PRODUCT MONOGRAPH

PrESTALIS®140/50

(Norethindrone Acetate and Estradiol-17ß)
140/50 µg/day

PrESTALIS®250/50

(Norethindrone Acetate and Estradiol-17ß)
250/50 µg/day

Transdermal Therapeutic System

Progestin-Estrogen

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.,
Dorval, Quebec H9S 1A9

Date of Revision:
August 18, 2017

Control # 201794

Table of Contents

[Pr]ESTALIS® 140/50 µg
(Norethindrone Acetate and Estradiol-17ß)
140/50 µg/day
[Pr]ESTALIS® 250/50 µg
(Norethindrone Acetate and Estradiol-17ß)
250/50 µg/day

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Patch 140/50 µg/day and 250/50 µg/day	The other substances are silicone (BIO PSA® X7-4603), acrylic (Gelva® 737)-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

INDICATIONS AND CLINICAL USE.

ESTALIS® (NETA/estradiol-17ß) is indicated for:

- the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states e.g. hot flushes, sleep disturbances and vulvar and vaginal atrophy.

The above indication is only for women with intact uteri since the regimen includes a progestin whose role is to prevent endometrial hyperplasia/carcinoma.

Geriatrics (> 65 years of age):
No clinical studies were conducted to evaluate the effect of ESTALIS on women more than 65 years old.

Pediatrics:
ESTALIS is not indicated for use in children

CONTRAINDICATIONS

- Known or suspected hypersensitivity to this drug or to any ingredient in the formulation or to any component of the patch. For a complete listing, see Dosage Forms, Composition and Packaging section.
- Known or suspected estrogen-dependent or progestin-dependent malignant neoplasia such as

endometrial cancer.
- Endometrial hyperplasia
- Known, suspected or past history of breast cancer
- Known or suspected pregnancy
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis
- Known thrombophilic disorders
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Undiagnosed abnormal genital bleeding
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease)
- Porphyria
- Partial or complete loss of vision from ophthalmic vascular disease
- Classical Migraine
- Breast feeding

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years. [55, 10, 49]

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary emboli* and *deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo. [55]

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo. [49]

Therefore, the following should be given serious consideration at the time of prescribing:
- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the approved indication.

Carcinogenesis and Mutagenesis

Breast Cancer

Available epidemiological data indicate that the use of combined *estrogen plus progestin* by postmenopausal women is associated with an increased risk of invasive breast cancer.
In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).[55]

The WHI study also reported that the invasive breast cancers diagnosed in the *estrogen plus progestin* group were similar in histology but were larger (mean (SD), 1.7 cm (1.1) vs. 1.5 cm (0.9), respectively; P=0.04) and were at a more advanced stage compared with those diagnosed in the placebo group. The percentage of women with abnormal mammograms (recommendations for short-interval follow-up, a suspicious abnormality, or highly suggestive of malignancy) was significantly higher in the *estrogen plus progestin* group versus the placebo group. This difference appeared at year one and persisted in each year thereafter.[10]

In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo.[49]

It is recommended that estrogens with or without progestins not be given to women with existing breast cancer or those with a previous history of the disease. (see CONTRAINDICATIONS)

There is a need for caution in prescribing estrogens with or without progestins for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (breast nodules, fibrocystic disease of the breast, abnormal mammograms and/or atypical hyperplasia at breast biopsy).

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients. It is important that the modest increased risk of being diagnosed with breast cancer after 4 years of treatment with combined estrogen plus progestin HRT (as reported in the results of WHI-trial) be discussed with the patient and weighed against its known benefits.

Instructions for regular self-examination of the breasts should be included in this counselling.

Endometrial Hyperplasia & Endometrial Carcinoma
Estrogen should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

The risk of endometrial hyperplasia/carcinoma in users of unopposed estrogens who have intact uteri is greater than in non-users and appears to depend on the duration of treatment and the estrogen dose. The greatest risk appears to be associated with prolonged use. It has been shown that adequate concomitant progestogen therapy lowers the incidence of endometrial hyperplasia and therefore the potential risk of endometrial carcinoma associated with prolonged use of estrogen therapy (see ACTION & CLINICAL PHARMACOLOGY-Coadministration Of Progestins).

Ovarian Cancer
Some recent epidemiologic studies have found that the use of hormone replacement therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer. Epidemiologic evidence from a meta-analysis suggests that while the risk of ovarian cancer diminishes over time after discontinuation, the risk is still significantly increased more than five years (median time of 10 years since last use) after stopping long duration hormone therapy (median duration of treatment of nine years) for serous or endometrioid tumours.

Hepatocellular Carcinomas
Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The causal relationship of this malignancy to these drugs is not known.

Cardiovascular

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women. [55, 28, 26] The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women. [55, 49]

WHI trial findings
In the combined *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:
• 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
• 7 more cases of CHD (37 on combined HRT versus 30 on placebo). [55]

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:
• 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
• no statistically significant difference in the rate of CHD. [49]

HERS and HERS II findings
In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years. [28]

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS, known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD. [26]

Blood pressure
Women using hormone replacement therapy sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

Ear/Nose/Throat

Otosclerosis
Estrogens should be used with caution in patients with otosclerosis.

Endocrine and Metabolism

Glucose and lipid metabolism
A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and post-menopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Women with familial hypertriglyceridemia need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Calcium and phosphorus metabolism
Because the prolonged use of estrogens with or without progestins influences the metabolism of calcium and phosphorus, estrogens with or without progestins should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia, and in patients with renal insufficiency.

Hypothyroidism
Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to ensure that thyroid hormone levels remain in an acceptable range. (see **Drug-Laboratory Test Interactions**)

Genitourinary

Vaginal bleeding
Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Uterine leiomyomata
Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Endometriosis
Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

Hematologic

Venous Thromboembolism
Available epidemiological data indicate that the use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the estrogen plus progestin arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.[55]

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism. [49]

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

A history of recurrent spontaneous abortions should be investigated to exclude thrombophilic predisposition. In patients in whom thrombophilia is confirmed, the use of ESTALIS is viewed as contraindicated.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery, or trauma in women on HRT, attention should be given to prophylactic measures to prevent VTE

following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately given the risks of long-term disability or fatality.

If feasible, estrogens with or without progestins should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. The treatment should not be restarted until the woman is completely mobile.

Hepatic/ Biliary/ Pancreatic

Benign Hepatic Adenomas
Benign hepatic adenomas have been associated with the use of combined estrogen and progestin oral contraceptives. Although benign and rare, these tumours may rupture and cause death from intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestin preparations, but they should be considered if abdominal pain and tenderness, abdominal mass, or hypovolemic shock occurs in patients receiving estrogen.

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

Hepatic hemangiomas
Particular caution is indicated in women with hepatic hemangiomas, as estrogen may cause an exacerbation of this condition.

Jaundice
Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

Liver function tests
Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see the section under **Monitoring and Laboratory Tests**.

Immune

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

Severe anaphylactic/anaphylactoid reactions

Cases of anaphylactic/anaphylactoid reactions, which developed anytime during the course of estradiol treatment and required emergency medical management, have been reported in the post marketing setting. Involvement of skin (hives, pruritus, swollen lips-tongue-face) and either respiratory tract (respiratory compromise) or gastrointestinal tract (abdominal pain, vomiting) has been noted.

Systemic lupus erythematosus
Particular caution is indicated in women with systemic lupus erythematosus.

Neurologic

Cerebrovascular insufficiency
Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication.

Dementia
Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women age 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical sub-study of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline. [42, 43]

In the *estrogen plus progestin* arm of the WHIMS (n=4532), women with intact uteri were treated with daily 0.625 mg conjugated equine estrogens (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) or placebo for an average of 4.05 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 23 more cases of probable dementia (45 on combined HRT versus 22 on placebo). [42]

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance. [43]

When data from the *estrogen plus progestin* arm of the WHIMS and the *estrogen alone* arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo). [43]

For transdermal estrogen-only or estrogen-progestogen combined products, no large randomized clinical trials have assessed the HRT-associated risk of probable dementia to date. Therefore, there are no data to support the conclusion that the frequency of probable dementia is different

with ESTALIS.

Epilepsy
Particular caution is indicated in women with epilepsy, as estrogen, with or without progestins, may cause an exacerbation of this condition.

