (see section 4.8). The addition of a progestogen for at least 12 days per cycle in non-hysterectomised women greatly reduces this risk. Withdrawal bleeding usually occurs following the 12 days or more of progestogen administration.

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

Breast cancer

A randomised placebo-controlled trial, the Women's Health Initiative study (WHI), and epidemiological studies including the Million Women Study (MWS), have reported an increased risk of breast cancer in women taking estrogens, estrogen-progestogen combinations or tibolone for HRT for several years (see section 4.8).

For all HRT, an excess risk becomes apparent within a few years of use and increases with duration of intake but returns to baseline within a few (at most five) years after stopping treatment.

In the MWS, the relative risk of breast cancer with conjugated equine estrogens (CEE) or estradiol (E2) was greater when a progestogen was added, either sequentially or continuously, and regardless of type of progestogen. There was no evidence of a difference in risk between the different routes of administration.

In the WHI study, the continuous combined conjugated equine estrogen and medroxyprogesterone acetate (CEE + MPA) product used was associated with breast cancers that were slightly larger in size and more frequently had local lymph node metastases compared to placebo.

HRT, especially estrogen-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

Venous thromboembolism

HRT is associated with a higher relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism.

One randomised controlled trial and epidemiological studies found a 2-3 fold higher risk for users compared with non-users. For non-users, it is estimated that the number of cases of VTE that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 8 per 1000 women aged between 60-69 years. It is estimated that in healthy women who use HRT for 5 years, the number of additional cases of VTE over a 5 year period will be between 2 and 6 (best estimate = 4) per 1000 women aged 50-59 years and between 5 and 15 (best estimate = 9) per 1000 women aged 60-69 years. The occurrence of such an event is more likely in the first year of HRT than later.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index > 30kg/m²) and systemic lupus erythematosus (SLE). There is no consensus about the role of varicose veins in VTE.

Patients with a history of VTE or known thrombophilic states have an increased risk of VTE. HRT may add to this risk. Personal or strong family history of thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a thorough evaluation of thrombophilic factors has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contra-indicated. Those women already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT.

The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative patients scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible. Treatment should not be restarted until the woman is completely mobilised.

If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

Coronary artery disease (CAD)

HRT should not be used to prevent cardiovascular disease.

There is no evidence from randomised controlled trials of cardiovascular benefit with continuous combined conjugated estrogens and medroxyprogesterone acetate (MPA). Two large clinical trials (WHI and HERS i.e. Heart and Estrogen/progestin Replacement Study) showed a possible increased risk of cardiovascular morbidity in the first year of use and no overall benefit. For other HRT products there are only limited data from randomised controlled trials examining effects in cardiovascular morbidity or mortality. Therefore, it is uncertain whether these findings also extend to other HRT products.

Stroke

One large randomised clinical trial (WHI-trial) found, as a secondary outcome, an increased risk of ischaemic stroke in healthy women during treatment with continuous combined conjugated estrogens and MPA. For women who do not use HRT, it is estimated that the number of cases of stroke that will occur over a 5 year period is about 3 per 1000 women aged 50-59 years and 11 per 1000 women aged 60-69 years. It is estimated that for women who use conjugated estrogens and MPA for 5 years , the number of additional cases will be between 0 and 3 (best estimate = 1) per 1000 users aged 50-59 years and between 1 and 9

(best estimate = 4) per 1000 users aged 60-69 years. It is unknown whether the increased risk also extends to other HRT products.

Ovarian cancer

Long-term (at least 5 to 10 years) use of estrogen–only HRT products in hysterectomised women has been associated with an increased risk of ovarian cancer in some epidemiological studies. It is uncertain whether long-term use of combined HRT confers a different risk than estrogen-only products.

Other conditions

Estrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Estalis 50/140 is increased.

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

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

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

Although observations to date suggest that estrogens, including transdermal estradiol, do not impair carbohydrate metabolism, diabetic women should be monitored during initiation of therapy until further information is available.

Women should be advised that Estalis 50/140 is not a contraceptive, nor will it restore fertility. Women requiring contraception should be advised to use non-hormonal contraception.

There is no conclusive evidence for improvement of cognitive function. There is some evidence from the WHI trial of increased risk of probable dementia in women who start using continuous combined CEE and MPA after the age of 65. It is unknown whether the findings apply to younger postmenopausal women or other HRT products

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

Herbal preparations containing St. John's wort (*Hypericum Perforatum*) may induce the metabolism of estrogens and progestogens.

