ESTALIS ® 25/125
(estradiol hemihydrate, norethisterone acetate)

PL 00101/0689

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 ® 25/125 (PL 00101/0689) 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 ® 25/125 delivers 25 micrograms estradiol and 125 micrograms norethisterone acetate per 24 hours.

Estalis ® 25/125 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 ® 25/125 outweigh the risk; hence a Marketing Authorisation has been granted.

ESTALIS ® 25/125
(estradiol hemihydrate, norethisterone acetate)

PL 00101/0689

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Novartis Pharmaceuticals UK Limited a Marketing Authorisation (MA) for the medicinal product Estalis ® 25/125 (PL 00101/0689) on 25th April 2007. The product is a prescription-only medicine used as HRT.

This is a complex abridged application for Estalis ® 25/125 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 ® 25/125 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 ® 25/125 was submitted and approved at the same time as the application for Estalis ®50/140 (PL 00101/0690). A Public Assessment Report is also available for Estalis ® 50/140.

PHARMACEUTICAL ASSESSMENT

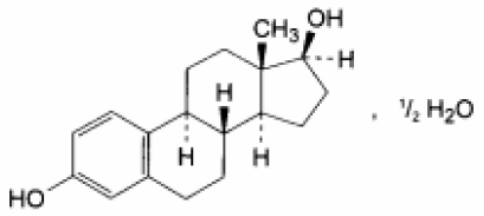
ACTIVE SUBSTANCE

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.

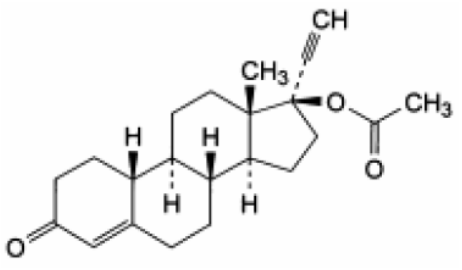
ACTIVE SUBSTANCE

Norethisterone acetate

Nomenclature:

INN:	Norethisterone acetate
Chemical name:	3-Oxo-19-nor-17β-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 25/125 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

A bioequivalence study was presented comparing the test product, Estalis 25/125, to the reference product, Estragest 25/125 (marketed by Novartis in the EU). With bioequivalence having been demonstrated, Estragest 25/125, rather than Estalis 25/125, was subsequently used in all the clinical efficacy and safety trials.

An evaluation of the bioequivalence study, and 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® 25/125 transdermal patches submitted by Novartis Pharmaceuticals UK Ltd. under article 8.3 of Council Directive 2001/83/EC, as amended.

Estalis® 25/125 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 25/125 patch delivers 25 µg E2 and 125 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 25/125 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® 25/125. It is concluded that there is no objection to the grant of a licence for Estalis® 25/125 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 25/125 would allow transdermal delivery of a low dose of oestrogen/progestogen, support the aim of dose individualisation/flexibility, and provide better patient acceptability.

Estragest 25/125, rather than Estalis 25/125, was used in all the clinical efficacy and safety trials. This was justified on the basis of the demonstrated bioequivalence between these formulations (see bioequivalence study, below).

I.1 GCP ASPECTS

All clinical studies were conducted in accordance with GCP.

II INDICATIONS

Estalis 25/125 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.

Both E2 and NET are metabolised by the liver and transdermal administration avoids first-pass metabolism; 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.

Pharmacokinetics - Bioequivalence study

A single bioequivalence study (2302) was performed comparing the proposed product Estalis 25/125 with the reference product Estragest 25/125. Both these patches nominally deliver 25μg 17β-estradiol and 125 μg norethisterone acetate per day. This was a Phase I open-label, steady-state, 4-way crossover, replicate design study to evaluate bioequivalence between a matrix-based transdermal system (Estalis) and a reservoir based transdermal system (Estragest) in healthy postmenopausal women. The secondary objective of the study was to assess local tolerability and patch adhesion.

Thirty suitable volunteers (healthy postmenopausal women aged 40-70 years) completed the study. This study involved four periods: each of the two treatments being given to each subject twice. Of the 30 subjects required to complete the study, 15 were randomised to the TRTR group and 15 to the RTRT group sequence

The study was a repeat dose study. Each treatment was applied for 10.5 days (1 identical patch applied every 3.5days) and then repeated. The washout period was 2 days; this is acceptable, given the short half-lives of the active substances.

Blood samples were taken before administration and up to 288 hours throughout the treatment period. Serum concentrations of estradiol, its active metabolite estrone and norethisterone were quantified using a validated LC/MS/MS method, appropriate LOQs (Limits of Quantification) are provided, C.V.s were not more than 13%.

Pharmacokinetic parameters were determined over the sampling interval 168 to 252 hours (day7 to day 10.5), during the administration of the third patch. Various statistical analysis was performed, including ANOVA, on log transformed C_{max}, $C_{average}$ and AUC values and 90% confidence intervals determined. The results are summarised in the Table 1.

Table 1: Mean (CV%) PK parameters for E1, E2 and NET (replicate design, n=30)

Analyte	Parameter	Estalis 25/125	Estragest 25/125
Estrone	$AUC_{168-252h}$ (pg.h/mL)	2093 (35)	2032 (35)
	C_{max} (pg/mL)	33 (35)	33 (33)
	C_{min}(pg/mL)	18 (46)	18 (49)
	FL_{rel}	0.68 (58)	0.69 (67)
Estradiol	$AUC_{168-252h}$ (pg.h/mL)	2097 (39)	2006 (25)
	C_{max} (pg/mL)	37 (47)	39 (24)
	C_{min}(pg/mL)	8 (112)	10 (80)
	FL_{rel}	1.23 (30)	1.31 (38)
Norethisterone	$AUC_{168-252h}$ (pg.h/mL)	32677 (57)	32661 (39)
	C_{max} (pg/mL)	493 (64)	607 (37)
	C_{min}(pg/mL)	251 (53)	283 (39)
	FL_{rel}	0.61 (30)	0.85 (24)

FL_{rel} = Relative fluctuation index ($(C_{max}-C_{min})/C_{ave}$)

The mean exposure PK parameters ($AUC_{168-252h}$) for E2 and NET as well as E1 were comparable between Estalis 25/125 and Estragest 25/125. This indicates that despite different release mechanisms, equivalent amounts of E2 and NET are delivered transdermally.

The relative bioavailability data are shown in the following tables:

Table 2: Relative bioavailability data – estradiol

Estradiol	90% CI of Treatment Comparisons
$AUC_{(168-252)}$ Ratio	95 - 111
C_{max} Ratio	83 - 99
C_{ave} Ratio	95 - 111

Table 3: Relative bioavailability data – estrone

Estrone	90% CI of Treatment Comparisons
$AUC_{(168-252)}$ Ratio	99 - 108
C_{max} Ratio	94 - 106
C_{ave} Ratio	99 - 108

Table 4: Relative bioavailability data – norethisterone

Norethisterone	90% CI of Treatment Comparisons
$AUC_{(168-252)}$ Ratio	89 - 104
C_{max} Ratio	71 - 83
C_{ave} Ratio	89 - 104

The confidence intervals for $AUC_{168-252}$ (E1, E2 and NET), C_{max} (E1 and E2) and C_{ave} (E1, E2 and NET) were within the accepted interval (0.8, 1.25) used for establishing bioequivalence. CIs for the C_{max} for NET did not meet the criteria for bioequivalence, but this is not considered to be of clinical relevance. Bioequivalence between Estalis 25/125 and Estragest 25/125 has been satisfactorily demonstrated. The bioequivalence study is used as a bridge to the efficacy and safety data provided for Estragest 25/125.