Renal

Fluid retention
Estrogens with or without progestins may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

Skin

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

Special Populations

Pregnant women: ESTALIS must not be used during pregnancy. Both estrogens and progestogens may cause foetal harm when administered to a pregnant woman (see CONTRAINDICATIONS).

Nursing women: ESTALIS must not be used while breastfeeding (see CONTRAINDICATIONS).

Pediatrics: ESTALIS is not indicated for use in children.

Geriatrics (> 65 years of age): No clinical studies were conducted to evaluate the effect of estradiol on women more than 65 years old.

Monitoring and Laboratory Tests

Before ESTALIS (norethindrone acetate (NETA)/estradiol-17ß) is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by

the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

Women should be advised that changes in their breasts should be reported to their doctor or nurse.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

See WARNINGS AND PRECAUTIONS regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combinations in general.

Blood and lymphatic system disorders
Altered coagulation tests (see DRUG INTERACTIONS **- Drug-Laboratory Tests Interactions**)

Cardiac disorders
Palpitations; increase in blood pressure (see WARNINGS AND PRECAUTIONS). Coronary thrombosis.

Endocrine disorders
Increased blood sugar levels; decreased glucose tolerance.

Eye disorders
Neuro-ocular lesions (e.g., retinal thrombosis, optic neuritis), visual disturbances; steepening of the corneal curvature; intolerance to contact lenses (dry eyes, tear film composition changes).

Gastrointestinal disorders
Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).

General disorders and administration site conditions
Fatigue; changes in appetite; changes in body weight; change in libido.

Hepatobiliary disorders
Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

Musculoskeletal and connective tissue disorders
Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

Nervous system disorders
Aggravation of migraine episodes; headaches; dizziness; neuritis.

Psychiatric disorders
Mental depression; nervousness; irritability.

Renal and urinary disorders
Cystitis; dysuria; sodium retention; edema.

Reproductive system and breast disorders
Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia, endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

Skin and subcutaneous tissue disorders
Loss of scalp hair; chloasma or melasma, which may persist when drug is discontinued; erythema nodosum; erythema multiforme; hemorrhagic skin eruptions; hirsutism, acne.

Vascular disorders
Isolated cases of thrombophlebitis; thromboembolic disorders.

Overview of Adverse Drug Reactions with ESTALIS®
This section summarizes adverse drug reaction data pooled from multiple sources including clinical trials, published investigations and post-marketing experience.

The most commonly reported adverse reaction to ESTALIS (NETA/estradiol-17ß) in clinical trials was erythema at the application site. Less than 1% of patients treated sequentially and about 5% of patients treated continuously discontinued therapy due to an application site reaction.

The data on adverse events from 5 pooled clinical trials are included. 3 clinical trials had a 2 years duration and 2 had a 1 year duration. A total safety population of 941 patients on HRT and 207 patients on placebo was identified.

Frequency estimate: very common ≥10%, common ≥ 1% to < 10%; uncommon ≥ 0.1% to < 1%; rare ≥ 0.01% to < 0.1%; very rare < 0.01%; with unknown frequency.

Table 1-Most Common Adverse Drug Reactions (≥1%)

Psychiatric disorders	
Common:	Depression, affect lability, insomnia, nervousness
Nervous system disorders	
Very common:	Headache
Common:	Dizziness
Gastrointestinal disorders	
Common:	Nausea, abdominal distension, abdominal pain, diarrhoea, dyspepsia
Skin and subcutaneous tissue disorders	
Common:	Acne, dry skin, pruritus, rash
Reproductive system and breast disorders	
Very common:	Breast pain, breast tenderness, dysmenorrhoea, menstrual disorder
Common:	Breast enlargement, endometrial hyperplasia, genital discharge, menorrhagia, uterine spasm, vaginal haemorrhage, vaginal infection
Musculoskeletal and connective tissue disorders	
Common:	Back pain, pain in extremity, pain
General disorders and administration site disorders	
Common:	Weight increased
General disorders and administration site disorders	
Very common:	Application site reaction†, asthenia
Common:	Oedema peripheral

(†) Application site reactions includes localized bleeding, bruising, burning, discomfort, dryness, eczema, edema, erythema, inflammation, irritation, pain, papules, paraesthesia, pruritus, rash, skin discolouration, skin pigmentation, swelling, urticaria, and vesicles.

Less Common Adverse Drug Reactions (<1%)

Gastrointestinal disorders
Uncommon: Vomiting
Hepatobiliary disorders:
Rare: Gallbladder disorder, cholelithiasis
Very rare: Jaundice cholestatic
Immune system disorders
Rare: Hypersensitivity
Investigations:
Uncommon: Transaminases increased, blood pressure increased
Neoplasms benign, malignant and unspecified (including cysts and polyps):
Uncommon: Breast cancer
Rare: Cervical polyps, uterine leiomyoma, Fallopian tube cysts
Nervous system disorders
Uncommon: Migraine
Rare: Paraesthesia
Psychiatric disorders
Rare: Libido increase or decrease
Skin and subcutaneous tissue disorders:
Uncommon: Skin discolouration

Vascular disorders:
Rare: Embolism Venous

Adverse Drug Reactions with unknown frequency

Skin and subcutaneous tissue disorders:

Not Known: Erythema nodosum, Erythema multiforme
Not Known: Hypersensitivity, including allergic contact dermatitis and isolated cases of anaphylactoid reactions (some of the patients had a history of previous allergy or allergic disorders)
Not Known: Reversible post-inflammatory pigmentation and precipitation or aggravation of porphyria cutanea tarda in predisposed individuals
Not Known*: Alopecia, chloasma, contact dermatitis

Vascular disorders

Not Known: varicose veins

Immune system disorders

Not known*: Anaphylactic reaction, anaphylactoid reaction

(*) Reported in post-marketing experience.

Abnormal Hematologic and Clinical Chemistry Findings

Table-2-Abnormal hematologic and clinical chemistry

Laboratory parameters	**Effect**
Antithrombin III	↓
Coagulation factors VII, VIII, IX, X	↑
Corticosteroid binding globulin (CBG)	CBG ↑ in serum ➔ increased circulating corticosteroids. free or biologically active hormone concentrations are unchanged
Fibrinogen and fibrinogen activity	↑ levels
Folate	↓ serum concentration
T_3	↓ Resin uptake , reflecting the elevated TBG
Free T_4	concentration unaltered
Glucose	impaired glucose tolerance
METOPIRONE test	Reduced response
Norepinephrine-induced platelet aggregability	↑
Prothrombin time and partial tromboplastin time	↑
Sex-hormone binding globulin (SHBG)	SHBG↑ in serum ➔ increased circulating sex steroids free or biologically active hormone concentrations are unchanged
Sulfobromophthalein	↑ retention
Triglyceride and Phospholipid	↑ serum concentration

Thyroxin-binding globulin (TBG)	↑ ➔ increased circulating total thyroid hormone (T_4) as measured by column or radioimmunoassay

If adverse symptoms persist, the prescription of HRT should be re-considered.

DRUG INTERACTIONS

Overview

- Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.
- Preparations inducing liver enzymes (e.g. barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.
- Estradiol is predominantly metabolized by CYP3A4; concomitant administration of inhibitors of CYP3A4 such as ketoconazole, erythromycin or ritonavir may therefore result in an increase of approximately 50% in estradiol exposure.

Drug-Drug Interactions

The following section contains information on drug interactions with ethinyl estradiol-containing products (specifically, oral contraceptives) that have been reported in the public literature. It is unknown whether such interactions occur with drug products containing other types of estrogens.