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

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

4.6 PREGNANCY AND LACTATION

Pregnancy

Estalis 50/140 is not indicated during pregnancy. If pregnancy occurs during medication with Estalis 50/140 treatment should be withdrawn immediately. Data on a limited number of exposed pregnancies indicate adverse effects of norethisterone on the fetus. At doses higher than normally used in OC and HRT formulations masculinisation of female fetuses was observed.

The results of most epidemiological studies to date relevant to inadvertent fetal exposure to combinations of estrogens and progestogens indicate no teratogenic or foetotoxic effect.

Lactation

Estalis 50/140 is not indicated during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

None known.

4.8 UNDESIRABLE EFFECTS

Approximately one third of the patients treated with Estalis 50/140 can be expected to experience adverse drug reactions. Most of these effects are mild and transient. The most commonly reported adverse experiences are breast tenderness (16%) and application site reactions[+] (11%, mostly mild erythema).

The following adverse events, listed in the table below, have been observed:

Organ Class	Very Common (>1/10)	Common (> 1/100 to <1/10)	Uncommon (> 1/1,000 to <1/100)	Rare (>1/10,000 to <1/1,000)	Very Rare (>1/100.000 to 1/10,000)
Nervous system disorders	Headache	Dizziness, depression, nervousness, insomnia, emotional lability	Migraine, Vertigo	Paraesthesia	
Cardiovascular disorders	-	-	Hypertension, varicose veins.	Venous throm boembolism	-
Gastro-intestinal disorders	-	Nausea, dyspepsia, diarrhoea, abdominal pain, bloating	Vomiting, elevated transaminases	Gallstones, gallbladder disease	Cholestatic jaundice
Skin and subcutaneous tissue disorders	Application site reactions,	Acne, rash, dry skin, pruritus	Skin discoloration		
Musculo-skeletal disorders	-	Back pain, pain in extremity	-	-	-
Reproductive system and breast disorders	Breast pain, breast tenderness, dysmenorrhoea, menstrual disorders	Breast enlargement, menorrhagia, leucorrhoea, vaginal bleeding, uterine spasms, vaginitis, endometrial hyperplasia	Breast cancer(+)	Uterine leiomyomata, paratubular cysts, endocervical polyps	-
General disorders	-	Pain, peripheral oedema, weight changes	-	Libido changes, allergic reaction, paraesthesia	-

Frequency listed for application site reactions has been extrapolated from the Estalis 50/140 and Estalis 50/250 data.

(+)Breast Cancer

According to evidence from a large number of epidemiological studies and one randomised placebo-controlled trial, the Women's Health Initiative (WHI), the overall risk of breast cancer increases with increasing duration of HRT use in current or recent HRT users.

For estrogen plus progestogen combined HRT, several epidemiological studies have reported an overall higher risk for breast cancer than with estrogens alone.

The MWS reported that, compared to never users, the use of various types of estrogen-progestogen combined HRT was associated with a higher risk of breast cancer (RR = 2.00, 95%CI: 1.88 – 2.12) than use of estrogens alone (RR = 1.30, 95%CI: 1.21 – 1.40) or use of tibolone (RR=1.45; 95%CI 1.25-1.68).

The WHI trial reported a risk estimate of 1.24 (95%CI 1.01 – 1.54) after 5.6 years of use of estrogen-progestogen combined HRT (CEE + MPA) in all users compared with placebo.

The absolute risks calculated from the MWS and the WHI trial are presented below:

The MWS has estimated, from the known average incidence of breast cancer in developed countries, that:

For women not using HRT, about 32 in every 1000 are expected to have breast cancer

diagnosed between the ages of 50 and 64 years.

For 1000 current or recent users of HRT, the number of additional cases during the

corresponding period will be:

For users of estrogen-only replacement therapy

between 0 and 3 (best estimate = 1.5) for 5 years' use

between 3 and 7 (best estimate = 5) for 10 years' use.

For users of estrogen plus progestogen combined HRT

between 5 and 7 (best estimate = 6) for 5 years' use

between 18 and 20 (best estimate = 19) for 10 years' use.

The WHI trial estimated that after 5.6 years of follow-up of women between the ages of 50 and 79 years, an additional 8 cases of invasive breast cancer would be due to estrogen-progestogen combined HRT (CEE + MPA) per 10,000 women years.

According to calculations from the trial data, it is estimated that:

For 1000 women in the placebo group,

about 16 cases of invasive breast cancer would be diagnosed in 5 years.

For 1000 women who used estrogen + progestogen combined HRT (CEE + MPA), the number of additional cases would be

between 0 and 9 (best estimate = 4) for 5 years' use.

The number of additional cases of breast cancer in women who use HRT is broadly similar for women who start HRT irrespective of age at start of use (between the ages of 45-65) (see section 4.4).