Safety and tolerability findings are discussed further in the Clinical Safety section (section V). Local tolerability of the patch systems using the Draize 5-point erythema scale and assessment of skin irritability showed that there was a greater incidence of more intense local erythema (higher Draize scale scores) with Estragest 25/125 compared to Estalis 25/125. The former was also associated with a greater number of other signs of irritation (itching, erythema, scaling, papules and vesicles). With regard to patch adhesion, there was no difference in patch adhesion grading between the two patches. However, there was a difference in the number that required securing with adhesive tape (16 out of 188 applications with Estalis 25/125 vs. 58 out of 192 applications with Estragest 25/125).

Overall conclusions on pharmacokinetics

At steady state, the extent of total exposure to E1, E2 and NET was comparable between Estalis and Estragest and bioequivalence criteria at steady state were met for the AUC of E2, E1 and NET and also for C_{max} for E2 and E1. Thus, both patches deliver equivalent amounts of E2 and NET transdermally, despite using a different release mechanism, i.e. matrix (Estalis) versus reservoir (Estragest). The major difference between the two patches was observed in the pattern of the mean concentration-time profiles of NET. After Estalis application, lower C_{max} and shorter T_{max}, but similar C_{min} values, were observed compared with Estragest. C_{max} for NET failed to meet bioequivalence criteria but C_{min} was similar and the relative fluctuation index was, in fact, less in the Estalis group. These slight PK differences were not deemed significant. The bioequivalence study was of adequate design and bioequivalence between Estalis 25/125 and Estragest 25/125 has been demonstrated.

Estalis 25/125 appeared to be better tolerated than Estragest 25/125 with less frequent, and milder, local skin reactions. Although there were no differences in patch adhesion grading scores between the two treatments, Estalis 25/125 required less secondary securing with adhesive tape, indicating better skin adhesion.

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

The demonstration of bioequivalence between Estragest 25/125 and the proposed product, Estalis 25/125, allows extrapolation of efficacy and safety data from Estragest 25/125. The clinical studies for Estragest 25/125 are summarised in Table 5.

Table 5: Summary of Studies

Study	Design	n*	Treatment Duration	Medication dose/day	Efficacy endpoint
Pivotal Placebo- Controlled Studies					
2007 Pivotal Efficacy (postmenopausal symptoms)/Safety study	Double-blind, placebo-controlled, parallel group	138†	24 weeks + 2 weeks max run-in	Estragest TTS 25/125 or Placebo	1° Kupperman Index at 4, 12,24 weeks 2° Greene Climacteric Scale Urogenital symptoms, vaginal smear (%age superficial cells)
2008 Efficacy (prevention of postmenopausal osteoporosis) /Safety study	Double-blind, placebo-controlled, parallel group	124‡	96 weeks + 6 weeks maximum run-in	Estragest TTS 25/125 or Placebo	
2015 Endometrial safety, safety, PK	Double-blind, parallel group	228	48 weeks + 4 week run-in	Estragest TTS 25/125 or Placebo patches	
Supportive controlled efficacy trials					
PCC3 Efficacy postmenopausal symptoms/Safety study	Open, randomised, active comparator, parallel group	494	52 weeks + 4-5 week run-in	Estragest TTS 25/125 Or Estragest TTS 50/250 Or Estracombi TTS (sequential, 50µg E2 then 50µg E2 + 250 µg NETA)	Postmenopausal symptoms by WHQ at weeks 12, 24 and 36
PCC4 Efficacy postmenopausal symptoms/Safety study	Open, randomised, active comparator, parallel group	441	52 weeks + 4-5 week run-in	Estragest TTS 25/125 Or Estragest TTS 50/250 Or Kliogest (2 mg E2 + 1mg NETA orally)	Postmenopausal symptoms by WHQ
Uncontrolled trials					
DE01 Endometrial safety	Open-label	411	48 weeks + 4 week run-in	Estragest TTS 25/125	
2015E Endometrial safety	Open-label long-term	144	48 weeks	Estragest TTS 25/125	

**number of patients randomised to treatment*
† two did not receive any study medication
‡ one patient did not receive medication
WHQ=women's health questionnaire

Rationale for Dose

Formal dose-finding trials were not performed. However, inclusion of an Estragest TTS 50/250 treatment arm in studies PCC3 and PCC4, enabling an efficacy comparison between the 25/125 and 50/250 strengths, has shown no significant difference between the two treatments (see 'Supportive Studies' section).

Treatment of Postmenopausal Symptoms

Pivotal Phase III study

Study 2007 – A double-blind, randomised, multicentre, between-patient (parallel group), 24-week trial comparing the efficacy and tolerability of Estragest TTS 25/125, 10cm2 (nominal delivery:0.025mg estradiol and 0.125mg norethisterone acetate per day) with placebo (placebo-controlled), in postmenopausal women aged ≥45 years with mild to moderate postmenopausal symptoms.

- **Study Participants**

Postmenopausal women aged ≥ 45 years with an intact uterus and amenorrhoea for ≥ 2 years with mild/moderate postmenopausal symptoms (Kupperman Index score ≥ 16 but ≤ 25). This population was considered to be representative of the target population. They had to have an acceptable gynaecological examination, normal Papanicolaou (PAP) smear and mammogram, and no contraindications to oestrogen therapy or any of the other patch constituents. The following wash-out periods were used for the following categories at enrolment:

- 6-months for women who were being treated with injected HRT
- 4-weeks for women who were being treated with oral HRT
- 2-weeks for women who were being treated with transdermal patch or vaginal HRT

These wash-out periods were considered adequate to avoid any carry-over effects.

- **Treatments**

Treatments were administered in cycles. Each cycle consisted of 4 weeks (=28 days).

Treatment Group 1: Estragest TTS 25/125
Treatment Group 2: Matched placebo

Patches were applied twice a week, on the same day of the week and to the buttocks or abdomen, on clean, undamaged, dry skin. They were not affixed twice in succession to the same site. They were worn continuously until it was time to replace them.

- **Objectives**

(a) To demonstrate that Estragest TTS 25/125 is superior to placebo in the treatment of mild to moderate postmenopausal symptoms.

(b) To determine safety and tolerability of Estragest TTS 25/125

(c) To evaluate the effects of Estragest TTS 25/125 compared to those of placebo on the following biochemical variables:

i) lipid/lipoprotein profile
ii) glucose tolerance
iii) coagulations/fibrinolysis functions
iv) circulating plasma levels of E2 and NET after Estragest TTS 25/125 administration.

- **Endpoints**

Primary:

Reduction of the Kupperman Index score. The Kupperman Index is an overall scoring system based on the presence/severity (e.g. no, little, moderate, heavy) of the most common postmenopausal symptoms, including vasomotor, paraesthesia, insomnia, nervousness, melancholia, vertigo, fatigue, arthralgia, myalgia, headaches, palpitations and formication.

