PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrESTALIS®140/50

Norethindrone Acetate and Estradiol-17ß
Patch, 140/50 mcg/day, Transdermal

PrESTALIS®250/50

Norethindrone Acetate and Estradiol-17ß
Patch, 250/50 mcg/day, Transdermal

Transdermal Therapeutic System

Progestin-Estrogen

Sandoz Canada Inc.
110 Rue de Lauzon
Boucherville, Quebec
J4B 1E6

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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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.

1.1 Pediatrics

Pediatrics: ESTALIS is not indicated for use in children.

1.2 Geriatrics

Geriatrics (> 65 years of age): No clinical studies were conducted to evaluate the effect of ESTALIS on women more than 65 years old. Therefore, ESTALIS is not recommended in women over 65 years of age.

2 CONTRAINDICATIONS

ESTALIS is contraindicated in:

- Patients with 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 6 DOSAGE FORMS, STRENGHTS, COMPOSITION AND PACKAGING.
- Patients with known or suspected estrogen-dependent or progestin-dependent malignant neoplasia such as endometrial cancer.
- Patients with endometrial hyperplasia
- Patients with known, suspected or past history of breast cancer
- Patients with known or suspected pregnancy
- Patients with active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis
- Patients with known thrombophilic disorders
- Patients with liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Patients with undiagnosed abnormal genital bleeding
- Patients with active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease)
- Patients with Porphyria
- Patients with partial or complete loss of vision from ophthalmic vascular disease
- Patients with Classical Migraine
- Patients who are breastfeeding

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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.

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.

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.

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.

4 DOSAGE AND ADMINISTRATION

4.1 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.

Combination progestin/estrogen regimens are indicated for women with intact uteri. Two ESTALIS (NETA/estradiol-17ß) patches are available: 140 mcg norethindrone acetate with 50

mcg estradiol per day (9 cm^2) and 250 mcg norethindrone acetate with 50 mcg 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.

4.2 Recommended Dose and Dosage Adjustment

Continuous Combined Regimen*:*
ESTALIS 140/50 or ESTALIS 250/50 mcg 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 amenorrheic 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.

No studies were performed in patients with renal and hepatic impairment. All estrogen preparations are contraindicated in the patients with severe hepatic impairment (see 2 CONTRAINDICATIONS).

ESTALIS is not indicated for use in children.

4.4 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.

4.5 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.

5 OVERDOSAGE

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.

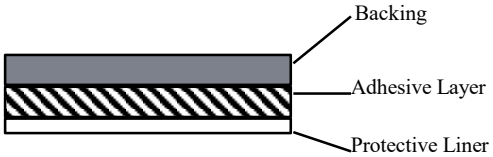
For management of a suspected drug overdose, contact your regional poison control center.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Transdermal	Patch 140/50 mcg/day and 250/50 mcg/day	Acrylic (Gelva® 737)-based multipolymeric adhesive, dipropylene glycol, oleic acid NF, povidone USP, and silicone (BIO PSA® X7-4603).

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 17ß-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 mcg/day	50 mcg/day
NETA Dosage Nominal *in vivo* delivery	140 mcg/day	250 mcg/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

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

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).

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.

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.

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 2 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 10 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. 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.

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).

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.

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.

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.

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 9.7 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.

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.

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 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.

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.

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.
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).

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.

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).

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.

7.1 Special Populations

7.1.1 Pregnant Women

ESTALIS must not be used during pregnancy. Both estrogens and progestogens may cause fetal harm when administered to a pregnant woman (see 2 CONTRAINDICATIONS).

7.1.2 Breast-feeding

ESTALIS must not be used while breastfeeding (see 2 CONTRAINDICATIONS).

7.1.3 Pediatrics

Pediatrics (<18 years of age): ESTALIS is not indicated for use in children.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): No clinical studies were conducted to evaluate the effect of ESTALIS on women more than 65 years old; therefore, ESTALIS is not recommended in women > 65 years of age. The use of combined estrogen plus progestin in women aged 65 and over may increase the risk of developing probable dementia (see 7 WARNINGS AND PRECAUTIONS, Neurologic.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

See 7 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 9 DRUG INTERACTIONS, 9.7 Drug-Laboratory Tests Interactions).