Table 3- Established or Potential Drug-Drug Interactions

Drug	Ref	Effect	Clinical Comment
Anticonvulsants (phenobarbital, phenytoin, carbamazepin)	T	↑ metabolism of ethinyl estradiol	↓ plasma concentration of estradiol
Acetaminophen	T	↑ AUC and/or plasma concentration of ethinyl estradiol ↓ plasma concentration of acetaminophen	Therapeutic monitoring is recommended
Acid ascorbic	T	↑ AUC and/or plasma concentration of ethinyl estradiol	Therapeutic monitoring is recommended
Aminoglutethimide with medroxyprogesterone acetate (MPA)	T	↓ bioavailability of MPA	Therapeutic monitoring is recommended

Atorvastatin	T	↑ AUC values for ethinyl estradiol by 20 %	Therapeutic monitoring is recommended
Clofibric acid		↑ clearance of clofibric acid	Therapeutic monitoring is recommended
Cyclosporin	T	↑ plasma concentration of cyclosporine.	Therapeutic monitoring is recommended
Morphine	T	↑ clearance of morphine	Therapeutic monitoring is recommended
Prednisolone	T	↑ plasma concentration of prednisolone	Therapeutic monitoring is recommended
Rifampicin[a]	T	↑ metabolism of ethinyl estradiol	↓ plasma concentration of estradiol
Salicylic acid	T	↑ clearance of salicylic acid	Therapeutic monitoring is recommended
Temazepam	T	↑ clearance of temazepam	Therapeutic monitoring is recommended
Theophylline	T	↑ plasma concentration of theophylline	Therapeutic monitoring is recommended
Troglitazone	T	↓ plasma concentrations of ethinyl estradiol by 30 %	Therapeutic monitoring is recommended

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

[a] Clinical pharmacokinetics studies have not demonstrated any consistent effect of antibiotics (other than rifampicin) on plasma concentrations of synthetic steroids.

Drug-Food Interactions

The interaction of ESTALIS with food has not been studied.

Drug-Herb Interactions

It was found that some herbal products (e.g., St. John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism, and therefore, alter the efficacy

and safety of estrogen/progestin products.

Physicians and other health care providers should be made aware of other non-prescription products concomitantly used by the patient, including herbal and natural products obtained from the widely spread health stores.

Drug-Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T_4) as measured by column or radioimmunoassay; T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered;
- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged;
- impaired glucose tolerance;
- increased serum triglyceride and phospholipid concentration.

(See also **table in Abnormal Hematological Clinical Chemistry Findings** section**)**

With ESTALIS, no effect on fibrinogen, antithrombin III, TBG, CBG or SHBG and decreases in serum triglycerides have been observed.

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks. The pathologist should be informed that the patient is receiving hormone replacement therapy (HRT) when relevant specimens are submitted.

Drug-Lifestyle Interactions:

Specific drug-lifestyle interaction studies have not been conducted with ESTALIS.
Acute alcohol ingestion during HRT may lead to elevations in circulating estradiol levels.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- For initiation and maintenance of treatment, the lowest effective dose should always be used.
- Hormone replacement therapy (HRT) involving either estrogen alone or estrogen-progestogen combined therapy should only be continued as long as the benefits outweigh the risks for the individual.
- ESTALIS is used as a continuous treatment (uninterrupted application twice weekly).
- In women who are not currently taking oral estrogens, treatment with ESTALIS (NETA/estradiol-17ß) can be initiated at once. In women who are currently taking

oral estrogen, treatment with ESTALIS can be initiated on reappearance of menopausal symptoms, following discontinuation of oral therapy.

Therapeutic Regimens: Combination progestin/estrogen regimens are indicated for women with intact uteri. Two ESTALIS (NETA/estradiol-17ß) patches are available: 140 µg norethindrone acetate with 50 µg estradiol per day (9 cm^2) and 250 µg norethindrone acetate with 50 µg estradiol per day (16 cm^2). For all regimens, the requirement for hormone replacement therapy for menopausal symptoms should be reassessed periodically. Attempts to taper or discontinue the medication should be made at 3- to 6-month intervals.

Recommended Dose and Dosage Adjustment

Continuous Combined Regimen*:*
ESTALIS 140/50 or ESTALIS 250/50 µg per day (16 cm^2) is worn continuously on the abdomen or buttocks. A new patch should be applied twice weekly during a 28-day cycle. Irregular uterine bleeding may occur particularly in the first 6 months, but generally decreases with time, and often to an amennorheic state.

If irregular uterine bleeding persists and uterine pathology has been ruled out by appropriate diagnostic measures, it may be more appropriate instead to prescribe ESTALIS using a sequential regimen.

Special population

Patients with renal and / or hepatic impairment

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

All estrogen preparations are contraindicated in the patients with severe hepatic impairment.

Pediatric population

ESTALIS is not indicated for use in children.

Missed Dose
Patients who miss applying a patch of ESTALIS 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 breakthrough bleeding and spotting.

Administration
Patch Application

The physician should discuss the most appropriate placement of the patch with the patient. Immediately after removal of a patch from the pouch and removal of one-half of the protective liner, the adhesive side of the ESTALIS patch should be placed on a clean, dry area of intact skin and peel off the remaining one-half of the protective liner. The area selected should not be oily, damaged or irritated, and not exposed to the sun. The site selected should also be one at which

little wrinkling of the skin occurs during movement of the body (buttocks and lower abdomen). The waistline should be avoided, since tight clothing may dislodge the patch. The patch should be pressed firmly in place with the palm of the hand for at least 10 seconds, making sure there is good contact, especially around the edges. In the event that a patch should fall off, it can be reapplied. If it fails to adhere then a new patch may be applied. In either case, the original treatment schedule should be continued. Patches should not be applied to the same skin site for at least one week.

ESTALIS must not be applied to the breasts to avoid potentially harmful effects on the breast tissue.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Center.

Symptoms of overdose

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Progestin (norethindrone acetate) overdosage has been characterized by depressed mood, tiredness, acne and hirsutism.

Treatment of overdose

Owing to the mode of administration (transdermal), plasma levels of estradiol-17ß or norethindrone acetate can be rapidly reduced by removal of the patch. Symptomatic treatment should be given.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ESTALIS (norethindrone acetate (NETA)/estradiol-17ß) is designed to provide continuous estrogen and progestin therapy, in a 28-day treatment cycle, for women with intact uteri.

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

In a pharmacokinetic study, it was shown that ESTALIS matrix transdermal delivery system achieves estradiol serum levels and estrone to estradiol ratios in the range of those observed in premenopausal women at the early (estradiol >147 pM/L (40 picogram/mL)) to mid-follicular

phase. These features are maintained for an entire 84 to 96 hour wear period. Multiple applications of ESTALIS (250/50 µg/day, 140/50 µg/day) matrix transdermal delivery system resulted in average estradiol serum concentrations at steady-state of 184 and 165 pM/L (50 and 45 picogram/mL), respectively. At the end of the application periods, the average estradiol serum concentrations were 136 and 99 pM/L (37 and 27 picogram/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 matrix transdermal delivery system is removed. After removal of the matrix transdermal delivery system, serum concentrations of estradiol return to untreated postmenopausal levels (<73 pM/L (20 picogram/mL)) within 4 - 8 hours.

In a pharmacokinetic study it was shown that multiple applications of ESTALIS (250/50 µg/day, 140/50 µg/day) matrix transdermal delivery systems resulted in average norethindrone serum concentrations at steady-state of 2815 and 1639 pM/L (840 and 489 picogram/mL), respectively. At the end of the application period, the average serum concentrations of norethindrone were 2299 and 1293 pM/L (686 and 386 picogram/mL), respectively. Serum norethindrone concentrations of ESTALIS increased linearly with increasing doses of NETA. The elimination half-life of norethindrone is reported to be 6 to 8 hours. After removal of the ESTALIS matrix transdermal delivery system, norethindrone serum concentrations diminish rapidly and are less than 168 pM/L (50 picogram/mL) within 48 hours.

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

Pharmacodynamics

Hormone Replacement Therapy

ESTALIS (NETA/estradiol-17ß) provides continuous, controlled transdermal delivery of estradiol-17ß such that estradiol-17ß levels as well as the E_2/E_1 ratio in postmenopausal women are restored to those seen in the early follicular phase of the premenopausal range (see **Pharmacokinetics**). ESTALIS thus alleviates the symptoms of estradiol-17ß deficiency in postmenopausal women.

Coadministration of Progestins

Estrogen replacement therapy should be supplemented by sequential progestin therapy only in women with intact uteri.

It is not possible to give accurate values for the relative clinical effectiveness of different progestins because careful comparisons are limited in number, and different responses have been used in the published studies. In various tests in women, the relative potencies of the progestins are not the same. Furthermore, some progestins possess more or less estrogenic and androgenic activities than do others.