Secondary:

- Greene Climacteric Scale – a sum of 21 symptoms including psychological, somatic, vasomotor and sexual dysfunction sub-scales, where negative changes denote improvements in climacteric symptoms and vice versa.
- Urogenital symptoms (vaginal dryness, dyspareunia, burning, micturition) assessed by visual analogue scale. In addition the percentage of parabasal, intermediate and superficial cells in the vaginal smear were recorded.
- Other evaluations: safety evaluations, breast tenderness, lipid/lipoprotein profile, coagulation/fibrinolysis function tests and glucose tolerance test, vaginal bleeding, patch adhesion.

- **Statistical methods**

Two data sets were analysed for the primary efficacy variable.

Intention-to-treat population (ITT)
Confirmation of efficacy was based on this population, which included all patients who received at least one treatment (provided a Kupperman rating was performed at baseline and at least one further rating up to Visit 4 (week 12)). Secondary endpoints were also analysed in the ITT population.

Acceptable for efficacy population (AFE)
This was defined as including randomised patients who met the inclusion criteria and were treated for at least 11 weeks with a Kupperman score at baseline and Visit 4 (week 12). This population was only used for a sensitivity analysis of the primary efficacy variable and was not necessarily expected to show a statistically significant treatment difference (two-sided level of 5%) because of the lower sample size for this population.

Primary endpoints: Analysis was by ANCOVA with baseline as covariate and treatment centre as factors. For the test on treatment effect, a two-sided significance level of 5% was applied. The p-value, the estimated treatment difference and the 95% CI for the treatment difference were calculated. Least squares estimates of the post-treatment values for each treatment difference group were calculated and presented with the standard error.

Secondary endpoints: These were assessed in the ITT population only. The same statistical methods as were used for the primary endpoints were applied, with the exception of the sexual dysfunction sub-scale of the Greene Climacteric Scale and the assessment of diurnal polyuria which are presented using descriptive statistics. Values of the vaginal dryness VAS (Visual Analogue Scale) were analysed only in those with

a baseline score >40mm. For the Kupperman Index, the least squares estimate of the treatment difference was presented graphically with the 95% CIs.

- **Participant flow**

169 patients were screened in 16 centres and 138 were randomised. Of the 136 treated patients, 113 (83.1%) completed the trial – 58 (85.3%) in the Estragest TTS 25/125 group and 55 (80.9%) in the placebo group. All 136 randomised patients were included in the safety analysis.

- **Baseline data**

There were no relevant differences in demographic and baseline data between the two groups.

- **Outcomes and estimation**

Primary endpoint:

Kupperman Index - Treatment comparisons for the change from baseline score, using ANCOVA, are shown in Table 6. The ITT population showed statistically significant superiority of Estragest TTS 25/125 over placebo ($p< 0.001$). The estimated difference for Estragest – placebo was - 6.8, indicating that after 12 weeks treatment with Estragest the Kupperman Index was reduced by 6.8 over placebo. The mean baseline Kupperman Index was similar in both groups (20 and 20.4 for Estragest and placebo groups, respectively).

Table 6: Kupperman Index Score Findings

	Estragest TTS		Placebo		Estimate of Treatment difference†	95% CI	p-value
	N	LSM	N	LSM			
Week 4	66	11.9	67	15.8	-3.9	(-6.0,-1.8)	<0.001
Week 12‡	66	8.9	67	15.7	-6.8	(-8.8,-4.8)	<0.001
Week 24	66	8.2	67	16.1	-7.9	(-10.0,-5.8)	<0.001

† Estragest TTS vs placebo
LSM = least squares mean
‡ Primary variable timepoint for efficacy comparison

Secondary endpoints:

- Greene Climacteric Scale – statistically significant improvement in total score (reduction in score) after 12 ($p=0.002$) and 24 weeks ($p<0.001$) of therapy with Estragest 25/125 compared with placebo. The effect was not statistically significant at 4 weeks ($p=0.0830$). For the vasomotor subscale, the difference between treatments was statistically significant at all time points ($p<0.001$), while for the psychological subscale improvement for Estragest TTS 25/125 compared with placebo was statistically significant at 12 weeks ($p=0.017$). There were no relevant differences between treatments in the somatic sub-scale.
- Visual analogue scale (VAS) for urogenital symptoms (vaginal dryness, dyspareunia, burning, dysuria). After 12 and 24 weeks therapy with Estragest, statistically significant improvements, compared to placebo, were seen for vaginal dryness and dyspareunia, but not dysuria.

- Vaginal smears – at 12 and 24 weeks showed an increase in the percentage of superficial cells at both timepoints compared with placebo ($p<0.001$), indicating an improvement in oestrogen-induced stimulation.

Supportive Studies

Studies PCC3 and PCC4 used the Women's Health Questionnaire (WHQ) to assess oestrogenic and progestogenic effects of treatment, using a 24-question survey. Estragest 25/125 significantly improved climacteric symptoms overall (increase in total score) and in relation to the oestrogenic effects (irritability, sleep disturbance, palpitations, hot flushes, vaginal dryness) in both studies. Estragest 25/125 was as effective (numerically) as Estracombi TTS and Kliogest and no differences were shown between the Estragest doses of 25/125 and 50/250. The mean scores for the progestogenic effects (sadness/misery, anxiety, restlessness, greasiness of hair or skin) for all treatments showed little change during the course of treatment indicating that no progestogen-induced unwanted effects occurred. Sleep disturbance, hot flushes and pain in joints or limbs were also analysed separately and showed a clinically meaningful increase in the number of patients free of hot flushes and sleep disturbance between baseline and 36 weeks for Estragest TTS and its comparators.

Published Data

This has been reviewed in the Clinical Overview. There are published data supporting the efficacy of low doses of oestrogens in controlling postmenopausal symptoms. In a placebo-controlled trial (De Aloysio 2000), transdermal patches releasing 25μg/day and 37.5μg/day of E2 were both significantly more effective than placebo in relieving climacteric symptoms (frequency and severity of hot flushes; Kupperman Index). A further study (Parsey 2000) showed that this dose was comparable to 300μg/day of oral conjugated equine estrogens (CEE) in relieving hot flushes. Utian (1999) showed that transdermal doses of 25, 50 and 100 μg/day E2 were effective in the treatment of moderate to severe vasomotor symptoms compared to placebo, with oestrogen-related adverse events less frequent in the 25μg/day group compared with higher doses.

Efficacy in postmenopausal symptoms

The applicant has submitted clinical studies of Estragest 25/125 to support the efficacy of Estalis 25/125. Study 2007 compared the efficacy and safety of Estragest TTS 25/125 with placebo over 24 weeks. Study PCC3 compared Estragest TTS 25/125 with Estragest TTS 50/250 and Estracombi TTS 50/250. Study PCC4 compared Estragest TTS 25/125 with Estragest TTS 50/250 and Kliogest (2mg estradiol, 1mg NETA (orally)). These studies clearly demonstrate the efficacy of Estragest TTS 25/125.

Assessor's overall conclusions on clinical efficacy

It is considered that adequate bioequivalence at steady-state, between Estalis 25/125 and Estragest TTS 25/125, has been shown and, therefore, efficacy data for the latter may be used to support this application. The most important parameters, exposure to E2 and NET as measured by AUC, fulfil the accepted criteria for bioequivalence and the only quantitative difference in PK is in the NET C_{max} (lower for Estalis) though C_{min} values are similar. The difference in the NET C_{max} between Estragest and Estalis is of no clinical relevance.

