PRODUCT MONOGRAPH

PrESTRACOMB*

PrESTRADERM* + PrESTRAGEST*
(Estradiol-17ß + Norethindrone Acetate and Estradiol-17ß)

Transdermal Therapeutic System

Progestin-Estrogen

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* registered trademark

Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Patches of PrESTRADERM*50µg + Patches of PrESTRAGEST*250/50 µg	Cellulose compounds, ethanol, ethylene-vinyl acetate copolymer, light mineral oil, polyester and polyisobutylene.

INDICATIONS AND CLINICAL USE

ESTRACOMB* (estradiol-17ß and NETA/estradiol-17ß) is indicated for:

- the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states.

- the prevention of osteoporosis in naturally occurring or surgically induced estrogen-deficiency states in addition to other important therapeutic measures such as adequate diet, calcium and vitamin D intake, cessation of smoking and regular weight-bearing exercise. ESTRACOMB* is to be considered in light of other available therapies for osteoporosis prevention and therapy should only be continued as long as the benefits outweigh the risks for the individual. (see Boxed Warning)

ESTRACOMB* is recommended for the above indications only in 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 ESTRACOMB* on women more than 65 years old.

Pediatrics: ESTRACOMB* should not be used 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.
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Known or suspected estrogen-dependent or progestin-dependent malignant neoplasia such as endometrial cancer.
- Endometrial hyperplasia
- Known, suspected or past history of breast cancer
- Undiagnosed abnormal genital bleeding
- Known or suspected pregnancy
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease)
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis
- Partial or complete loss of vision from ophthalmic vascular disease
- Known thrombophilic disorders
- Porphyria
- 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.[57, 8, 52]

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.[57]

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.[52]

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.
- For the prevention of osteoporosis, ESTRACOMB* should be considered in light of other available therapies.
- 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).[57]

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. [8]

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. [52]

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 DOSAGE AND ADMINSITRATION-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.

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. [57, 25, 23] 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. [57, 52]

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). [57]

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. [52]

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. [25]

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. [23]

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 assure 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.[57]

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. [52]

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 ESTRACOMB* 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.

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 substudy 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. [44, 45]

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). [44]

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. [45]

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). [45]

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 ESTRACOMB*.

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

Nursing women: ESTRACOMB* must not be used while breastfeeding.

Pediatrics: ESTRACOMB* should not be used 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 ESTRACOMB* (estradiol-17ß and NETA/estradiol-17β) 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 WARNINGS AND PRECAUTIONS**- 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.

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 ESTRACOMB*
This section summarizes adverse drug reaction data pooled from clinical trials, published

investigations and post-marketing experience.

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.

The most commonly reported adverse reaction to ESTRACOMB* (estradiol-17ß and NETA/estradiol-17 β) in clinical trials was redness and irritation at the application site. This occurred in about 17% of the women treated and caused approximately 2% to discontinue therapy.

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%)

Nervous system disorders		
	Common:	Headache
Gastrointestinal disorders		
	Common:	Nausea, Abdominal pain, Abdominal distension
Reproductive system and breast disorders		
	Very common:	Breast tenderness , menstrual disorder
	Common:	Endometrial hyperplasia, premenstrual syndrome, dysmenorrhoea
General disorders and administration site conditions		
	Very common:	Application site reaction

Less Common Adverse Drug Reactions (<1%)

Cardiovascular system disorders:
Very rare: Blood pressure increased
General disorders and administration site conditions:
Rare: Oedema, weight fluctuation, pain in extremity
Hepatobiliary system disorders:
Very rare: Jaundice cholestatic, liver function test abnormal
Immune system disorders:
Very rare: Anaphylactoid reactions
Nervous system disorders:
Rare: Dizziness
Reproductive system and breast disorders:
Uncommon: Breast cancer
Skin and subcutaneous tissue disorders:
Very rare: Pruritus, rash, pigmentation disorders
Vascular disorders:
Very rare: Embolism, varicose veins

Adverse Drug Reactions with unknown frequency

Immune system disorders:

Not Known: Hypersensitivity

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

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 corticosteroids. 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.

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
Temazepam	T	↑ clearance of temazepam	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 ESTRACOMB* 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)

In clinical trials with ESTRACOMB*, no effect on fibrinogen, antithrombin III, TBG, CBG or SHBG was seen.