Cardiac disorders: Palpitations; increase in blood pressure (see 7 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 2 – 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 include localized bleeding, bruising, burning, discomfort, dryness, eczema, edema, erythema, inflammation, irritation, pain, papules, paraesthesia, pruritus, rash, skin discolouration, skin pigmentation, swelling, urticaria, and vesicles.

8.3 Less Common Clinical Trial Adverse Reactions

Gastrointestinal disorders: Vomiting.

Hepatobiliary disorders: Gallbladder disorder, cholelithiasis, jaundice cholestatic.

Immune system disorders: Hypersensitivity.

Investigations: Transaminases increased, blood pressure increased.

Neoplasms benign, malignant and unspecified (including cysts and polyps): Breast cancer, cervical polyps, uterine leiomyoma, fallopian tube cysts.

Nervous system disorders: Migraine, paraesthesia.

Psychiatric disorders: Libido increase or decrease.

Skin and subcutaneous tissue disorders: Skin discolouration, erythema nodosum, erythema multiforme, hypersensitivity including allergic contact dermatitis and isolated cases of anaphylactoid reactions (some of the patients had a history of previous allergy or allergic disorders), reversible post-inflammatory pigmentation and precipitation or aggravation of porphyria cutanea tarda in predisposed individuals.

Vascular disorders: Embolism venous, varicose veins.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 3 – 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

<u>If adverse symptoms persist, the prescription of HRT should be re-considered.</u>

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of ESTALIS.

Immune system disorders: Anaphylactic reaction, anaphylactoid reaction.

Skin and subcutaneous tissue disorders: Alopecia, chloasma, contact dermatitis.

9 DRUG INTERACTIONS

9.2 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.

9.3 Drug-Behavioural 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.

9.4 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 4 – Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical Comment
Anticonvulsants (phenobarbital, phenytoin, carbamazepin)	T	↑ metabolism of ethinyl estradiol	↓ plasma concentration of estradiol

Proper/Common name	Source of Evidence	Effect	Clinical Comment
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

Proper/Common name	Source of Evidence	Effect	Clinical Comment
Lamotrigine	T	↓ plasma concentration of lamotrigine	Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, concomitant administration of lamotrigine with estradiol has been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may lead to a reduction in seizure control among women taking both medicinal products together.
Morphine	T	↑ clearance of morphine	Therapeutic monitoring is recommended
Prednisolone	T	↑ plasma concentration of prednisolone	Therapeutic monitoring is recommended
Rifampicinª	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.

9.5 Drug-Food Interactions

The interaction of ESTALIS with food has not been studied.

9.6 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.

9.7 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 3 in 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data 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.

10 CLINICAL PHARMACOLOGY

10.1 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 pmol/L (40 pg/mL)) to mid-follicular phase. These features are maintained for an entire 84 to 96 hour wear period. Multiple applications of ESTALIS (250/50 mcg/day, 140/50 mcg/day) matrix transdermal delivery system resulted in average estradiol serum concentrations at steady-state of 184 and 165 pmol/L (50 and 45 pg/mL), respectively. At the end of the application periods, the average estradiol serum concentrations were 136 and 99 pmol/L (37 and 27 pg/mL), respectively. Estradiol has a short elimination half-life of approximately 2 to 3 hours. Therefore, a rapid decline in serum levels is observed after the matrix transdermal delivery system is removed. After removal of the matrix transdermal delivery system, serum concentrations of estradiol return to untreated postmenopausal levels (<73 pmol/L (20 pg/mL)) within 4 - 8 hours.

In a pharmacokinetic study it was shown that multiple applications of ESTALIS (250/50 mcg/day, 140/50 mcg/day) matrix transdermal delivery systems resulted in average norethindrone serum concentrations at steady-state of 2815 and 1639 pmol/L (840 and 489 pg/mL), respectively. At the end of the application period, the average serum concentrations of norethindrone were 2299 and 1293 pmol/L (686 and 386 pg/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 pmol/L (50 pg/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.

10.2 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 10.3 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

Clinical Pharmacology of Estrogens

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.

Clinical Pharmacology of Progestins

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.

10.3 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 45 to 50 pg/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.

Elimination
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 (<20 pg/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.