Estragest TTS 25/125 has been shown to be statistically more efficacious than placebo in the treatment of mild/moderate postmenopausal symptoms, including vasomotor and urogenital symptoms in women >2 years post menopause (Study 2007).

The efficacy of Estragest TTS 25/125 in the relief of postmenopausal symptoms was shown in the supportive studies PCC3 and PCC4 to be similar to that of the active comparators providing a higher dose of E2 combined with NETA such as Estragest TTS 50/250, Estracombi TTS 50/250 and Kliogest 2mg/1mg. This is consistent with published reports relating to efficacy of 25μg/d transdermal E2 in the target population.

There is no evidence from the clinical studies, or literature, of tachyphylaxis during long-term use or rebound worsening of symptoms upon withdrawal of therapy.

Estragest TTS 25/125 maintains high rates of amenorrhoea in postmenopausal women and control of bleeding seems to be at least as effective as with the best continuous combined regimens on the market.

V CLINICAL SAFETY

Introduction

Recently the risk-benefit profile for HRT has been placed under scrutiny following publication of the results of large studies such as the UK's Women Study and the final results of the US Women's Health Initiative (WHI) trial. The consensus is that benefit may still outweigh risk but that treatment should be for the shortest period necessary and at the lowest effective dose. Estalis 25/125 offers low-dose treatment with the benefits associated with transdermal application.

The safety profile of the licensed product Estragest TTS 25/125 can be extrapolated to Estalis 25/125 because of the demonstrated bioequivalence of these products (study 2302). In addition Estalis 25/125, being a matrix rather than a reservoir product, appears to demonstrate better local tolerability, better skin adhesion and has a less obtrusive appearance.

The main safety data are taken from six studies, plus the extension to one, in postmenopausal women taking Estragest TTS 25/125:

- Phase III double-blind, placebo-controlled studies (2007, 2008 and 2015 plus its extension 2015E).
- Supportive open-label, active-controlled trials (PCC3, PCC4)
- Endometrial safety – open-label, non-comparative (DE01, 2015E)

Patient exposure

For patients who received at least one dose of study medication in each of the six studies, exposure is summarised in Table 7. More than 1000 patients were exposed to Estragest TTS 25/125 and 60% of these were exposed for >12 months. The Estragest TTS 25/125 group had a much greater total exposure (almost 1000 patient years) compared with the other treatment groups (118-239 patient years). Only Estragest TTS 25/125 and placebo were used in 48 week studies. Most of the Estragest TTS 25/125 patients participated in 48 week studies.

Table 7: Overall Exposure

Duration of Treatment	Estragest TTS 25/125 (n=1026)	Estragest TTS 50/250 (n=312)	Kliogest (n=144)	Estracombi TTS (n=165)	Placebo (n=186)
n (non missing)	1013	309	139	163	184
Mean (days)±SD	348.9±162.1	282.4±123.7	310±101.0	307.0±107.3	345.3±224.3
Median (days)	340	353	357	357	331
0-4 weeks n (%)	22 (2.2)	11 (3.6)	2 (1.4)	5 (3.1)	5 (2.7)
4-12 wks	52 (5.1)	37 (12.0)	10 (7.2)	10 (6.1)	9 (4.9)
3-6mths	72 (7.1)	29 (9.4)	8 (5.8)	13 (8.0)	45 (24.5)
6-9mths	40 (3.9)	10 (3.2)	5 (3.6)	5 (3.1)	20 (10.9)
9-12mths	219 (21.6)	13 (4.2)	11 (7.9)	5 (3.1)	29 (15.8)
12-18mths	466 (46.0)	209 (67.6)	103 (74.1)	125 (76.7)	27 (14.7)
18mths – 24mths	57 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)	16 (8.7)
>24 mths	85 (8.4)	0 (0.0)	0 (0.0)	0 (0.0)	33 (17.9)
Patient years (sum)	967.7	238.9	118.3	137.0	173.9

Studies DE01, PCC3, PCC4, 2008, 2007, 2015, 2015E (patients on Estragest in core only
Estracombi TTS (sequential 50μgE2 then 50μgE2+250μg NETA per day)
1 month = 28 days
1 patient year 365.25

The main safety focus is prevention of endometrial hyperplasia and the relevant exposure data are summarised in Tables 8 and 9. This population included patients:

- from studies 2015 and DE01 who received treatment and had a biopsy with sufficient tissue after 11 cycles (308 days)
- patients in 2015E who received Estragest 25/125 in the core study and were eligible for the acceptable endometrial safety population
- patients in 2015E who received placebo in the core study who received at least one dose of Estragest 25/125 in the extension and had a biopsy with sufficient tissue after 11 cycles in the extension
- Any patient who had endometrial hyperplasia or cancer diagnosed at any time point in studies 2015, 2015E or DE01.

Table 8: Summary of Trials providing Endometrial Safety Data

Study #	Design	Randomised Patients	Treatment Duration	Medication Dose/day	Type of Control
2015	Double-blind, parallel group	228	48 weeks + 4 weeks run-in	Estragest 25/125	Placebo
2015E	Open-label	144	48 weeks	Estragest 25/126	None
DE01	Open-label	441	48weeks + 4 weeks run-in	Estragest 25/125	None

Table 9: Endometrial Safety Population

	Estragest TTS 25/125		
	DE01 and 2015	**DE01, 2015 and 2015E**	**Placebo**
Duration of Treatment	**Estragest TTS 25/125 (n=406)**	**Estragest TTS 50/250 (n=444)**	**(n=33)**
Mean (days)±SD	336.4 ± 10.9	407.6 ± 138.0	335.4 ± 6.1
Median (days)	336	337	335
0-4 weeks n (%)	0 (0.0)	0 (0.0)	0 (0.0)
4-12 wks	0 (0.0)	0 (0.0)	0 (0.0)
3-6mths	0 (0.0)	0 (0.0)	0 (0.0)
6-9mths	2 (0.5)	2 (0.5)	0 (0.0)
9-12mths	204 (50.2)	163 (36.7)	20 (60.6)
12-18mths	200 (49.3)	187 (42.1)	13 (39.4)
18mths – 24mths	-	40 (9.0)	-
>24 mths	-	52 (11.7)	-
Patient years (sum)	374.0	495.4	30.3

1 month = 28 days
1 patient year 365.25 days

Endometrial safety

The primary endpoint was the post-treatment incidence of endometrial hyperplasia/cancer assessed by pre- and post-treatment endometrial biopsies. In accordance with the CPMP Guideline 'Points to Consider on Hormone Replacement Therapy' 1997, biopsies were evaluated by two independent pathologists, with a third making the final decision in the case of disagreement. The histological definition of endometrial hyperplasia/cancer included simple and complex endometrial hyperplasia or atypical endometrial hyperplasia and endometrial carcinoma but excluded endometrial polyps and other malignancies.

Study 2015

In this one year study, the objectives were evaluation of the:

- frequency of endometrial hyperplasia
- effects on serum lipids and coagulation profiles

during treatment with Estragest TTS 25/125 compared to placebo.

228 postmenopausal women received Estragest TTS 25/125 (n=173) or placebo (n=55). Patches were applied twice weekly for the duration of the treatment period. More than 85% completed the study. The discontinuation rate was higher for Estragest TTS 25/125 (17.3%) compared to placebo (5.5%); this was predominantly due to AE-related discontinuations. There were no relevant differences between treatments in demography or baseline characteristics.