In general, progestins have been administered sequentially for 10 to 14 days during each estrogen cycle. Published data suggest that 12 to 14 days of sequential progestin treatment during estrogen replacement therapy virtually eliminates the occurrence of endometrial hyperplasia, and thereby irregular bleeding and endometrial carcinoma, compared to estrogen

treatment alone. The progestin requirements may vary amongst patients

Pharmacokinetics

Estradiol-17β

Absorption and distribution: Metabolism and plasma levels of estradiol-17ß delivered transdermally are similar to those in premenopausal women. Estradiol-17β circulates in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Administration of ESTALIS every 3 to 4 days in postmenopausal women produces average steady-state estradiol serum concentrations of 165 to 184 pM/L (45 to 50 picogram/mL), which are equivalent to the normal ranges observed at early follicular phase in premenopausal women. These concentrations are achieved within 12 to 24 hours following ESTALIS application and are sustained for the entire patch wear period. Minimal fluctuations in serum estradiol concentrations are observed following ESTALIS application, indicating consistent hormone delivery over the application interval. Additionally, transdermal administration of estradiol is reported to produce mean serum concentrations of estradiol comparable to those produced by daily oral administration (oral dose about 20 times the daily transdermal dose).

Concentration data from Phase II and III studies indicate that the pharmacokinetics of estradiol did not change over time, suggesting no evidence of the accumulation of estradiol following extended patch wear period (up to 1 year).

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

Transdermally applied estradiol is metabolised in the same way as the endogenous hormone. Estradiol is metabolised to estrone, then later – primarily in the liver – to estriol, epiestriol and catechol estrogens, which are then conjugated to sulphates and glucuronides.

Excretion: Estradiol has a short elimination half-life of approximately 2 to 3 hours. Therefore, a rapid decline in serum levels is observed after the ESTALIS system is removed. Within 4 to 8 hours following ESTALIS removal, serum estradiol concentrations return to untreated, postmenopausal levels (<73 pM/L (20 picogram/mL)).

Norethindrone Acetate

Absorption and distribution: Progestins used in therapy are well-absorbed through the skin, mucous membranes, and gastrointestinal tract.

Norethindrone steady concentrations are attained within 24 hours of application of the ESTALIS transdermal delivery systems. Minimal fluctuations in serum norethindrone concentrations are

observed following ESTALIS treatment, indicating consistent hormone delivery over the application interval. Steady-state norethindrone concentrations are maintained throughout the application interval and are within a therapeutic range sufficient to prevent endometrial hyperstimulation. Serum concentrations of norethindrone increase linearly with increasing doses of norethindrone acetate.

Concentration data from Phase II and III studies indicate that the pharmacokinetics of norethindrone did not change over time, suggesting no evidence of the accumulation of norethindrone following extended patch wear period (up to 1 year).

Metabolism: In plasma, norethisterone is bound approximately 90% to SHBG and albumin.

Norethindrone acetate is hydrolyzed to the active moiety, norethindrone, in most tissues including skin and blood. Norethindrone is primarily metabolized in the liver, however, transdermal administration significantly decreases metabolism because hepatic first-pass uptake is avoided.

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

Excretion: The elimination half-life of norethindrone is reported to be 6 to 8 hours. Norethindrone serum concentrations diminish rapidly and are less than <168 pM/L (50 picogram/mL) within 48 hours after removal of the ESTALIS transdermal delivery system.

Special Populations and Conditions

Pediatrics: ESTALIS is not indicated for use in children

Geriatrics (> 65 years of age): No clinical studies were conducted to evaluate the effect of estradiol on women more than 65 years old.

Gender: ESTALIS should be used in women only

Estrogen pharmacology

Estradiol-17ß is the major estrogenic hormone secreted by the human ovary. Among numerous effects, estradiol-17ß is largely responsible for the development and maintenance of the female reproductive system and of secondary sexual characteristics. It promotes growth and development of the vagina, uterus, fallopian tubes, and breasts. Estradiol-17ß contributes to the shaping of the skeleton, to the maintenance of tone and elasticity of urogenital structures, to changes in the epiphyses of the long bones that allow for the pubertal growth spurt and its termination, to the growth of axillary and pubic hair, and to the pigmentation of the nipples and genitals. Estradiol-17ß also affects the release of pituitary gonadotropins.

After menopause, when the ovaries have ceased to function, only small amounts of estradiol-17ß are still produced, i.e., from the aromatization of androstenedione to estrone and to a lesser extent, testosterone to estradiol-17ß. Estrone is transformed to estradiol-17ß by the enzyme 17ß-hydroxysteroid-dehydrogenase. Both enzymes prevail in fat, liver and muscle tissue.

In premenopausal women, the ratio of estradiol-17ß (E_2) to estrone (E_1) (i.e., E_2/E_1 ratio) in the plasma is in the range of 0.5 to 2, depending on the phase of the menstrual cycle. The E_2/E_1 ratio for untreated postmenopausal women is below 0.5.

Loss of the ovarian estradiol-17ß production after menopause can result in the following: instability of thermoregulation causing hot flushes associated with sleep disturbance and excessive sweating; accelerated loss of bone matrix and mineral, resulting in osteoporosis; alterations in lipid metabolism; urogenital atrophy, causing dyspareunia and urinary incontinence.

The protection against endometrial hyperplasia in women with intact uteri is necessary during long-term therapy. Published data suggest that 12 to 14 days of sequential progestin treatment during estrogen replacement therapy reduces the occurrence of endometrial hyperplasia, and thereby irregular bleeding and endometrial carcinoma, compared to estrogen treatment alone.

Progestin pharmacology

Norethindrone acetate (NETA) is a potent progestin that essentially mimics the biological effects of progesterone. Tissue effects of NETA are dependent on prior estrogen stimulation, and NETA receptors have been identified in all tissues containing estrogen receptors **(see Estradiol-17ß above)**.

NETA induces protein synthesis and also reduces the number of estrogen and progestin receptors, thereby limiting excessive growth stimulation of target tissues by estrogen. 17-hydroxysteroid-dehydrogenase, which locally oxidizes estradiol-17ß to its weaker estrogenic metabolite estrone, is also induced by NETA.

One of the major targets of NETA is the uterus, where it induces secretory transformation of the estrogen-primed endometrium. Once transformation of the endometrium is completed, the estrogen-primed endometrium is shed resulting in a regular cyclical bleeding.

Progestin is combined to estrogen for protection against endometrial hyperplasia during long-term therapy of women with intact uteri.

STORAGE AND STABILITY

ESTALIS: Store between 2°C and 8°C prior to dispensing. Do not freeze.

After dispensing, the patches may be stored unrefrigerated at 20 to 25°C, in which case they should be used within 6 months or before the expiry date, whichever comes first. If the patches are stored in the refrigerator, in this case, they should be used before the expiry date and should be allowed to reach room temperature before application in order to ensure proper adhesion.

Do not store the patches in areas where extreme temperatures can occur. Each patch is individually sealed in a separate pouch. Do not store out of the pouch. Apply immediately upon removal from the protective pouch. Apply whole patches.

Keep out of the reach and sight of children and pets both before use and when disposing of used patches.

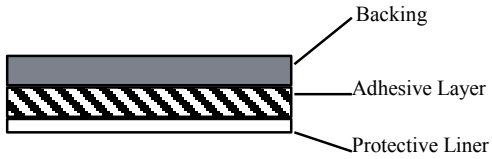
Do not use any ESTALIS pack that is damaged or shows signs of tampering

SPECIAL HANDLING INSTRUCTIONS

See DOSAGE AND ADMINISTRATION- Patch Application section.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ESTALIS is an alcohol-free, adhesive-based matrix transdermal patch comprising three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are: a backing, an adhesive layer, and a protective liner. The adhesive matrix containing 17β-estradiol and norethindrone acetate is applied to a polyester/ethylene vinyl acetate laminate film on one side and is protected on the other side by a transparent fluoropolymer coated release liner. The transparent release liner must be removed before the system can be used. Each patch is enclosed in a heat-sealed pouch.



ESTALIS 140/50 and 250/50 contain a fixed combination of norethindrone acetate (NETA) and estradiol-17ß. ESTALIS patches release controlled amounts of NETA and estradiol-17ß simultaneously through the skin for up to 4 days.