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 ESTRACOMB*

Acute alcohol ingestion during HRT may lead to elevations in circulating estradiol levels

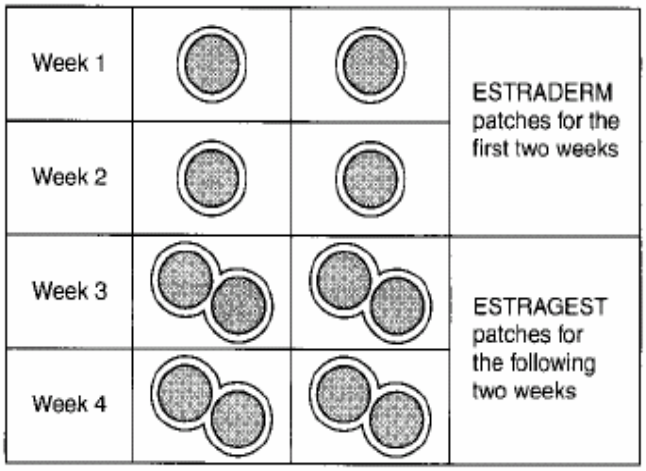
DOSAGE AND ADMINISTRATION

Dosing Considerations

- In women who are not currently taking oral estrogens, treatment with ESTRACOMB* (estradiol-17ß and NETA/estradiol-17ß) can be initiated at once. In women who are currently taking oral estrogen, treatment with ESTRACOMB* can be initiated on reappearance of menopausal symptoms, following discontinuation of oral therapy.
- One 28-day treatment cycle with ESTRACOMB* consists of 8 patches; 4 patches of ESTRADERM* 50 and 4 patches of ESTRAGEST* 250/50. Therapy is started with ESTRADERM* 50. For 2 weeks, one ESTRADERM* 50 patch is applied twice weekly,

i.e., the patch should be changed every 3-4 days. For the following 2 weeks, one ESTRAGEST* 250/50 patch is applied twice weekly, i.e., the patch should be changed every 3-4 days. Once the 8 patches of ESTRACOMB* have been used in the recommended sequence over a 28-day period, the subsequent treatment cycle is again started with ESTRADERM* 50 IMMEDIATELY after removal of the last ESTRAGEST* 250/50 patch. See Figure 1.

Figure 1:



ESTRACOMB* (estradiol-17ß followed by NETA/estradiol-17ß) provides, therefore, 14 days of progestin per cycle. The addition of sufficient NETA to induce secretory transformation of the endometrium during estrogen replacement therapy is mandatory.

- As observed in the normal menstrual cycle, cyclical administration of NETA from ESTRAGEST* 250/50 should induce REGULAR CYCLICAL bleeding with mean onset towards the end of the ESTRAGEST* 250/50 application phase. The normal duration of vaginal bleeding associated with ESTRACOMB* is around 6 days. This cyclical bleeding is expected to be of light intensity or spotting for 60-70% of this time. There are individual variations in these parameters. Once all 8 patches of ESTRACOMB* have been used as recommended, the first ESTRADERM* 50 patch of the new cycle is applied even if some vaginal bleeding still persists. Vaginal bleeding should stop early in the new cycle.
- Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, in any patient receiving hormone replacement therapy requires institution of prompt diagnostic measures like endometrial biopsy or curettage to rule out the possibility of uterine malignancy.
- The short-term effects of NETA co-administration may include vaginal bleeding during or after NETA treatment, breast tenderness, and mood and weight changes. The long-term effects generally depend on the dosage and type of progestin used. The lowest effective dose of estrogen and progestin should be prescribed (see **Coadministration of Progestins**).

See WARNINGS AND PRECAUTIONS section on the examination of the patient before ESTRACOMB* administration.

Recommended Dose and Dosage Adjustment

1. Menopausal symptoms

Treatment of menopausal symptoms is usually initiated with a patch that releases 50µg estradiol-17ß per day. Therefore, therapy can be initiated with ESTRACOMB* in women with an intact uterus. Thereafter the dosage should be adapted to the needs of the individual.

Breast discomfort, breakthrough or heavy vaginal bleeding, water retention, bloating or nausea (if persisting for more than six weeks), are generally signs that the estrogen dose is too high and needs to be lowered. If on the other hand, the selected dose fails to eliminate the signs and symptoms of estrogen deficiency, a higher dose of estrogen may be considered.

Women with intact uterus whose menopausal symptoms require ESTRADERM* 25 or ESTRADERM* 100 should receive appropriate treatment with oral progestins in order to prevent endometrial hyperplasia (see **Coadministration of Progestins-**Details provided in the ESTRADERM* Product Monograph).

For maintenance therapy one should always use the lowest dose that still proves effective. 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.