A total of 130 Estragest TTS 25/125 patients and 40 placebo patients had biopsies at baseline and after ≥ 24 weeks treatment. One Estragest patient was found to have endometrial hyperplasia and none on placebo. The upper limit of the one-sided 95% CI for the incidence of hyperplasia/endometrial cancer was 3.57% after one year of treatment.

Study 2015E (Extension to 2015)

This was a 48-week extension. Patients who had completed the core period of 2015 were eligible to enter the extension study. All, irrespective of their previous treatment, received Estragest TTS 25/125. Thus patients from the former Estragest TTS 25/125 group in the core (n=101) had a total treatment period of 24 cycles (96 weeks). Those from the placebo group (n=43) received Estragest TTS 25/125 for a total of 12 cycles. Endometrial biopsies were obtained at the final visit of the core study and at the final visit of the extension. Those who discontinued before completing 6 cycles in the extension phase did not have a biopsy at their final visit.

No cases of endometrial hyperplasia were found. The overall incidence of endometrial hyperplasia after a total of 2 years on Estragest TTS 25/125 was 0% with the upper limit of the one-sided 95% CI 3.68%.

Study DE01

Open-label study in 37 centres. 411 patients were treated for 12 cycles (48 weeks). Endometrial biopsies were obtained at baseline in all patients and in 379 patients at the final visit, but 65 of these produced insufficient tissue for analysis (usually

because of market endometrial atrophy). The results were corroborated by an Advisory Board including the specialists involved in the study, which made a post hoc blind evaluation of selected cases that required an additional post-treatment biopsy.

Combined results - discussion

In the endometrial safety population there were no cases of endometrial carcinoma. In the Estragest TTS 25/125 treated patients there were four cases of endometrial hyperplasia, corresponding to a rate of 0.833 cases per 100 patient years and an incidence of 0.985% with the upper limit of the one-sided 95% CI at 2.24%. No cases of endometrial hyperplasia were observed in the placebo group. Only one of the observed cases of endometrial hyperplasia in the Estragest TTS 25/125 group was atypical hyperplasia. The incidence of endometrial hyperplasia is both sufficiently small, and has been estimated with sufficient precision, to meet the requirements of the CPMP Points to consider on hormone replacement therapy (CPMP 1997).

There were three cases of endometrial hyperplasia in the endometrial safety population (two simple, one complex) giving a point estimate for hyperplasia of 1.08% (upper limit of the one-sided 95% CI 2.78%). This met the requirements of the CPMP Guideline, i.e. a point estimate of ≤ 2% with the upper limit of the one-sided 95% CI not exceeding the point estimate by more than 2%.

There was one case of possible endometrial cancer in a patient receiving Estragest TTS 25/125 but it was unclear whether the tumour had arisen from the body of the uterus or cervix, which was also involved. This occurred in a patient in study PCC4 who, having had no baseline biopsy, was unsuitable for inclusion in the endometrial safety population.

In consideration of the results of the studies and the analysis of the data, the endometrial safety of Estragest TTS 25/125 has been established.

Table 10: Incidence of endometrial hyperplasia –Pooled data – Acceptable for Endometrial Safety Population

Incidence	**Estragest 25/125**	
CI	**25/125**	**Placebo**
One year data (DEO1 + 2015)		
No of patients	406	33
Endometrial hyperplasia n (%)	4 (0.985)	0(0.000)
One-sided 95% CI, upper limit	2.24%	8.678%
Inclusion of 2015E		
No of patients	444	33
Patient years observed (1 year=12 cycles of 28 days)	521.8	32.8
Endometrial hyperplasia/cancer per patient year (rate)	(0.767)	(0.000)
Patient years observed (1 year=365days)	480.3	30.2
Endometrial hyperplasia/cancer per patient year (rate)	(0.833)	(0.000)
One-sided 95% CI, upper limit	1.906	9.929

Studies DE01, 2015, 2015E

1. *CIs were calculated as exact binomial CIs*
2. *Patients who were taking placebo in the core study 2015 and were later switched to Estragest for the extension study 2015E are counted under both treatments (their first year's data are in the placebo column and second year's data in the Estragest column*
3. *Observation time is taken as the time from the start of treatment until the final biopsy*
4. *CI calculated using Poisson distribution*

Adverse Events

Most AEs in the Estragest TTS 25/125 groups were rated mild to moderate, <10% were rated severe. The most frequently observed AEs by event and body system are shown in Tables 11 and 12. For the Estragest TTS 25/125 group the most common AEs were breast tenderness, headache and events related to the application. The overall rate of AEs in the Estragest TTS 25/125 population (excluding the open study DE01) was 442/615 (71.9%) which was comparable to that on placebo and the incidence of most individual events were also comparable with placebo; the exceptions being application site reactions (erythema, pruritus, irritation), breast pain and metrorrhagia. Given that the Estragest TTS 25/125 group involves a different delivery system from Estalis, the application site data are of limited relevance; however local reactions were less with Estragest TTS 25/125 than with the active comparators. Estragest TTS 25/125 was generally better tolerated than the active comparators.

Individual study data were generally similar across studies and similar to the pooled data for the most frequently observed AEs. However, the frequency of AEs in DE01, the open, non-comparator study, was lower than for other studies (50.9% had ≥ one AE in DE01 compared with 66.5%-83.8% for the Estragest TTS 25/125 groups in other studies).

Table 11: Number of patients with most frequent AEs (≥ 5% in any group) – main safety population

Duration of Treatment	Estragest TTS 25/125 n (%)	Estragest TTS 50/250 n (%)	Kliogest n (%)	Estracombi TTS n (%)	Placebo n (%)
Patients studied • **Total no studied** • **Total no with AE**	1026 640 (62.4)	312 243 (77.9)	144 108 (75.0)	165 121 (73.3)	186 129 (69.4)
AEs					
Breast tenderness	176 (17.2)	101 (32.4)	66 (45.8)	47 (28.5)	33 (17.7)
Headache	70 (6.8)	20 (6.4)	15 (10.4)	9 (5.6)	25 (13.4)
Application site erythema	56 (5.5)	66 (21.2)	0 (0.0)	36 (21.8)	0 (0.0)
Application site pruritus	48 (4.7)	69 (22.1)	0 (0.0)	33 (20.0)	0 (0.0)
Nasopharyngitis	32 (3.1)	6 (1.90	3 (2.1)	0 (0.0)	12 (6.5)
Application site irritation	27 (2.6)	36 (11.5)	0 (0.0)	26 (15.8)	0 (0.0)
Arthralgia	26 (	209 (67.6)	103 (74.1)	125 (76.7)	27 (14.7)
Back pain	25 (2.4)	8 (2.6)	8 (5.6)	1 (0.6)	10 (5.4)
Influenza	22 (2.1)	8 (2.6)	6 (4.2)	3 (1.8)	13 (7.0)
Breast pain	15 (1.5)	21 (6.7)	6 (4.2)	19 (11.5)	1 90.5)
Metrorrhagia	12 (1.2)	23 (7.4)	9 (6.3)	3 (1.8)	0 (0.0)
Postmenopausal haemorrhage	7 (0.7)	17 (5.4)	0 (0.0)	13 (7.9)	0 (0.0)

Studies DE01, PCC3, PCC4, 2008, 2007, 2015, 2015E (patients on Estragest TTS in core only)
Estracombi TTS 50/250 (sequential 50μg E2 then 50 μgE2 + 250 μg NETA per day

Table 12: Adverse events occurring with a frequency of ≥ 5% in any group.