Elimination
The elimination half-life of norethindrone is reported to be 6 to 8 hours. Norethindrone serum concentrations diminish rapidly and are less than <50 pg/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; therefore, ESTALIS is not recommended in women over 65 years of age.

- **Sex:** ESTALIS should be used in women only.

11 STORAGE, STABILITY AND DISPOSAL

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 1 month. 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.

12 SPECIAL HANDLING INSTRUCTIONS

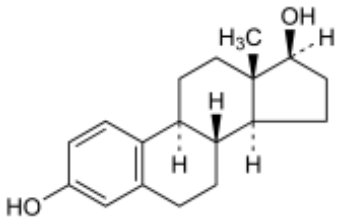
See 4 DOSAGE AND ADMINISTRATION, 4.4 Administration, Patch Application section.

PART II: SCIENTIFIC INFORMATION

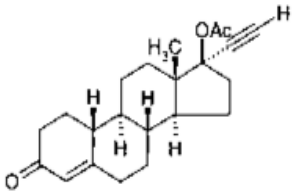
13 PHARMACEUTICAL INFORMATION

Drug Substance

Estradiol USP (Estradiol-17ß)

Proper name:	Estradiol hemihydrate
Chemical name:	estra-1,3,5 (10)-triene-3,17ß-diol
Molecular formula and molecular mass:	$C_{18}H_{24}O_2.½H_2O$; 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-17-pregn-4-en-20-yn-3-one acetate
Molecular formula and molecular mass:	$C_{22}H_{28}O_3$; 340.47
Structural formula:	
Physicochemical properties:	White to creamy white, odorless, crystalline powder.

Solubilities: Insoluble in water; Soluble 1 in 4 in acetone

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Treatment of vasomotor symptoms

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 5 – 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 mcg/day estradiol in combination with either 140 or 250 mcg/day norethindrone acetate), In study 304: Patients received ESTALIS in a sequential regimen (50 mcg/day estradiol only (VIVELLE®) for the first 14 days of each 28-day cycle followed by 50 mcg/day estradiol in combination with either 140 or 250 mcg/day norethindrone	446 non-hysterectomized healthy postmenopausal women with moderate-to-severe vasomotor symptoms (≥ 8 hot flushes/day of moderate-to-severe intensity with sweating)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=446)
		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.	

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

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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

Carcinogenicity:
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.

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

PATIENT MEDICATION INFORMATION
READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrESTALIS® 140/50
norethindrone acetate/estradiol-17β patch

PrESTALIS® 250/50
norethindrone acetate/estradiol-17β patch

Read this carefully before you start taking **ESTALIS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ESTALIS**.

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.

What is ESTALIS 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).

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

How does ESTALIS work?
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.

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.

What are the ingredients in ESTALIS?
Medicinal ingredients: estradiol (an estrogen hormone) USP and norethindrone acetate (NETA – a progesterone hormone) USP.

Non-medicinal ingredients: a silicone and acrylic -based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

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

ESTALIS 140/50: 9 cm^2 patch, containing 2.7 mg of norethindrone acetate and 0.62 mg estradiol and releasing 140 mcg of norethindrone acetate and 50 mcg of estradiol per day.

ESTALIS 250/50: 16 cm^2 patch, containing 4.8 mg of norethindrone acetate and 0.51 mg estradiol and releasing 250 mcg of norethindrone acetate and 50 mcg of estradiol per day.

Do not use ESTALIS if:
- you are allergic to estradiol, norethindrone acetate or any of the non-medicinal ingredients in ESTALIS or a component of the container (see **What are the ingredients in ESTALIS?**)
- you are pregnant or think you may be pregnant. Since pregnancy may be possible early in menopause while you are still having spontaneous periods, you should talk to your healthcare professional about using non-hormonal birth control. If you take estrogen during pregnancy, there is a small risk of your unborn child having birth defects.
- you are breastfeeding. Talk to your healthcare professional about how to fed your baby.
- you have or have a history of cancer of the breast, or uterus or endometrium (lining of the womb) or any other cancer which is sensitive to estrogen
- you have been diagnosed with overgrowth of the lining of the uterus (endometrial hyperplasia)
- you have unusual vaginal bleeding without a known reason
- you have inflamed varicose veins (thrombophlebitis)
- you have or have a history of blood clots in legs or somewhere else in your body
- you have or have a history of heart attack, stroke or coronary heart disease (including angina pectoris)
- you have serious liver disease
- you have or have a history of migraines
- you have had partial or complete loss of vision due to blood vessel disease in the eye
- you have a disease of blood pigment called porphyria