2. Prevention of Oteoporosis

For optimal prevention of postmenopausal bone loss in women for whom the drug is indicated, therapy should be initiated as soon as possible after diagnosis of menopause. The dosage of estradiol-17ß may require adjustment according to the patient's clinical status, the plasma estradiol-17ß levels and the results of bone mineral density studies.

Women with an intact uterus whose condition requires ESTRADERM* 25 or ESTRADERM* 100 should receive appropriate treatment with oral progestins in order to prevent endometrial hyperplasia (see **Coadministration of Progestins-**Details provided in the ESTRADERM* Product Monograph).

Discontinuation of hormone replacement therapy may reestablish the natural rate of bone loss.

Missed Dose

Patients who miss applying a patch of ESTRACOMB*, 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.

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 the protective liner, the adhesive side of the ESTRADERM* 50 or ESTRAGEST* 250/50 patch should be placed on a clean, dry area of intact skin. 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, preferably the buttocks, lower abdomen or hip. The patch may also be placed on the side or lower back. Experience to date has shown that less irritation of the skin occurs on the buttocks than on other sites of application. Therefore, it is advisable to apply ESTRADERM* 50 or ESTRAGEST* 250/50 to the buttocks. 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, 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 twice in succession. After use, ESTRACOMB* patches should be folded (adhesive surfaces pressed together) and discarded out of the reach of children.

ESTRADERM* 50 and ESTRAGEST* 250/50 must not be applied to the breasts to avoid potentially harmful effects on the breast tissue.

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

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 can be rapidly reduced by removal of the patch. Symptomatic treatment should be given.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

ESTRACOMB* contains two types of transdermal therapeutic systems, ESTRADERM* 50 (10 cm^2) and ESTRAGEST* 250/50 (20 cm^2). ESTRADERM* 50 contains estradiol-17ß and ESTRAGEST* 250/50 contains norethindrone acetate (NETA) and estradiol-17ß, respectively.

Both transdermal therapeutic systems included in ESTRACOMB* are designed to deliver daily about 50µg estradiol-17ß, a physiologic hormone, transdermally into the systemic circulation. Due to the transdermal route of administration, the estradiol-17ß does not undergo first-pass liver metabolism. Resultant estradiol-17ß plasma levels, which are between 110-147 pM/L (30-40 pg/mL) above baseline (typically 37 pM/L (10 pg/mL)), are comparable to those seen in premenopausal women in the early follicular phase of the menstrual cycle. Estradiol-17ß stimulates target tissues such as the uterus, breast and vagina.

NETA is administered only when the transdermal therapeutic system ESTRAGEST* 250/50 is correctly used. NETA, after hydrolysis to the active form, NET (norethindrone), shares some of the biological effects of the endogenously produced progestin, progesterone. Like progesterone, NET induces protein synthesis thereby limiting excessive growth stimulation of the endometrium by estrogen. NET induces the enzyme 17ß-hydroxysteroid-dehydroxygenase, which locally oxidizes estradiol to estrone. After application of an ESTRAGEST* 250/50 patch, plasma NET levels range between 0.5 and 1.0 ng/mL (1675 to 3351 pM/L).

The tissue effects of NET are dependent on prior estrogen stimulation. One of the major target organs for NET is the uterus, where it acts by inducing 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. However, amenorrhea has also been reported to occur during treatment with ESTRACOMB*.

Estrogen replacement therapy decreases the rate of bone loss in menopausal women; evidence of estrogen receptors on bone cells suggests there is a direct effect of estrogen on bone.

Pharmacodynamics

Hormone Replacement Therapy

ESTRACOMB* (estradiol-17ß and NETA/estradiol-17ß) provides continuous, controlled transdermal delivery of estradiol-17ß such that estradiol-17ß levels as well as the E2/E1 ratio in postmenopausal women are restored to those seen in the early follicular phase of the premenopausal range (see **Pharmacokinetics**). ESTRACOMB* thus alleviates the symptoms of estradiol-17ß deficiency in postmenopausal women.

Placebo-controlled clinical studies have demonstrated that treatment with ESTRADERM* 50 or ESTRADERM* 100 (50 μg and 100 μg per day respectively) prevents bone loss in postmenopausal women. Treatment with ESTRADERM* 50 showed maintenance of bone density. In addition, urinary excretion of both calcium and hydroxyproline are reduced during ESTRADERM* 50, ESTRADERM* 100 and ESTRACOMB* treatment.

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.

There are possible additional risks that may be associated with the inclusion of a progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism, mood changes and edema. The choice and dose of progestin may be important in minimizing these adverse effects and may differ among women.

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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.