The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive; they are: a silicone (BIO PSA X7-4603) and acrylic (Gelva 737)-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

The ESTALIS (NETA/estradiol-17ß) package consists of the following systems:

	ESTALIS 140/ 50	ESTALIS 250/50
Estradiol-17ß Dosage Nominal *in vivo* delivery	50 µg/day	50 µg/day
NETA Dosage Nominal *in vivo* delivery	140 µg/day	250 µg/day
Total Estradiol-17ß Content	0.62 mg	0.51 mg
Total NETA Content	2.7 mg	4.8 mg
Drug-Releasing Area	9 cm^2	16 cm^2
Shape of patch	Round	Round
Presentation	Cartons of 8 patches	Cartons of 8 patches

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

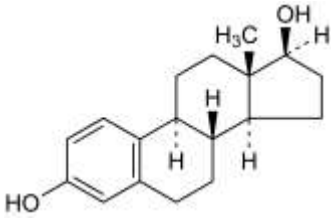
Estradiol USP (Estradiol-17β)

Proper name Estradiol hemihydrate
Chemical name estra-1,3,5 (10)-triene-3,17ß-diol

Molecular formula $C_{18}H_{24}O_2.½H_2O$

Molecular mass 281.4

Structural formula



Physicochemical properties White to creamy white, odorless, crystalline powder.
Solubilities: Practically insoluble in water; Soluble 1 in 28 of alcohol Soluble 1 in 17 of acetone

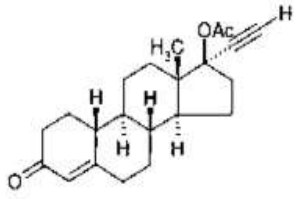
Norethindrone acetate USP:

Proper name Norethindrone acetate
Chemical name 17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate

Molecular formula $C_{22}H_{28}O_3$

Molecular mass 340.47

Structural formula



Physicochemical properties White to creamy white, odorless, crystalline powder.
Solubilities: Insoluble in water; Soluble 1 in 4 in acetone

CLINICAL TRIALS

Treatment of vasomotor symptoms

Study demographics and trial design

Efficacy and safety of ESTALIS in the relief of menopausal and postmenopausal symptoms have been studied in two 3-month multicenter, randomized, double-blind, placebo-controlled, parallel group studies.

Table 4- Summary of patient demographics for clinical trials in the treatment of vasomotor symptoms

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=446)
303 304	two 3-month multicenter, randomized, double-blind, placebo-controlled, parallel group studies.	In study 303: Patients received ESTALIS as a continuous regimen (50 µg/day estradiol in combination with either 140 or 250 µg/day norethindrone acetate), In study 304: Patients received ESTALIS in a sequential regimen (50 µg/day estradiol only (VIVELLE®) for the first 14 days of each 28-day cycle followed by 50 µg/day estradiol in combination with either 140 or 250 µg/day norethindrone acetate for the remaining 14 days of each 28-day cycle). Duration: Over 3 months (3 cycles of 28 days), the study systems were applied on the skin twice weekly.	446 non-hysterectomized healthy postmenopausal women with moderate-to-severe vasomotor symptoms (8 hot flushes/day of moderate-to-severe intensity with sweating)

Study results

In both studies 303 and 304, ESTALIS was better than placebo in reducing the number of hot flushes per day from baseline to endpoint ($p<0.001$), as well as reducing the intensity of hot flushes ($p<0.001$) and sweating ($p<0.001$). In studies 303 and 304 combined, the discontinuation rate was 8%. In the ESTALIS 140/50 and 250/50 groups, the discontinuation rate due to adverse events was 4.5% compared to 2% in the placebo group.

Protection against endometrial hyperplasia

Study demographics and trial design

Table 6- Summary of patient demographics for clinical trials in the protection against endometrial hyperplasia

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=955)
201 and 202	two phase II clinical trials, randomized, double-blind, multicenter,	955 women were treated with: • a continuous regimen of ESTALIS alone *(Continuous Combined* regimen) or, • a sequential regimen with an estradiol-only transdermal system (VIVELLE®) followed by an ESTALIS transdermal system (*Continuous Sequential* regimen) or, • continuous regimen with an estradiol-only transdermal system. Duration: 1year	955 postmenopausal women (with intact uteri)

Study results

ESTALIS was effective in reducing the incidence of estrogen-induced endometrial hyperplasia after 1 year of therapy in two Phase II clinical trials.

A regular and predictable bleeding pattern occurred in approximately two-thirds of women in each of the sequential regimen (ESTALIS + VIVELLE®) groups. By comparison, the estrogen-only group had an increasing incidence of unpredictable irregular bleeding and spotting which contributed to the higher dropout rate of 37% for this group.

DETAILED PHARMACOLOGY

See Action and Clinical Pharmacology (Part I)

TOXICOLOGY

There was no significant dermal irritation seen with ESTALIS. The effects observed in dermal toxicity studies in rats are expected effects of estradiol and norethindrone acetate in rodents. ESTALIS was negative in a contact sensitization study in guinea pigs, a phototoxicity study in rabbits, and a photoallergy study in guinea pigs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The toxicity profile of estradiol and norethisterone are well established in the literature. Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver. Long-term, continuous administration of norethisterone in certain animal species increases the frequency of tumours of the hypophysis and ovary in females, and of liver and breast in males

Norethindrone acetate was not mutagenic in a battery of *in vitro* or *in vivo* genetic toxicity assays.

REFERENCES

1. Armstrong BK. Oestrogen therapy after menopause-boon or bane? Med J 1988 Aug;148:213-4.

2. Balfour J, Heel R. Transdermal Estradiol: A Review of its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Efficacy in the Treatment of Menopausal Complaints. Drugs 1990;40:561-82.

3. Barret-Connor E. Risks and Benefits of Replacement Estrogen. Annu Rev Med 1992;43:240-2.

4. Beral V. Million W, Bull D, Green J, Reeves. G. Ovarian cancer and hormone replacement therapy in the Million Women Study. Lancet 2007;69(9574):1703-10.

5. Bergkvist L, Adami HO, Persson I, Hoover R, Schairer C. The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med 1989;321(5):293-297.

6. Brinton LA, Hoover RN, Fraument JF Jr. Menopausal estrogens and breast cancer risk: an expanded case-control study. Br J Cancer 1986;54:825-32.

7. Campos H, McNamara J, Wilson P, Ordovas JM, Schaefer EJ. Differences in Low Density Lipoprotein Subfractions and Apolipoproteins in Premenopausal and Postmenopausal Women. J Clin Endocrinol Metab 1988;67:30-5.

8. Cheang A, Sitruk-Ware R, Utian W. A Risk-Benefit Appraisal of Transdermal Estradiol Therapy. Drug Safety 1993;9:367-79.

9. Chetkowski RJ, Meldrum DR, Steingold KA, Randle D, Lu JK, Eggena P, et al. Biologic effects of transdermal estradiol. N Engl J Med 1986;314 (25):1615-20.

10. Chlebowski RT, Hendrix SL, Langer RD, Stefanick ML, Gass M, Lane D, et al. The Women's Health Initiative randomized trial. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women. JAMA 2003;289(24):3243-53.

11. Clisham P, et al. Bleeding patterns and endometrial histology (EH) with long-term transdermal estrogen therapy (TE). Fertil and Steril 1988; Suppl.:24f.

12. Colditz GA, Stampfer MJ, Willett WC, Hennekens CH, Rosner B, Speizer FE. Prospective study of estrogen replacement therapy and risk of breast cancer in postmenopausal women. JAMA 1990;264(20):2648-53.

13. Colditz GA, Hankinson SE, Hunter DJ, Willett WC, Manson JE, Stampfer MJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332(24):1589-93.

14. Colditz GA, Egan KM, Stampfer MJ. Hormone replacement therapy and risk of breast cancer: Results from epidemiologic studies. Am J Obstet Gynecol 1993;168:1473-80.

15. COLLABORATIVE GROUP on hormonal factors in breast cancer. Breast Cancer and Hormone Replacement Therapy. The Lancet 1997;350:1047-59.

16. Crook D, Cust MP, Gangar KF, Worthington M, Hillard TC, Stevenson JC, et al. Comparison of transdermal and oral estrogen-progestin therapy: Effects of serum lipids and lipoproteins. Am J Obstet Gynecol 1992;116:950-5.

17. Cust MP, Gangar KF, Hillard TC, Whitehead MI. A Risk-Benefit Assessment of Estrogen Therapy in Postmenopausal Women. Drug Safety, 1990;5:345-58.

18. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of Venous thromboembolism in users of hormone replacement therapy. Lancet 1996; 48:977-80.

19. Daly E, Vessey MP, Painter R. Case-control study of venous thromboembolism risk in users of hormone replacement therapy. Lancet 1996;348:1027-30.

20. Davis GF, and Winter L. Cumulative irritation study of placebo transdermal estrogen patches. Curr Ther Res 1987;42:719-21.

21. Dupont WD, Page DL. Menopausal estrogen replacement therapy and breast cancer. Arch Intern Med 1991;151:67-72.

22. Editorial Transdermal estrogen. Med Lett Drugs Ther 1985;27(699):119-20.

23. Gambrell RD. Update on hormone replacement therapy. Am Fam Phys 1992;46:87-96S.

24. Gambrell RD. Evidence supports estrogen-progestogen replacement therapy. Postgrad Med 1985;78(1):35-8.

25. Gambrell RD. Hormones in the etiology and prevention of breast and endometrial cancer. South Med J 1984;77(12):1509-15.

26. GradyD, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, et al for the HERS Research Group. Cardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/progestin replacement study follow-up (HERS II). JAMA 2002;288(1):49-57.

27. Grodstein F, Stampfer MJ, Goldhaber SZ, Manson JE, Colditz GA, Speizer FE, et al. Prospective study of exogenous hormones and risk of pulmonary embolism in women. Lancet 1996;348:983-7.

28. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of

estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998;280(7):605-13.

29. Hunt K, Vessey M, McPherson K. Long term surveillance of mortality and cancer incidence in women receiving hormone replacement therapy. Obstet Gynaecol 1987;94:620-35.

30. Jick H, Derby LE, Myers MW, Vasilakis C, Newton KM. Risk of hospital admission for idiopathic venous thromboembolism among users of postmenopausal oestrogens. Lancet 1996;348:981-3.

31. Kaufman DW, Miller DR, Rosenberg G L, Helmrich SP, Stolley P, Schottenfeld D, et al. Non-contraceptive estrogen use and the risk of breast cancer. JAMA 1984;252:63-7.

32. La Vecchia C, Decarli A, Parazzini F, Gentile A, Liberati C, Franceschi S. Non-contraceptive oestrogens and the risks of breast cancer in women. Int J Cancer 1986;38:853-8.

33. Laufer LR, DeFazio JL, Lu JK, Meldrum DR, Eggena P, Sambhi MP, et al. Estrogen replacement therapy by transdermal estradiol administration. Am J Obstet Gynecol 1983;146(5):533-40.

34. Lacey JV Jr, Brinton LA, Leitzmann MF, Mouw T, Hollenbeck A, Schatzkin A, et al. Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. J Natl Cancer Inst. 2006;98(19):1397-405.

35. Martindale: Drugdex evaluations. Estrogens, Mechanism of Action/Pharmacology. On line, June 22, 2006.

36. Matthews K, Meilahn E, Kuller L, Kelsey SF, Caggiula AW, Wing RR. Menopause and Risk Factors for Coronary Heart Disease. N Engl J Med 1989;321:641-6.

37. Padwick ML, Pryse-Davies J, Whitehead MI. A simple method for determining the optimal dosage of progestogen in postmenopausal women receiving estrogens. N Engl J Med 1986;315(15):930-4.

38. Palmer JR, RosenbergG L, Clarke EA, Miller DR, Shapiro S. Breast cancer risk after estrogen replacement therapy: Results from the Toronto breast cancer study. Am J Epidemiol 1991;134:1386-95.

39. Pérez Gutthann S, Garcia Rodrigues LA, Castellsague J, Duque Oliart A. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. Br Med J 1997;314:796-800.

40. Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17ß-estradiol: Comparison with

conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol 1985;152(8):1099-106.

41. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal Estrogen and Estrogen-Progestin Replacement Therapy and Breast Cancer Risk, JAMA 2000:283(4):485-91.

42. Shumaker SA, Legault, C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. The Women's Health Initiative Memory Study : A randomized controlled trial. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. JAMA 2003;289(20):2651-62.

43. Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. Women's Health Initiative Memory Study. JAMA 2004;291(24):2947-58.

44. Sillero-Arenas M, Delgado-Rodriguez M. Rodrigues-Canteras R, Bueno-Cavanillas A, Galvez-Vargas R. Menopausal hormone replacement therapy and breast cancer: A meta-analysis. Obstet Gynecol 1992;79:286-94.

45. Stanford JL, Weiss NS, Voigt LF, Daling JR, Habel LA, Rossing MA. Combined estrogen and progestin hormone replacement therapy in relation to risk of breast cancer in middle-aged women. JAMA 1995;274(2):137-42.

46. Steinberg KK, Thacker SB, Smith SJ, Stroup DF, Zack MM, Flanders WD, et al. A meta-analysis of the effect of estrogen replacement therapy on the risk of breast cancer. JAMA 1991;265(15):1985-90.

47. Steingold KA, Laufer L, Chetkowski RJ, DeFazio JD, Matt DW, Meldrum DR, et al. Treatment of hot flashes with transdermal estradiol administration. J Clin Endocrinol Metab 1985;61(4):627-32.

48. Sureau C, Ribot C., Limouzin-Lamothe M. A., Jamin C. Objectif, qualité de vie! Les estrogènes: Une approche globale du traitement de la ménopause. Sem Hop Paris 1989;65(36-37):2225-32.

49. The Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative randomized controlled trial. JAMA 2004; 291(14):1701 –12.

50. Utian WH. Biosynthesis and physiologic effects of estrogen and pathophysiologic effects of estrogen deficiency: A review. Am J Obstet Gynecol 1989;161:1828-31.

51. Vandenbroucke JP, Helmerhorst FM. Risk of venous thrombosis with hormone-replacement therapy. Lancet 1996;348: 972.

52. Whitehead MI, Padwick ML, Endacott J, Pryse-Davies J. Endometrial responses to transdermal estradiol in postmenopausal women. Am J Obstet Gynecol 1985;152(8):1079-84.

53. Wiseman L, McTavish D. Transdermal Estradiol-Norethisterone. A Review of its Pharmacological Properties and Clinical Use in Postmenopausal Women. Drugs Aging 1994;4:238-56.

54. Winter MI, and Fraser D. Controversies concerning the safety of estrogen replacement therapy. Am J Obstet Gynecol 1987;56:1313-22.

55. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. Principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA 2002;288(3):321-33.

PART III: CONSUMER INFORMATION

PrESTALIS® 140/50
(estradiol-17β + Norethindrone Acetate transdermal system)

PrESTALIS® 250/50
(estradiol-17β + Norethindrone Acetate transdermal system)

This leaflet is part III of a three-part "Product Monograph" published when ESTALIS® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ESTALIS. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

- ESTALIS should only be used if you have a uterus (it has not been surgically removed) to reduce moderate or severe menopausal symptoms
- To treat vulval and vaginal atrophy (itching, burning or dryness in or around the vagina, difficulty or burning on urination)

ESTALIS should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

What it does:

Treatment with ESTALIS offers relief from menopausal symptoms for women with uteri. With ESTALIS used in a continuous regimen, you receive estradiol and norethindrone acetate (NETA), a progestin, throughout the entire 28-day cycle. The progestin provides important protection for your uterus (See **Uses of Progestins**).

Uses of Estrogens

The main estrogen produced by your ovaries prior to menopause is estradiol, and this is the same estrogen that is in ESTALIS. When applied to the skin, the ESTALIS patches continually release small, controlled quantities of estradiol, which pass through your skin and into your bloodstream. The amount of estrogen prescribed depends on your body's needs.
By providing estradiol, ESTALIS offer relief from menopausal symptoms.

Your body normally makes estrogens and progestins (female hormones) mainly in the ovaries. Between ages 45 and 55, the ovaries gradually stop making estrogens. This leads to a decrease in body estrogen levels and a natural menopause (the end of monthly menstrual periods). If both ovaries are removed during an operation before natural menopause takes place, the sudden decrease in estrogen levels causes "surgical menopause".

Menopause is not a disease - it is a natural life event and different women experience menopause and its symptoms differently. Not all women suffer obvious symptoms of estrogen deficiency. When the estrogen levels begin decreasing, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden intense episodes of heat and sweating ("hot flashes" or "hot flushes"). Using estrogen drugs can help the body adjust to lower estrogen levels and reduce these symptoms.