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ESTALIS. Talk about any health conditions or problems you may have, including 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 or acquired angioedema or if you have had episodes of rapid swelling of the hands, feet, face, lips, eyes, tongue, throat (airway blockage) or digestive tract
- have a history of breast disease (including breast lumps) and/or breast biopsies, or a family history of breast cancer
- have uterine fibroids or endometriosis
- have or 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 high blood pressure
- have a family history of blood clots, heart disease or stroke
- have inflamed varicose veins (phlebitis)
- have had several miscarriages
- have kidney problems
- have asthma
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have or have a family history of diabetes
- have systemic lupus erythematous. This is a disease of the immune system that affects the joints, skin, kidneys, blood cells, brain, heart and lungs.
- have gall bladder disease
- have a history of depression
- have hearing loss due to otosclerosis. This is a condition caused by abnormal bone growth in the middle ear.
- have a history of epilepsy (seizures) or other neurological disorders
- have high cholesterol or high triglycerides
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- are undergoing surgery or need long bed rest
- have hypothyroidism. This is a condition in which your thyroid gland does not produce enough thyroid hormone.

Other warnings you should know about:

Cancer:

- **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 talk to their healthcare professional before starting hormone replacement therapy.

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

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

- **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.

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 healthcare professional. You should also report any unexpected or unusual vaginal bleeding to your healthcare professional.

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.

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 healthcare professional 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.

Check-ups and Tests:
ESTALIS should be used only under the supervision of a healthcare professional, with regular follow-up visits, at least once a year, to check for 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 healthcare professional. Your healthcare professional may recommend some blood tests.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with ESTALIS:

- aminoglutethimide with medroxyprogesterone acetate (MPA), often used together for the treatment of breast cancer
- medicines used to help you relax or sleep such as meprobamate, temazepam, barbiturates
- medicines used to prevent organ rejection such as cyclosporin
- medicines used for the treatment of epilepsy such as phenobarbital, phenytoin, carbamazepine, lamotrigine
- medicines used to treat fever, pain or inflammation such as phenylbutazone, acetaminophen, salicylic acid
- medicines used to treat bacterial infections such as erythromycin
- medicines used in the treatment of tuberculosis such as rifampicin, rifabutin
- medicines used for the treatment of HIV and AIDS such as nevirapine, efavirenz, ritonavir, nelfinavir
- medicines used to treat fungal infections such as ketoconazole
- herbal products containing St John's wort (*Hypericum perforatum*) used to treat depression and other conditions
- morphine, used for the treatment of severe pain
- prednisone, a corticosteroid used to treat a variety of conditions including allergies and inflammation
- medicines used to treat lung and breathing problems such as theophylline
- some nutritional supplements such as vitamin C
- medicines used to lower cholesterol such as atorvastatin, clofibric acid
- medicines used to thin the blood and prevent blood clots
- medicines used to lower high blood pressure
- insulin and other medicines used to treat diabetes such as troglitazone
- alcohol

Tell your healthcare professional that you are being treated 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.

How to use ESTALIS:

1. Preparing the Skin

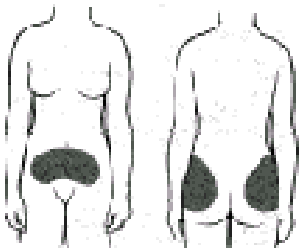
In order for the patch to stick, the skin should be clean, dry, cool and free of any powder, moisturizer, lotions or oils. If you wish, you may use body lotion after the patch has been properly applied to the skin. The skin should not be irritated or broken, since this may alter the amount of hormone 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 1). 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.

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 often if there is any redness under the patch).

Figure 1



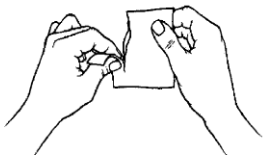
Avoid areas of the skin where clothing may rub the patch off or areas where the skin is very hairy or folded. Also, avoid areas where the patch is likely to be exposed to the sun since this may affect how the patch works.