Endometrial cancer

In women with an intact uterus, the risk of endometrial hyperplasia and endometrial cancer increases with increasing duration of use of unopposed estrogens. According to data from epidemiological studies, the best estimate of the risk of endometrial cancer is that for women not using HRT, about 5 in every 1000 are expected to have endometrial cancer diagnosed between the ages of 50 and 65. Depending on the duration of treatment and estrogen dose, the reported increase in endometrial cancer risk among unopposed estrogen users varies from 2-

to 12-fold greater compared with non-users. Adding a progestogen to estrogen-only therapy greatly reduces this increased risk.

Other adverse reactions have been reported in association with oestrogen/progestogen treatment:

Estrogen-dependent neoplasms, benign and malignant, e.g. endometrial cancer

Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, exacerbation of varicose veins, is more frequent among hormone replacement therapy users than among non-users. For further information, see sections 4.3 and 4.4.

Myocardial infarction and stroke

Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura

Cholestatic jaundice

Gall bladder disease

Probable dementia (see section 4.4)

4.9 OVERDOSE

Due to the mode of administration, overdose of estradiol or norethisterone is unlikely to occur.

Signs and symptoms: The effects of overdosage with oral estrogens are breast tenderness, nausea, vomiting and/or metrorrhagia. Overdosage of progestogens may lead to a depressive mood, fatigue, acne and hirsutism.

Treatment: Overdosage can if necessary be reversed by removal of the patch(es).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group (Genito urinary system and sex hormones),

ATC code: G 03 FAO1.

The active ingredient, synthetic 17β-estradiol is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of estrogen production in menopausal women, and alleviates menopausal symptoms such as flushes and swelling. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. Norethisterone acetate (a progestogen) is given to greatly reduce the risk of estrogen-induced endometrial hyperplasia in non-hysterectomised women.

Amenorrhea was seen in 83% of the women during months 10-12 treatment. Breakthrough bleeding and/or spotting appeared in 31% of the women during the first three months of treatment and in 17% during months 10-12 of treatment.

A decrease of total cholesterol, LDL-cholesterol, Apoprotein B, Lp (a) and triglycerides, from baseline, was observed with Estalis. There was also a decrease of HDL cholesterol. All plasma lipoproteins remained within the normal range.

5.2 PHARMACOKINETIC PROPERTIES

Transdermally delivered estradiol by-passes the first-pass effect seen with orally administered estrogen products.

Estalis 50/140 transdermal 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 the transdermal patch resulted in average estradiol serum concentrations at steady-state of 24 pg/ml. At the end of the application periods, the average estradiol serum concentrations were 20 pg/ml, respectively. Estradiol has a short elimination half-life of approximately 2 to 3 hours, therefore, a rapid decline in serum levels is observed after the transdermal patch is removed. After removal of the transdermal patch, serum

concentrations of estradiol return to untreated postmenopausal levels (<20 pg/ml) within 4 -8 hours.

Multiple applications of the transdermal patch resulted in average serum norethisterone concentrations at steady-state of 346 pg/ml. At the end of the application period, the average serum concentrations of norethisterone were 321 pg/ml. The elimination half-life of norethisterone is reported to be 6 to 8 hours. After removal of the transdermal patch, norethisterone serum concentrations diminish rapidly and are less than <50 pg/ml within 48 hours.

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.

5.3 PRECLINICAL SAFETY DATA

Animal studies with estradiol and norethisterone acetate have only shown effects that can be expected from an estrogenic and a progestogenic substance, respectively.

Acute toxicity of estrogens is low. Because of marked differences between animal species and between animals and humans, preclinical results possess a limited predictive value for the application of estrogens in humans.

In experimental animals, estradiol or estradiol valerate displayed an embryolethal effect even at relatively low oral doses; malformations of the urogenital tract and feminisation of male fetuses were observed.

Norethisterone, like other progestogens, caused virilisation of female fetuses in rats and monkeys. After high oral doses of norethisterone embryolethal effects were observed.

Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential revealed no particular human risks beyond those discussed in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Adhesive matrix:
silicone adhesive
acrylic adhesive
povidone
oleic acid
dipropylene glycol
Backing layer:
polyester film laminate
Protective (release) liner:
fluoropolymer coated polyester film.

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

The shelf-life is 30 months: 24 months when refrigerated (2 to 8°C) plus 6 months when stored up to 25°C.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not freeze. Store between 2 and 8°C until dispensed to the patient. Then, Estalis can be stored up to 25°C for a maximum period of 3 months. Do not store the transdermal patches unpouched.