	Estragest TTS 25/125 n (%)	Estragest TTS 50/250 n (%)	Kliogest n (%)	Estracombi TTS n (%)	Placebo n (%)
Patients studied					
Total # studied	1026	312	144	165	186
Total # with an AE	640 (62.4)	243 (77.9)	108 (75.0)	121 (73.3)	129 (69.4)
Body System (MedDRA)					
Reproductive System and breast disorders	280 (27.3)	153 (49.0)	79 (54.9)	83 (50.3)	45 (24.2)
General disorders and administration site conditions	132 (12.9)	131 (42.0)	6 (4.2)	71 (43.0)	9 (4.8)
Gastrointestinal disorders	112 (10.9)	29 (9.3)	23 (16.0)	13 (7.9)	30 (16.1)
Infections and infestations	109 (10.6)	29 (9.3)	21 (14.6)	12 (7.3)	33 (17.7)
Nervous system disorders	109 910.6)	34 (10.9)	22 (15.3)	14 (8.5)	33 (17.7)
Musculoskeletal and connective tissue disorders	101 (9.8)	21 (6.7)	14 (9.7)	9 95.5)	39 (21.0)
Skin and subcutaneous tissue disorders	85 (8.3)	20 (6.4)	7 (4.9)	4 (2.4)	20 (10.8)
Respiratory, thoracic and mediastinal disorders	64 (6.2)	22 (7.1)	5 (3.5)	7 (4.2)	21 (11.3)
Psychiatric disorders	61 (5.9)	19 (6.1)	9 (6.3)	10 (6.1)	18 (9.7)
Vascular disorders	45 (4.4)	12 (3.8)	4 (2.8)	9 (5.5)	11 (5.9)

Among the less frequent AEs there were no major differences between Estragest and placebo. Vaginal bleeding was slightly more common with Estragest TTS 25/125 than placebo (1.4% vs. 0.5%, respectively). The occurrence of uterine polyps were also more common (1.2%) with Estragest TTS 25/125 than with placebo (0.5%) but there was no relationship to Estragest dose (0.3% in the Estragest 50/250 group). Endometrial hypertrophy was more frequent in the Estragest TTS 25/125 group (1.1%) than in the Estragest 50/250 or placebo groups (0% in both). Hypertension was also more common in the Estragest TTS 25/125 group compared with placebo (1.7% and 0.5%, respectively). The placebo group was considerably smaller than the Estragest TTS 25/125 group and this makes comparison of the frequency of the rarer events difficult.

The more frequent AEs according to body system in study 2015E are shown in Table 13. All patients received Estragest TTS 25/125 during the extension study. The overall incidence of AEs and the incidence of AEs affecting most body systems were similar in patients who had previously received placebo and in those who had been treated with Estragest TTS 25/125. Infection and infestations, and nervous system disorders were more common in former Estragest TTS 25/125 patients, whereas psychiatric disorders, skin and subcutaneous disorders and vascular disorders were more common in the former placebo group. Among individual AEs, headache was more common in former Estragest TTS 25/125 patients and back pain and vaginal discharge were more common in the former placebo group. However there were no major differences in the pattern of AEs seen in the different groups.

Table 13: Study 2015E AEs by body system occurring in ≥ 5% of patients

Patients studied	Estragest TTS 25/125 in core n (%)	Placebo in core n (%)
Total # studied	101	43
Total # with an AE	43 (42.6)	20 (46.5)
Body system (MedDRA) & AE		
Reproductive system and breast disorders	21 (20.8)	8 (18.6)
Breast tenderness	15 (14.9)	5 (11.6)
Nervous system disorders	8 (7.9)	1 (2.3)
Headache	6 (5.9)	1 (2.3)
Infections and infestations	8 (7.9)	1 (2.3)
Musculoskeletal and connective tissue disorders	7 (6.9)	3 97.0)
Skin and subcutaneous tissue disorders	4 (4.0)	3 (7.0)
Vascular disorders	3 (3.0)	4 (9.3)
Psychiatric disorders	2 (2.0)	4 (9.3)

Apart from application site reactions, drug-related events were no more frequent in the former Estragest group compared to the former placebo group. Overall, the frequency of drug-related events especially affecting the reproductive system and breast was higher for the active comparators than for Estragest 25/125.

Serious Adverse Events (SAEs) and Deaths

There were no deaths. The overall incidence of SAEs was highest in the Kliogest group (7% of patients). The Estragest TTS 25/125 group had a similar incidence (3%) to placebo (4%). The small number of SAEs reported and the disparity in size between the different treatment groups did not permit assessment of the possible relationship between SAEs and dose/duration of treatment.

There were six reports of breast cancer in the Estragest TTS 25/125 safety population. In addition, two cases of benign breast disease, considered to be SAEs were reported in the Estragest TTS 25/125 group – one case of fibroadenoma and one other benign tumour. One patient in the Estragest TTS 25/125 group in study 2008 had cervical carcinoma *in situ*; this was considered to be unrelated to treatment.

Assessor's comment:

Rare serious events known or suspected to be related to this class of drug include breast cancer, myocardial infarction and venous thromboembolism. From a database of 1000+ patients (almost 1000 patient years' exposure) the safety data have revealed some six cases of breast cancer – in four, the investigator causality assessment was "possibly related" to treatment; in the remaining cases there was evidence of pre-existing abnormality on mammography. The Estragest group had a much greater total exposure, (almost 1000 patient years), compared with the other treatment groups (118-239 patient years). Given the known background incidence of breast cancer in this age group, the incidence of breast carcinoma possibly related to treatment for Estragest TTS 25/125 can be considered to be consistent with the risk data given in the SmPC.

Discontinuation due to AEs/SAEs

The rate of AE-related discontinuation in the Estragest TTS 25/125 group was slightly higher than that in the placebo group, but considerably lower than that in the other active treatment groups. The main differences between Estragest TTS 25/125 and placebo groups were the rates of discontinuation due to application site reactions and

metrorrhagia. The rate of discontinuation due to AEs affecting the nervous system was higher in the placebo group than the Estragest TTS 25/125 group.

Discontinuation due to SAEs was rare – but most commonly seen in the Kliogest group. No relationship with Estragest dose was apparent.

Local Tolerability and Patch Adhesion

As Estragest TTS 25/125 uses a different transdermal delivery system to Estalis (reservoir compared to a matrix) tolerability data cannot be extrapolated. Skin tolerability and patch adhesion data for Estalis 50/250 have been provided as it is made from the same laminate, with identical composition and hormone concentration as Estalis 25/125. Although there was some variation between studies, tolerability was generally good with 22% of patients, overall, reporting application site reactions, the most frequent being erythema. Apart from scaling/glazing (5.3%), other local reactions were reported in <5% of patients.

In the main study population, application site reactions appeared to show a relationship with dose, being much more common with Estragest 50/250 than with Estragest TTS 25/125. It is possible, therefore, that the Estalis 25/125 patch would be better tolerated than the larger, higher-strength, Estalis patch.

The bioequivalence study (2302) provided a direct comparison between Estalis 25/125 and Estragest TTS 25/125. The Draize 5 point erythema scale and an assessment of skin irritation was made immediately after application, at 30 minutes, then at one hour after removal of each patch. A lower frequency and severity of local skin reactions was seen with Estalis 25/125 compared to Estragest TTS 25/125 – with more intense local erythema and more itching, oedema, scaling and appearance of papules and vesicles with Estragest.