Uses of Progestins

Progestins used in hormone replacement therapy have similar effects to the female sex hormone progesterone. During the child bearing years, progesterone is responsible for regulation of the menstrual cycle. The estradiol delivered by ESTALIS not only relieves your menopausal symptoms, but, like estrogens produced by your body, may also stimulate growth of the inner lining of the uterus, the endometrium. In menopausal and postmenopausal women with intact uteri, stimulation of growth of the endometrium may result in irregular bleeding. In some cases this may progress into a disorder of the uterus known as endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus). The development of estrogen-mediated disorders of the uterus can be reduced if a progestin, such as norethindrone acetate, is given regularly for a certain number of days with your estrogen replacement therapy. For women receiving ESTALIS in a continuous combined regimen, it is expected that uterine bleeding will stop

within a period of a few months and such treatment should also be protective of endometrial hyperplasia.

When it should not be used:
Certain medical conditions may be aggravated by estrogens and progestins, therefore these hormones should not be used at all under these conditions.

ESTALIS should not be used under the following conditions:

- if you are pregnant or think you may be pregnant. Since pregnancy may be possible early in menopause while you are still having spontaneous periods, the use of non-hormonal birth control should be discussed with your physician at this time. If you take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.
- if you are breast-feeding. Ask your doctor or pharmacist for advice.
- if you currently have or have ever had cancer of the breast, or uterus or endometrium (lining of the womb) or any other estrogen-dependent cancer
- if you have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus)
- if you have unexpected or unusual genital bleeding
- if you have active thrombophlebitis (inflamed varicose veins)
- if you currently have a problem with blood clots forming in your blood vessels or have ever had such a problem in the past. This may cause painful inflammation of the veins (thrombophlebitis) or blockage of a blood vessel in the legs (deep vein thrombosis), lungs (pulmonary embolism) or other organs
- if you have ever had coronary heart disease, a heart attack or stroke
- if you have serious liver disease
- if you have migraine
- if you have had partial or complete loss of vision due to blood vessel disease in the eye.
- if you have a disease of blood pigment called porphyria
- if you have had any unusual allergic reaction to estrogens or any other component of ESTALIS (see **What the medicinal ingredient is** and **What the-nonmedicinal ingredients are**).

Talk to your doctor if you have any further questions or if you think that any of the above may apply to you.

What the medicinal ingredients are:
The active components of the system are estradiol (an estrogen hormone) USP and norethindrone acetate (NETA – a progesterone hormone) USP.

What the nonmedicinal ingredients are:
a silicone and acrylic -based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

What dosage forms it comes in:
ESTALIS packs contain 8 patches. ESTALIS (NETA/17ß-estradiol) patches are available in two strengths: ESTALIS 140/50 and ESTALIS 250/50.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined *estrogen plus progestin*.

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone*.

Therefore, you should highly consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestins should be used at **the lowest effective dose** and for **the shortest period of time** possible. Regular medical follow-up is advised.

- **Breast cancer**

The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal women

taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated no difference in the risk of breast cancer in postmenopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer.
In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting hormone replacement therapy.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. You should review technique for breast self-examination with your doctor.

- **Overgrowth of the lining of the uterus and cancer of the uterus**

The use of estrogen-alone therapy by post menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

The purpose of adding a progestin medication to estrogen therapy is to reduce the risk of endometrial hyperplasia.

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with your doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

- **Ovarian cancer**

In some studies, the use of *estrogen-alone* and estrogen *plus progestin therapies*for 5 or more years has been associated with an increased risk of ovarian cancer.

Heart disease and Stroke
The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking *estrogen alone* compared to women taking placebo.

- **Abnormal blood clotting**

The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

The risk of blood clots increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

- **Gallbladder disease**

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

- **Dementia**

The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in post-menopausal women age 65 and over taking oral combined *estrogen plus progestin* compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

BEFORE you use ESTALIS talk to your doctor or pharmacist if you:

- have a history of severe allergic reaction or

intolerance to any medications or other substances
- have been told that you have a condition called hereditary angioedema of if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage) or digestive tract
- have a personal history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease or liver tumours, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- phlebitis (inflamed varicose veins)
- have had several miscarriages.
- have a history of kidney disease or asthma
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have been diagnosed with lupus
- gall bladder disease
- depression
- have been diagnosed with hearing loss due to otosclerosis
- epilepsy (seizures) or other neurological disorders
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- are breastfeeding
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- are undergoing surgery or need long bed rest.
- have been told that you have hypothyroidism (a condition in which your thyroid gland fails to produce enough thyroid hormone) and you are treated with thyroid hormone replacement therapy

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

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medications, including prescription medications, over-the-counter medications, vitamins or herbal products.

This particularly includes the following:

- Acetaminophen
- Aminoglutethimide with medroxyprogesterone acetate (MPA)
- anti-anxiety medicines (meprobamate, temazepam)
- cyclosporin
- anti-epileptic medicines (e.g. phenobarbital, phenytoin or carbamazepine)
- an anti-inflammatory medicine called phenylbutazone
- antibiotics and other anti-infective medicines (e.g. ketoconazole, erythromycin, rifampicin, rifabutin, nevirapine, efavirenz, ritonavir and nelfinavir), and
- herbal medicines (e.g. St John's wort)
- morphine
- prednisone
- salicylic acid
- theophylline
- Vitamin C

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.

Tell your doctor that you are on treatment with ESTALIS if you are going to have laboratory tests. Some laboratory tests, such as tests for glucose tolerance or thyroid function, may be affected by ESTALIS therapy.

PROPER USE OF THIS MEDICATION

Usual dose:

ESTALIS: ESTALIS packs contain 8 patches. ESTALIS (NETA/17ß-estradiol) patches are available in two strengths, called ESTALIS 140/50 and ESTALIS 250/50, each containing and releasing different amounts of estradiol and norethindrone acetate, as follows:

- ESTALIS 140/50: 9 cm^2 patch, containing 0.620 mg estradiol and 2.70 mg NETA, and releasing around 50 µg estradiol and 140 µg NETA per day.
- ESTALIS 250/50: 16 cm^2 patch, containing 0.512 mg estradiol and 4.80 mg NETA, and releasing around 50 µg estradiol and 250 µg NETA per day.

Your doctor will prescribe the patches in a continuous regimen.

Continuous Regimen
The ESTALIS patch is worn continuously for the 4 weeks of the cycle (see Figure 1). The ESTALIS patches are applied twice weekly on the same days of each week. Each patch should be worn continuously for 3-4 days.

Figure 1

Week 1	○	○	ESTALIS patch for the 4 weeks of the cycle
Week 2	○	○	
Week 3	○	○	
Week 4	○	○	

The next treatment cycle is started immediately after removal of the last ESTALIS patch. Irregular uterine bleeding may occur particularly in the first 6 months, but generally decreases with time.

It is important that you take your medication as your physician has prescribed. Do not discontinue or change your therapy without consulting your physician first.

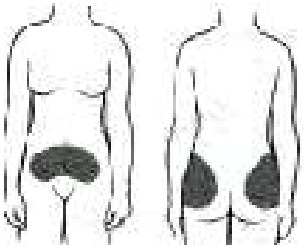
How and Where to Apply ESTALIS
It is recommended that you change the site of application each time the patch is applied. In other words, each time you apply a patch, place it on a different area of your abdomen or buttocks than used before. The same area should not be used again for at least one week. However, each time you apply a patch you should always apply it to the same area of your body (i.e., if the patch is applied to the buttocks, move the patch from right side to left side, twice a week or more if there is any redness under the patch).

Apply whole patches.

1. Preparing the Skin
In order for the patch to stick, the skin should be clean, dry, cool and free of any powder, moisturizer, lotions or oils. If you wish, you may use body lotion after the patch has been properly applied to the skin. The skin should not be irritated or broken, since this may alter the amount of hormone you get. Contact with water (bath, pool, or shower) should not affect the patch **(see Helpful Hints)**.

2. Where to Apply the ESTALIS Patches
The patches may be applied to the buttocks or abdomen (see Figure 2). Change the site of application each time you put a patch on. A **one week period** should elapse before applying the patch to a previously used spot.