6.5 NATURE AND CONTENTS OF CONTAINER

Estalis 50/140 transdermal patches are packed individually in heat-sealed pouches. Top and bottom layers of the pouch are made of a four layer composite laminate consisting of paper bonded to aluminium, with an inner sealing layer.

Estalis 50/140 packs contain 2, 8 or 24 transdermal patches.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Estalis 50/140 transdermal patch should be placed on the abdomen. It must never be applied to or near the breasts. Care should be exercised when applying Estalis 50/140. It should be placed on a clean, dry area of the abdomen which is not irritated, abraded or oily (i.e. should not be used with any moisturizing cream, lotion or oil).

The waistline should be avoided, since tight clothing may rub the system off. The sites of application should be changed with an interval of at least one week allowed between applications to a particular site.

After opening the pouch, remove one half of the protective liner taking care not to touch the adhesive part of the transdermal patch with the fingers. Apply the transdermal patch to the skin immediately. Remove the second half of the protective liner and press the transdermal patch firmly to the skin with the palm of the hand for at least 10 seconds, carefully smoothing down the edges. Care should be taken during bathing or other activities so that the transdermal patch does not become dislodged.

If the transdermal patch falls off (after strenuous physical activity, excessive sweating or friction from tight clothing), the same transdermal patch may be reapplied to another area. The original treatment should be thereafter followed, i.e. the transdermal patch should be exchanged on the same days as before. Once in place, the transdermal patch should not be exposed to the sun for prolonged periods of time.

Should any adhesive remain after removal of the transdermal patch, the skin area should be gently rubbed with an oil-based cream or lotion.

Once used, Estalis 50/140 transdermal patch should be folded (adhesive surfaces pressed together) and discarded.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited
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8 MARKETING AUTHORISATION NUMBER(S)

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25/04/2007

PATIENT INFORMATION LEAFLET

NOVARTIS

(estradiol and norethisterone acetate)

Patient Information Leaflet

Read all of this leaflet carefully before you start using ESTALIS® (estradiol and norethisterone acetate)

- Keep this leaflet. You may need to read it again.
- Ask your doctor or pharmacist if you have further questions.
- Do not give Estalis ® to anyone else, even if they have the same condition as you.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

IN THIS LEAFLET

1. WHAT ESTALIS IS AND WHAT IT IS USED FOR

Estalis is a type of treatment known as hormone replacement therapy (HRT). It provides estradiol plus norethisterone (NETA), and is therefore know as a continuous combined HRT product. Estradiol is female sex hormone (or estrogen), which your ovaries produce in large amounts before the menopause. NETA is also a female sex hormone which helps protect the lining of the womb in women who have not had a hysterectomy (surgical removal of the womb) (see the section below on endometrial cancer). Estalis is not a contraceptive nor will it restore fertility.

Estalis® is supplied as a stick-on patch. When the patch is applied to your skin it releases small amounts of estradiol and NETA, which passes directly through your skin and into your bloodstream.

The patches come in 2 strengths:

- Estalis 25/125: One 8 cm² patch contains 0.256 mg estradiol (as hemihydrate) and 2.40 mg norethisterone acetate, and delivers a nominal 25 micrograms estradiol and 125 micrograms norethisterone acetate per 24 hours
- Estalis 50/140: One 9 cm² patch contains 0.62 mg estradiol (as hemihydrate) and 2.70 mg norethisterone acetate, and delivers 50 µg estradiol and 140 µg norethisterone acetate per 24 hours.

A one month calendar pack contains 8 patches of one size; a 3 month pack contains 24 patches.

Relief of the symptoms of the menopause:

Estalis is used to help relieve the discomfort that you may experience after the menopause (the time when your menstrual periods stop). Menopause occurs naturally in all women, usually between the ages of 45 and 55. It will also occur in younger women who have their ovaries removed by surgery. After the menopause, your body produces much less estrogen than it did before. This can cause unpleasant symptoms such as hot face, neck and chest, "hot flushes" (sudden waves of heat and sweating in the whole body), sleep problems, irritability, and depression. Some women also have problems with urine control or dryness of the vagina, which may cause discomfort during or after sexual intercourse. Estrogens can be given to reduce or eliminate these symptoms.

Estalis should not be used to prevent heart disease.

You and your doctor should discuss the benefits and risks of Estalis and other alternative therapies, and how long you should carry on taking it.

Ask your doctor if you have any questions about how Estalis works or why this medicine has been prescribed for you.

2. BEFORE YOU USE ESTALIS

You should read this section carefully because, there are some conditions your doctor should know about before you start your treatment.