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 2). Do not use scissors, as you may accidentally cut and destroy the patch.

Figure 2



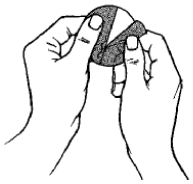
4. Removing the Liner

Make sure that you have removed your old patch before applying the new one.

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 3). Try to avoid touching the sticky side of the patch with your fingers.

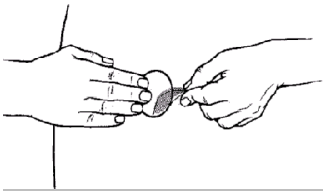
Figure 3



Using the other half of the backing as a handle, apply the sticky side of the patch 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 4). Avoid touching the adhesive.

Figure 4



Don't worry if the patch buckles slightly. You can flatten it out after the liner has been removed.

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

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 and sight 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 medicine 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. This varies according to the sensitivity of your skin.

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 talk to your healthcare professional.

Usual dose:
Follow all instructions given to you by your healthcare professional. Your healthcare professional will explain when to start using ESTALIS. ESTALIS is used as a continuous therapy. You will need to wear the patch all the time.

The ESTALIS patch is worn continuously for the 4 weeks of the cycle (see Figure 5). 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 5

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 ESTALIS as your healthcare professional has prescribed. Do not discontinue or change your therapy without talking to your healthcare professional.

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 think you, or a person you are caring for, have used too much ESTALIS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

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.

What are possible side effects from using ESTALIS?

These are not all the possible side effects you may have when taking ESTALIS. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- abdominal pain, nausea, vomiting,
- back pain or menstrual period-like pain,
- breast tenderness,
- changes in vaginal discharge, vaginal infection,
- change in weight,
- headache,
- nervousness,
- pain in the extremities,
- pelvic pain,
- skin irritation,
- rash, itching, acne, dryness,
- change in your sex drive,
- painful and/or heavy periods (may be signs of fibroids (benign growths) in uterus),
- discoloration of the skin, purple skin patches,
- tingling or numbness,
- 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.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Application site reaction: persistent irritation, redness, rash or itching of the skin after the patch has been removed, bleeding, bruising, burning, discomfort, dryness, skin boils, inflammation, irritation, pain, tiny solid skin bumps, skin discolouration, hives, blisters	√		
UNCOMMON			
Breast changes (breast lumps/breast cancer): pain and tenderness, lumps, nipple discharge		√	
Myocardial infarction (heart attack): crushing chest pain or chest heaviness, pressure or squeezing pain in the chest, jaw, left arm, between the shoulder blades or upper abdomen, shortness of breath, dizziness, fatigue, light-headedness, clammy skin, sweating, indigestion, anxiety, feeling faint, irregular heartbeat			√
Deep vein thrombosis (blood clot in the leg): pain or swelling in the			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
leg, difficulty standing or walking, feeling of warmth in the leg, red or discoloured skin			
Depression: persistent sad mood that won't go away			√
Pulmonary embolism (blood clot in the lung): sharp pain in the chest, coughing blood or sudden shortness of breath			√
Blood clot in the eye: sudden partial or complete loss of vision			√
Stroke: sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech, weakness or numbness in the face, arm or leg			√
Migraine: severe headache often accompanied by nausea, vomiting and sensitivity to light			√
Unexpected or excessively heavy vaginal bleeding		√	
Liver problems: yellowing of the skin or eyes (jaundice), dark urine, light coloured stool, itching all over your body			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Allergic reaction: rash, itching, hives, breathlessness or difficulty breathing wheezing or coughing, light-headedness, dizziness, changes in levels of consciousness, low blood pressure, skin reddening, swelling of the face throat, lips, tongue, skin and eyes			√
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		√	
Gallbladder disease: nausea, vomiting, pain on the upper right side of the abdomen, especially after meals, loss of appetite, fever		√	
Edema: unusual swelling of the arms, legs or abdomen		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
ESTALIS patches can be stored at room temperature (20- 25°C) up to 1 month. 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.

If you want more information about ESTALIS:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sandoz.ca, or by calling 1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

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