Patch adhesion for the Estalis 50/140 patch was assessed at each visit in three studies. The 50/140 patch rather than the 50/250 patch was assessed because the former is closer in size to the Estalis 25/125 patch and the results are therefore more relevant. Patch adhesion was generally very good with almost 90% of patients having more than 90% adhesion. Less than 5% had less than 75% adhesion. A direct comparison between Estalis 25/125 and Estragest TTS 25/125 was made in the bioequivalence study (2302) at the end of each individual patch wear period at 84, 168 and 252 hours in each treatment period. Estalis 25/125 showed superior adhesion; 16/188 (8.5%) required the use of adhesive tape compared with 58/192 (30%) for Estragest.

Vaginal Bleeding

The Estragest TTS 25/125 group had the lowest number of bleeding days and the highest level of amenorrhoea of any of the active treatments. In all active groups the occurrence of bleeding became less with time. Although bleeding-related AEs were more frequent in Estragest TTS 25/125 compared with placebo, they were less frequent than with the active comparators, particularly metrorrhagia, post-menopausal bleeding and, to a lesser extent, dysmenorrhoea.

Laboratory Data including lipids, coagulation parameters and glucose homeostasis

In accordance with the guideline "Points to consider on hormone replacement therapy" (CPMP 1997), data regarding effects on lipid profiles, coagulation profiles and glucose homeostasis were obtained (studies 2007 and 2015). Clinical chemistry was also monitored. These data have revealed no new safety concerns. In relation to lipids, Estragest TTS 25/125 had, if anything, a favourable effect in that total and LDL cholesterol concentrations became statistically and clinically significantly lower in the Estragest TTS 25/125 groups, in both studies, compared with placebo after 24 and 48 weeks of treatment. In study 2007, statistically significant differences between Estragest TTS 25/125 and placebo were also seen for triglycerides, HDL cholesterol and HDL3 cholesterol. There were no significant differences between groups in terms of fibrinogen, plasminogen activity and platelet counts. However, Factor VII levels and antithrombin III activity was statistically lower in the Estragest TTS 25/125 group in 2007. Glucose homeostasis was unaffected.

Vital signs and other findings

Blood pressure and body weight were determined at screening and at each visit in all studies and no relevant changes were observed.

Post marketing experience

Estragest TTS is currently approved in 28 countries worldwide and total exposure from June 30th 1998 to March 15th 2003 was 529,079 patient-years. No new safety findings have been identified from periodic safety update reports.

Published Data

These have been reviewed in the clinical expert report and no new issue has been highlighted.

Assessor's overall conclusions on clinical safety

The safety profile of Estragest TTS 25/125 is acceptable. The AE profile was generally comparable with placebo. As would be expected for this class of product, breast tenderness was the most common AE but occurred with similar frequency in the Estragest TTS 25/125 and placebo groups though it was more frequent in the active comparator groups. AEs which were more common with Estragest TTS 25/125 compared to placebo were breast pain, metrorrhagia and vaginal bleeding but they occurred in <2% of the Estragest TTS 25/125 population. The higher dose Estragest TTS 50/250 comparator was associated with a generally higher frequency of these events, indicating a relationship to dose and discontinuations due to AEs were more common in the latter. No new concerns have arisen from the adverse events/serious adverse events reported. No concerns regarding laboratory parameters have arisen. Given the bioequivalence of Estalis 25/125 compared to Estragest TTS 25/125, a similar safety profile is to be expected, though there are data to suggest that local tolerability and skin adhesion may be superior with Estalis. Aside from publicised concerns regarding HRT, which are addressed satisfactorily in the product literature wording, no new safety concerns have arisen.

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

The bioequivalence study comparing Estalis 25/125 to Estragest 25/125 was of an appropriate design and bioequivalence of the test and reference products was accepted. In view of the demonstrated bioequivalence, efficacy and safety data from Estragest 25/125 was extrapolated to Estalis 25/125. It is considered that the proposed licence for postmenopausal symptoms should be granted. There are no new safety concerns with Estalis 25/125 and the safety profile and tolerability is 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 25/125 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 ® 25/125 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 ® 25/125.

EFFICACY

Bioequivalence has been accepted between the applicant's Estalis ® 25/125 and the reference product, Estragest ® 25/125 (Novartis). The demonstration of bioequivalence allows extrapolation of efficacy and safety data from Estragest ® 25/125 to Estalis ® 25/125. These data support the efficacy of ® Estalis 25/125 in the indication of HRT for estrogen deficiency symptoms in non-hysterectomised postmenopausal women.

No new or unexpected safety concerns arise from this application.

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 ® 25/125
(estradiol hemihydrate, norethisterone acetate)

PL 00101/0689

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 ® 25/125 is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Estalis, 25/125

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One 8 cm^2 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.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

Translucent 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 25/125 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 25/125 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 25/125 directly.

Women currently using cyclic or sequential oestrogen/progestogen therapy should complete the on-going treatment cycle before treatment with Estalis 25/125 is initiated. The appropriate time to begin treatment with Estalis 25/125 would be the first day of a withdrawal bleeding or seven days after finishing the previous treatment cycle.

Estalis regimen

Estalis 25/125 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 25/125 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 25/125 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 25/125 should not be used in children.

4.3 CONTRAINDICATIONS

Estalis 25/125 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 25/125

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 25/125:

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 orthopaedic 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 25/125 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 25/125 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 25/125 is not indicated during pregnancy. If pregnancy occurs during medication with Estalis 25/125 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 25/125 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 25/125 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 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 25/125 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 25/125 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 25/125 packs contain 2, 8 or 24 transdermal patches.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Estalis 25/125 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 25/125. 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 25/125 transdermal patch should be folded (adhesive surfaces pressed together) and discarded.

7 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley
Camberley
Surrey
GU16 7SR

8 MARKETING AUTHORISATION NUMBER(S)

PL 00101/0689

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/04/2007

10 DATE OF REVISION OF THE TEXT

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

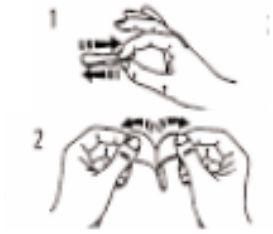
The recommended are area of skin is the abdomen. Avoid the waistline since tight clothing may rub the system off. The skin should not be inflamed, broken or irritated. To help the patch stick, the skin should be clean, non-hairy, dry, and free of creams, lotions, oil, or powder. You should use a different 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.