Medical check-ups

Before you start using HRT, your doctor should ask you about your own and your family's medical history. Your doctor may decide to examine your breasts and/or your abdomen and may do an internal examination – but only if these examinations are necessary for

you, or you have any special concerns. Once you have started HRT, you should see your doctor for regular check-ups (at least once a year). At these check-ups your doctor may discuss with you the benefits and risks of continuing to use HRT.

Be sure to:

- Go for regular breast screening and cervical smear tests
- Regularly check your breasts for any changes such as dimpling of the skin, changes in the nipple or any lumps you can see or feel.

Follow all instructions given to you by your doctor or pharmacist carefully.

Read the following information before you use Estalis.

Do not use Estalis if:

- you have ever had any unusual or allergic reaction to estrogens or any other component of the patch
- you have or have ever had breast cancer (See the section below on breast cancer)
- you have, or have ever had, a cancer of the endometrium (lining of the womb) or any other cancer which is sensitive to estrogens (See the sections below on endometrial and ovarian cancer)
- you have a disease of blood pigment called porphyria
- you have, or have ever had, a blood clot in a vein in your leg or anywhere else (a "deep vein thrombosis") or a clot that has traveled to your lung or another part of your body (an "embolus") (See the section below on blood clots)
- you have ever had a heart attack, stroke or angina (See the sections below on heart disease and stroke); or if your develop severe migraine headaches or an increase in blood pressure
- you have liver disease or a history of liver disease, or notice a yellowing of your skin or the whites of your eyes (this may be a symptom of jaundice)
- unexpected or very heavy vaginal bleeding
- endometrial hyperplasia (thickening of the lining of the womb)
- you think you may be pregnant or are breastfeeding.

Take special care with Estalis:

Tell your doctor if you have, or ever had any of the following conditions. They may happen again or become worse. If so, your doctor may want to see more often for check-ups:-

- breast cancer in your immediate family
- fibroids or other benign tumours of the womb
- endometriosis (disorder of the pelvis causing painful menstrual periods)
- high blood pressure
- heart or kidney problems
- if any of the reasons that make you more likely to have a blood clot (listed in the section "blood clots" below) apply to you
- gallbladder disease (See Section 4 Possible side effects)
- epilepsy (See the section on Taking other medicines)
- migraine or severe headache
- asthma
- diabetes
- systemic lupus erythematosus (a connective tissue disease)
- high cholesterol or fat levels in your blood,
- hearing loss due to otosclerosis (a problem with the bones in the ear)
- you are overweight.

As well as benefits, HRT has some risks which you need to consider when you are deciding whether to use it, or whether to carry on using it.

Below is some precautionary information common to all HRT products – please take time to look at it.

Effects on your heart or circulation

Heart disease

HRT is not recommended for women who have heart disease, or have had heart disease recently. If you have ever had heart disease, talk to your doctor to see if you should be using HRT.

HRT will not help to prevent heart disease.

Studies with one type of HRT (containing conjugated estrogen plus the progestogen MPA) have shown that women may be slightly more likely to get heart disease during the first year of taking the medication. For other types of HRT, the risk is likely to be similar, although this is not yet certain.

If you get:

- A pain in your chest that spreads to your arm or neck

See a doctor as soon as possible and do not use any more HRT until your doctor says you can. This pain could be a sign of heart disease.

Stroke

Recent research suggests that HRT slightly increases the risk of having a stroke. Other things that can increase the risk of stroke include:

- Getting older
- High blood pressure
- Smoking
- Drinking too much alcohol
- An irregular heartbeat

If you are worried about any of these things, or if you have had a stroke in the past, talk to your doctor to see if you should use HRT.

Compare

Looking at women in their 50s who are not using HRT – on average, over a 5–year period, 3 in 1000 would be expected to have a stroke.

For women in their 50s who are using HRT, the figure would be 4 in 1000.

Looking at women in their 60s who are not using HRT – on average, over a 5–year period, 11 in 1000 would be expected to have a stroke.

For women in their 60s who are using HRT, the figure would be 15 in 1000.

If you get:

Unexplained migraine-type headaches, with or without disturbed vision

See a doctor as soon as possible and do not use any more HRT until your doctor says you can. These headaches may be an early warning sign of a stroke.

Blood clots

HRT may increase the risk of blood clots in the veins (also called deep vein thrombosis, or DVT), especially during the first year of using it.

These blood clots are not always serious, but if one travels to the lungs, it can cause chest pain, breathlessness, collapse or even death. This condition is called pulmonary embolism, or PE.

DVT and PE are examples of a condition called venous thromboembolism, or VTE.

You are more likely to get a blood clot:

- If you are seriously overweight
- If you have had a blood clot before
- If any of your close family have had blood clots
- If you have had one or more miscarriages
- If you have any blood clotting problem that needs treatment with a medicine such as warfarin
- If you're off your feet for a long time because of major surgery, injury or illness
- If you have a rare condition called systemic lupus erythematosus (SLE – a connective tissue disease).