Figure 2



Avoid areas of the skin where clothing may rub the patch off or areas where the skin is very hairy or folded. Also, avoid areas where the patch is likely to be exposed to the sun since this may affect how the patch works.

DO NOT APPLY THE PATCHES TO YOUR BREAST, since this may cause unwanted effects and discomfort.

3. Opening the Pouch
The patches contained in ESTALIS are individually sealed in a protective pouch. **Tear** open this pouch at the indented notch and remove the patch (see Figure 3). Do not use scissors, as you may accidentally cut and destroy the patch.

Figure 3

4. Removing the Liner
One side of the patch has the adhesive that sticks to your skin. The adhesive is covered by a protective liner that must be removed.

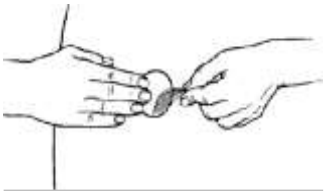
To separate the patch from the liner, hold the patch with the protective liner facing you. Peel off one side of the protective backing and discard it (see Figure 4). Try to avoid touching the sticky side of the patch with your fingers.

Figure 4

Using the other half of the backing as a handle, apply the sticky side of the system to a dry area of your abdomen or buttocks. Press the sticky side on the skin and smooth down.

Fold back the remaining side of the patch. Grasp the straight edge of the protective backing and pull it off the patch (see Figure 5). Avoid touching the adhesive.

Figure 5



5. Applying the ESTALIS patches

Apply the adhesive side to the spot you have chosen. Press it firmly in place with the palm of your hand for about 10 seconds, then run your finger around the edge, making sure there is good contact with the skin. Apply the patch soon after opening the pouch and removing the protective backing.

ESTALIS should be worn continuously until it is time to replace it with a new patch. You may wish to experiment with different locations when applying a new patch, to find sites that are most comfortable for you, where clothing will not rub against the patch.

6. When and How to Remove the Patch

Continuous Regimen: The ESTALIS patch should be changed twice weekly. Always change it on the same 2 days of the week. If you forget to change it at the scheduled time, there is no cause for alarm. Just change it as soon as possible and **continue** to follow your usual schedule.

After you remove the patch fold it in half with the adhesive sides inwards. **Throw it away, safely out of the reach of children or pets**.

Any adhesive left on your skin should rub off easily. You can also use mineral oil, baby oil or rubbing alcohol to remove adhesive from the skin. Apply a new ESTALIS patch on a different spot of clean, dry skin.

The drug in your patch is contained in the adhesive and not in a special reservoir.

Helpful Hints

What to do if the patch falls off

Should a patch fall off in a very hot bath or shower, shake the water off the patch. Dry your skin completely and reapply the patch as soon as possible (to a different area of skin) and continue your regular schedule. Make sure you choose a clean, dry, lotion-free area of skin. If it still does not stick completely to your skin, then use a **new** patch. No matter what day this happens, go back to changing this patch on the same days as the initial schedule.

If hot baths, saunas or whirlpools are something you enjoy and you find that the patch is falling off, you may consider removing the patch **temporarily** while you are in the water. If you do remove the patch temporarily, the adhesive side of the patch should be placed on the protective liner that was removed when originally applying the patch. Wax paper may be used as an alternate to the liner. This prevents the contents of the patch from emptying by evaporation while you are not wearing it.

In addition to exposure to very hot water, there are some other causes for the patch failing to stick. If you are having patches fall off regularly, this could be happening as a result of:

- using any type of bath oil
- using soaps with a high cream content
- using skin moisturizers before applying the patch

Patch adhesion may be improved if you avoid using these products, and by cleansing the site of application with rubbing alcohol before you apply the patch.

What to do if your skin becomes red or irritated under or around the patch

As with any product that covers the skin for a period of time (such as bandages), the ESTALIS patches can produce some skin irritation in some women. This varies according to the sensitivity of each woman.

Usually this redness does not pose any health concern to you, but to reduce this problem, you may change the site of application of the ESTALIS patches every time a new patch is applied.

Experience with another patch, VIVELLE®, has shown that if you allow the patch to be exposed to the air for approximately 10 seconds after the protective liner has been removed, skin redness may not occur.

If redness and/or itching continues, you should consult your physician.

Always Remember
Your doctor has prescribed ESTALIS for you after a careful review of your medical needs. Use it only as directed and do not give it to anyone else.

Use ESTALIS within 6 months of purchase or before the expiry date shown on the pack, whichever comes first.

Do not use any ESTALIS pack that is damaged or shows signs of tampering.
Do not expose the patch to direct sunlight.

Overdose:
Symptoms
Overdosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Progestin (norethindrone acetate) overdosage may cause depressed mood, tiredness, acne and hirsutism.

If you suspect an overdose, remove the patch, contact either your doctor, or emergency department of the nearest hospital, or your regional poison control center immediately.

Missed Dose:
If you forget to change a patch, replace it with another patch as soon as you remember. No matter when this happens, go back to changing this patch on the day as specified on your initial schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

All medicines can have side effects. Sometimes they are serious, most of the time they are not.

Check with your doctor as soon as possible if any of the following occur:

Most Common Adverse Drug Reactions (≥1%)
- back pain or menstrual period-like pain,
- breast tenderness and excessive vaginal secretions (may be a sign that too much estrogen is taken), vaginal thrush (vaginal fungal infection with severe itching, vaginal discharge),
- change in weight,
- headache,
- intolerable breast tenderness,
- itching under the patch, reddening of the skin after the patch has been removed (signs of application site reaction includes bleeding, bruising, burning, discomfort, dryness, skin boils, edema, erythema, inflammation, irritation, pain, tiny solid skin bumps, rash, skin discolouration, skin pigmentation, swelling, hives, and blisters),
- nervousness,
- pain in extremity,
- pelvic pain,
- persistent or severe skin irritation,
- rash, itching, acne, dryness.

Less Common Adverse Drug Reactions (<1%)
- breast cancer, abnormal tumour growth related to estrogens (e.g. cancer of the lining of the womb – endometrial cancer),
- change in your sex drive,
- gall bladder disease (tendency to form gall stones),
- painful and/or heavy periods (may be signs of growth of fibroids in uterus),
- or discoloration of the skin, purple skin patches,
- swelling of the lower legs, ankles, fingers or abdomen due to fluid retention (oedema) persisting for more than 6 weeks,
- tingling or numbness.

Adverse Drug Reactions with unknown frequency
- tender, red nodules under the skin (most common on the shins),
- spotty darkening of the skin, particularly on the face or abdomen (chloasma),
- easy bruising,
- excessive nose bleeds,
- sudden contraction of the womb,
- hair loss,
- excessive hairiness,
- decline of memory or mental ability,

- rapid change in mood,
- difficulty sleeping,
- contact lens discomfort,
- dry eyes,
- hearing loss,
- itchy rash.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	Symptom/side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abdominal pain, nausea or vomiting		√	
Uncommon	Breast lump		√	
	Crushing chest pain or chest heaviness			√
	Pain or swelling in the leg			√
	Persistent sad mood			√
	Sharp pain in the chest, coughing blood or sudden shortness of breath			√
	Sudden partial or complete loss of vision			√
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			√
	Migraine			√
	Unexpected or excessively heavy vaginal bleeding		√	
	Yellowing of the skin or eyes (jaundice)			√
Unc	Signs of a severe allergic reaction may include rash, itching, hives, breathlessness or difficult breathing wheezing or coughing, light-headedness, dizziness, changes in levels of consciousness, hypotension, with or without mild generalized itching, skin reddening, swelling of the face throat, lips, tongue, skin and periorbital edema.			
	Increase in blood pressure		√	

This is not a complete list of side effects. For any unexpected effects while taking ESTALIS contact your doctor or pharmacist.

HOW TO STORE IT

ESTALIS patches can be stored at room temperature (20- 25°C). In this case, use the patches within 6 months of purchase or before the expiry date shown on the pack, whichever comes first. You may also store the patches in a refrigerator (2-8°C), in which case you should use the patches before the expiry date shown on the pack and allow them to reach room temperature before you apply them.

Do not freeze. **Store in the original package.**
ESTALIS patches should be kept out of the reach and sight of children and pets before and after use.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.novartis.ca
or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at: 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last revised: August 18, 2017

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.,
Dorval, Quebec H9S 1A9

ESTALIS is a registered trademark