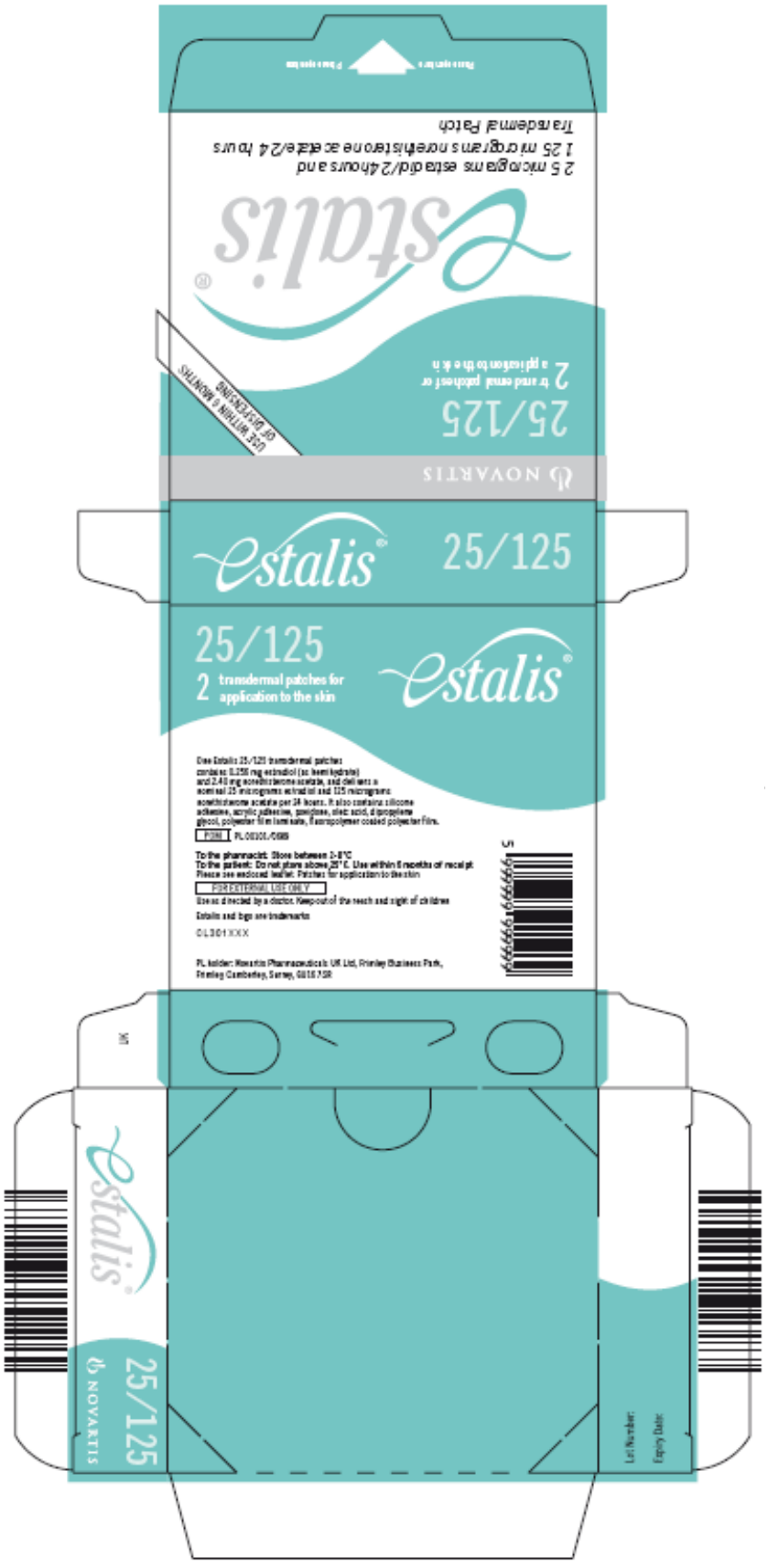
The information in this leaflet applies only to Estalis. If you have any questions or are not sure about anything, ask your doctor or pharmacist.

Date: 18th April 2006

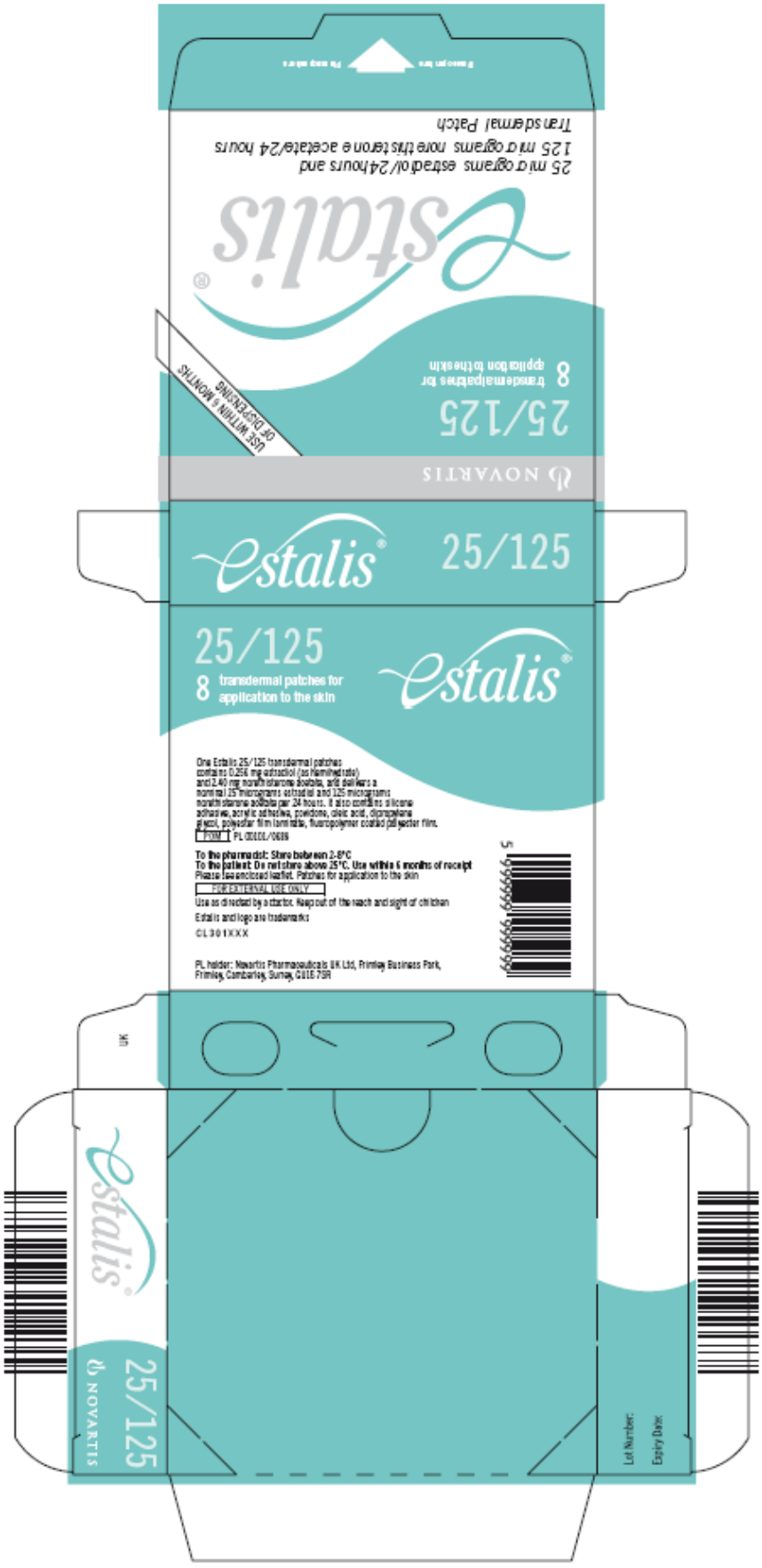
XXXXXX.XX

LABELLING

Carton – pack size 2



Carton – pack size 8



Carton – pack size 24