If any of these things apply to you, talk to your doctor to see if you should use HRT.

Compare

Looking at women in their 50s who are not using HRT – on average, over a 5–year period, 3 in 1000 would be expected to get a blood clot.

For women in their 50s who are using HRT, the figure would be 7 in 1000.

Looking at women in their 60s who are not using HRT – on average, over a 5–year period, 8 in 1000 would be expected to get a blood clot.

For women in their 60s who are using HRT, the figure would be 17 in 1000.

If you get:

- Painful swelling in your leg
- Sudden chest pain
- Difficulty breathing

See a doctor as soon as possible and do not use any more HRT until your doctor says you can. These may be signs of a blood clot.

If you're going to have surgery, make sure your doctor knows about it. You may need to stop using HRT about 4 to 6 weeks before the operation, to reduce the risk of a blood clot. Your doctor will tell you when you can start using HRT again.

Effects on your risk of developing cancer

Breast cancer

Women who have breast cancer, or have had breast cancer in the past, should not use HRT.

Using HRT slightly increases the risk of breast cancer; so does having a later menopause. The risk for a post-menopausal woman using estrogen-only HRT for 5 years is about the same as for a woman of the same age who's still having periods over that time and not using HRT. The risk for a woman who is using estrogen plus progestogen HRT is higher than for estrogen-only HRT (but estrogen plus progestogen HRT is beneficial for the endometrium, see "endometrial cancer" below).

For all kinds of HRT, the extra risk of breast cancer goes up the longer you use it, but returns to normal within about 5 years after stopping HRT.

Your risk of breast cancer is also higher:

- If you have a close relative (mother, sister or grandmother) who has had breast cancer
- If you are seriously overweight

Compare

Looking at women aged 50 who are not using HRT – on average, 32 in 1000 will be diagnosed with breast cancer by the time they reach the age of 65.

For women who start using estrogen-only HRT at age 50 and use it for 5 years, the figure will be between 33 and 34 in 1000 (i.e. an extra 1 –2 cases).

If they use estrogen-only HRT for 10 years, the figure will be 37 in 1000 (i.e. an extra 5 cases).

For women who start using estrogen plus progestogen HRT at age 50 and use it for 5 years, the figure will be 38 in 1000 (i.e. an extra 6 cases).

If they use estrogen plus progestogen HRT for 10 years, the figure will be 51 in 1000 (i.e. an extra 19 cases).

If you notice any changes in your breast, such as:

- Dimpling of the skin
- Changes in the nipple
- Any lumps you can see or feel

Make an appointment to see your doctor as soon as possible.

Endometrial cancer (cancer of the lining of the womb)

Using estrogen-only HRT for a long time can increase the risk of cancer of the lining of the womb (the endometrium). Taking a progestogen as well as the estrogen helps to lower the extra risk.

If you still have your womb, your doctor may prescribe a progestogen as well as estrogen. If so, these may be prescribed separately, or as a combined HRT product.

If you have had your womb removed (a hysterectomy), your doctor will discuss with you whether you can safely take estrogen without a progestogen.

If you've had your womb removed because of endometriosis, any endometrium left in your body may be at risk. So your doctor may prescribe HRT that includes a progestogen as well as an estrogen.

Estalis contains a progestogen.

XXXXXX XX

Compare
Looking at women who still have a uterus and who are not using HRT – on average 5 in 1000 will be diagnosed with endometrial cancer between the ages of 50 and 65 years.

For women who use estrogen-only HRT, the number will be 2–12 times higher, depending on the dose and how long you use it.

The addition of a progestogen to estrogen-only HRT substantially reduces the risk of endometrial cancer.

If you get breakthrough bleeding or spotting, it's usually nothing to worry about, especially during the first few months of taking HRT.

But if the bleeding or spotting:

- Carries on for more than the first few months
- Starts after you've been on HRT for a while
- Carries on even after you've stopped using HRT
- Make an appointment to see your doctor. It could be a sign that your endometrium has become thicker.

Ovarian cancer
Ovarian cancer (cancer of the ovaries) is very rare, but it is serious. It can be difficult to diagnose, because there are often no obvious signs of the disease.

Some studies have indicated that using estrogen-only HRT for more than 5 years may increase the risk of ovarian cancer. It is not yet known whether other kinds of HRT increase the risk in the same way.

Dementia
HRT will not prevent memory loss. In one study of women who started using combined HRT after the age of 65, a small increase in risk of dementia was observed.

Taking other medicines
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines without prescription.

This particularly includes the following:

- anti-epileptic medicines (e.g. phenylbarbital, phenytoin or carbamazepine),
- antibiotics and other anti-infective medicines (e.g. rifampicin, rifabutin, nevirapine, efavirenz, ritonavir, nelfinavir),
- herbal medicines (e.g. St John's wort, also known as *Hypericum perforatum*).

These medicines may be affected by Estalis or, conversely, they may affect how well Estalis works. Your doctor may need to adjust the dose of your treatment.

Estalis and children
Estalis should not be used in children.

Pregnant women
Do not use Estalis during pregnancy as it could harm your baby.

Ask your doctor or pharmacist for advice.

Breast-feeding mothers
Do not breast-feed while using Estalis.

Ask your doctor or pharmacist for advice.

Contraception whilst taking Estraderm
Estalis is not intended to be used as a contraceptive.

If you are using an oral or other hormonal contraceptive e.g. the 'pill' or depot injection, you must change to a non-hormonal contraceptive, for example a diaphragm or condom, BEFORE starting Estalis.

If your doctor has already told you that you no longer need to use any form of contraception, you do not need to do so whilst taking Estalis even if you experience monthly bleeding.

Driving and using machines
Estalis should not affect your ability to drive or use machines.

3. HOW TO USE ESTALIS
Follow all instructions given to you by your doctor or pharmacist carefully. Do not change the dose or stop the treatment without talking to your doctor.

How to start treatment
Estalis patches are applied twice weekly for 3–4 days each so that a patch is worn at all times. Your doctor will aim to give you the lowest dose that treats your symptoms.

During the course of treatment your doctor may adjust the dose according to your individual needs and will maintain your treatment at the lowest effective dose.

If you are not currently using any form of HRT (patch or tablets), or if you have been using a different continuous combined HRT product (where estrogen and the progestogen are given every day without interruption), you can start to use Estalis on any convenient day.

If you are changing from a cyclic or sequential HRT treatment (where the progestogen is added for 12–14 days of the cycle), you should finish your current cycle of treatment before starting Estalis. Menstrual type bleeding often occurs at the end of sequential HRT

treatment cycle, try to take Estalis on the first day of bleeding, or, no more than 7 days after finishing the previous treatment cycle.

How to use Estalis

You will need to wear a patch all the time. You will change your patch every 3 to 4 days.

Where to apply the patch

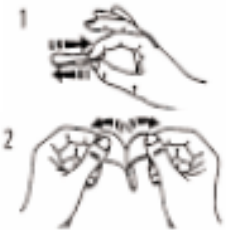
The recommended are area of skin is the abdomen. Avoid the waistline since tight clothing may rub the system off. The skin should not be inflamed, broken or irritated. To help the patch stick, the skin should be clean, non-hairy, dry, and free of creams, lotions, oil, or powder. You should use a different area of skin each time. Wait for a week before using the same area again. Never put a patch on or near to the breasts. Do not expose the patch to direct sunlight.

Opening the sachets

Each Estalis is sealed in an airtight sachet. Tear open one of the sachets (do not use scissors) and take out the patch. Make sure that other sachets are undamaged, because the patch becomes ineffective when exposed to the air before use. If you happen to tear open both sachets at the same time, throw one of them away.

Removing the lining

A stiff, transparent protective lining covers the sticky side of the system, i.e. the side that will be placed against your skin. Loosen this lining by rubbing the edge of the patch between your thumb and forefinger. Holding the patch at the edge, peel off the protective lining and throw it away. Try to avoid touching the adhesive. Now apply the patch.



Applying the patch

Press the sticky side of the patch firmly onto the spot you have chosen with the palm of your hand. Hold it there for about 10–20 seconds. Make sure that it sticks well, especially around the edges. Do not test the patch by pulling it once it is on your skin.

When and how to remove the patch

The patch should be changed twice each week i.e. every 3–4 days, always on the same two days, e.g. Mondays and Thursdays. You may find it helpful to tick the box on this leaflet for the day of the week when you apply your first Estalis patch. This then shows the two days each week when you should change your patch. When you finish an Estalis pack, start the next pack straightaway. There is no need to have a break between packs.

- ☐ Monday + Thursday
- ☐ Tuesday + Friday
- ☐ Wednesday + Saturday
- ☐ Thursday + Sunday
- ☐ Friday + Monday
- ☐ Saturday + Tuesday
- ☐ Sunday + Wednesday

When the time comes to change the patch, peel it off and fold it in half with the sticky side inside. Dispose of the patch carefully with household waste, making sure that it is out of the reach of children because it will still contain some medication. Stick a new patch onto a different area of skin.

Other useful information

- Bathing, swimming, showering or exercising should not affect the patch if it has been correctly applied. You may wear the patch under your swimming costume.
- If the patch does come off in the bath or shower it may be reapplied. Shake it to remove any water, dry the skin thoroughly, allow the area to cool and put it on again in the usual way.
- Never apply a patch on a sweaty area or straight after a hot bath or shower. Wait until the skin is completely cool and dry.
- Sunbathing: always make sure your patch is covered by clothing.
- Using a sunbed: either cover the patch or take it off and put it back on after showering when your skin is completely cool and dry.
- The drug in your patch is in a gel which is colourless. This does not mean that the patch is empty.

How long to use Estalis

Estalis should be used only as long as needed.

Usually, you will be using Estalis for several months or longer. This will help to control your symptoms.

Periodically, you should discuss with your doctor the possible risks and benefits associated with HRT and whether you still need the treatment. Your Doctor will aim to give you the lowest possible dose for the shortest possible duration to treat your symptoms.

What to do if a patch comes off

If a patch falls off, the same patch may be put on a different area of your skin (see Where to apply the patch). Make sure you choose a clean, dry, lotion-free area of the skin. If the patch does not stick completely to your skin, use a new patch. No matter what day this happens, go back to changing the patch on the same days as the initial schedule.

If you forget to use Estalis

If you miss applying a patch, apply a new patch as soon as you remember. No matter what day that happens, go back to changing this patch on the same day as your initial schedule. There is an increased chance of breakthrough bleeding or spotting if there is a break in treatment.

If you use too much Estalis (overdose)

Because of the way Estalis is administered, overdose is unlikely to occur but may be reversed by removal of the patch

While you are using Estalis

Tell your doctor or pharmacist as soon as possible if you do not feel well while you are using Estalis. (refer to Section 4 Possible side effects")

Ask your doctor or pharmacist to answer any questions you may have.

Remind your doctor that you are using Estalis if you are having a blood test as it may affect the result.

4. POSSIBLE SIDE EFFECTS

Most people who are prescribed Estalis will benefit from using it, but some people can be upset by it.

The following side effects have been reported with Estalis or other HRT:

- breast cancer
- endometrial cancer
- allergic reactions
- jaundice
- blood clots e.g. deep vein thrombosis or DVT
- heart attack
- stroke.

The above side effects are serious and require urgent medical attention. These side effects are rare.

Other side effects include:

- rash and itching over large areas of the skin. This sensitivity reaction may become severe if you carry on using the patches without talking to your doctor
- changes in the pigmentation in your skin (lightening or darkening of your skin colour)
- itching under the patch, reddening of the skin after the patch has been removed
- tender or painful breasts
- spotting (bleeding between menstrual periods)
- increase in blood pressure
- dizziness, feeling or being sick, abdominal cramps, bloating
- headache, vertigo, nervousness, depression, insomnia, feeling emotional
- unusual weight changes, fluid retention (swelling or accumulation of fluid in the lower legs or ankles), leg pains, increase in varicose veins
- dementia.

HRT has also been reported to cause gallbladder disease. It may also affect the way your liver works. Your doctor may want to do blood tests if he thinks your liver has been affected by the HRT.

If you notice any other side effect or are concerned about using Estalis, please inform your doctor or pharmacist.

5. STORING ESTALIS

Keep this medicine out of the reach and sight of children.

Store below at 2 to 8°C, away from direct sunlight.

Store in the original package.

Do not use Estalis after the expiry date shown on the pack.

Do not use Estalis pack that is damaged or shows signs of tampering.

6. FURTHER INFORMATION

The active substance in Estalis is estradiol (as hemihydrate).

The other ingredients in Estalis are:

Adhesive matrix:

- silicone adhesive
- acrylic adhesive
- povidone
- oleic acid
- dipropylene glycol.

Backing layer:

- polyester film laminate.

Protective (release) liner:

- fluoropolymer coated polyester film.

Manufactured by:
Noven Pharmaceuticals Inc,
11960 S.W. 144th Street,
Miami, Florida, 33186,
USA.

Released onto the market by:
Novartis Pharmaceuticals UK Limited,
Wimblehurst Road, Horsham,
West Sussex, RH12 5AB,
England.

Product licence/authorisation holder:
Novartis Pharmaceuticals UK Limited,
Frimley Business Park, Frimley, Camberley,
Surrey, GU16 7SR,
England.

REMEMBER: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if they have the same symptoms as you.

The information in this leaflet applies only to Estalis. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

Date: 18th April 2006

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LABELLING

Carton – pack size 2

Carton – pack size 8

Carton – pack size 24