As shown by endometrial biopsies, the administration of ESTRADERM* 50 for 2 weeks in sequence with ESTRAGEST* 250/50 for 2 weeks, resulted in the transformation of the estrogen-primed endometrium to a secretory state, and was effective in protecting against endometrial hyperplasia. In addition, control of menopausal symptoms and of cyclic bleeding was achieved. NETA administered by the transdermal route was effective at doses lower than those used orally, owing to the absence of first-pass metabolism.

There are possible additional risks that may be associated with the inclusion of a progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism, mood changes and edema. The choice and dose of progestin may be important in minimizing these adverse effects and may differ among women.

Treatment with ESTRACOMB* for up to 1 year decreased plasma total and LDL cholesterol as compared with pretreatment levels. HDL cholesterol was decreased slightly during the ESTRAGEST* 250/50 phase of treatment only. The effect on triglyceride levels was varied. In one trial triglyceride levels were decreased during both the ESTRADERM* 50 and ESTRAGEST* 250/50 phases of treatment. In two other trials treatment with ESTRACOMB* had no significant effect on triglyceride levels.

Pharmacokinetics

ESTRADERM* 50 And Estradiol-17ß

Absorption: Studies in postmenopausal women using ESTRADERM* 50, which provides 50 µg of exogenous estradiol-17ß per day, showed increased blood levels within 4 hours. Mean serum estradiol-17ß levels ranged from 110-147 pM/L (30 to 40 pg/mL) above baseline values, which are around 37 pM/L (10 pg/mL). Estradiol-17ß to estrone ratios were approximately 1. Serum concentrations of estradiol-17ß and estrone returned to pre-application levels within 24 hours after removal of the patch. The daily urinary output of estradiol-17ß conjugates increased 3 to 10 times the baseline values and returned to near baseline values within 2 days after removal of the patch.

Distribution: Estradiol-17ß delivered by the transdermal route results in an E_2/E_1 ratio of approximately 1. By comparison, typical E_2/E_1 ratios following oral estrogen therapy are 0.1 to 0.3 because estrone levels increase to a greater extent than estradiol-17ß levels. The extensive first-pass liver metabolism leads to supraphysiological plasma concentrations of estrone and, in patients on prolonged treatment, to accumulation of estrone and estrone sulphate.

Metabolism: Metabolism and plasma levels of estradiol-17ß delivered transdermally are similar to those in premenopausal women.

Estradiol-17ß is rapidly metabolized, primarily in the liver and gut. Its most important metabolites are estriol and estrone and their conjugates (glucuronides, sulphates); these are far less active than estradiol-17ß. The bulk of the metabolites is excreted in the urine as glucuronides and sulphates. Estrogen metabolites are also subject to enterohepatic circulation. The skin metabolizes estradiol-17ß only to a small extent.

Excretion: The plasma elimination half-life of estradiol-17ß is approximately 1 hour. Mean plasma clearance rates of estradiol-17ß and estrone in women have been estimated to be 735 L/(day•m^2) and 1213 L/(day•m^2), respectively. Because of its short half-life and rapid clearance, estradiol-17ß permits a rapid cessation of estrogen therapy when cycling is desirable.

ESTRAGEST* 250/50 And Norethindrone Acetate

Absorption: The skin is the rate limiting barrier for the uptake of NETA and NET, since the flux of NETA from the transdermal therapeutic system *in vitro* is several times higher than that of NETA/NET through the epidermis. The inter-individual variability of NETA/NET uptake is nevertheless low. After the first application of a patch, plasma NET levels rise within 2 days to steady-state levels ranging between 1675 to 3351 pM/L (0.5 and 1.0 ng/mL) (means 2346 to 2681 pM/L (0.7 to 0.8 ng/mL)) with repeated application. Two days after removal of the ESTRAGEST* 250/50 system, NET concentrations are again close to the pre-treatment measurement of 503 pM/L (0.15 ng/mL).

Throughout the application period of ESTRAGEST* 250/50 there is no accumulation of either NET or estradiol-17ß in plasma. Mean excretion of conjugates of NET and estradiol-17ß in urine corresponds to the respective concentration profile in plasma. With repeated application of ESTRAGEST* 250/50, NET plasma levels were in the same range as those found after single administration, demonstrating the absence of a skin depot.

For both NET and estradiol-17ß, the individual and mean AUC in plasma approximately doubles when two ESTRAGEST* 250/50 systems are applied simultaneously.

Distribution: ESTRAGEST* 250/50 delivers the same amount of estradiol-17ß as ESTRADERM* 50. The concentration profile of estradiol-17ß is similar to that produced by ESTRADERM* 50. Sequential application of ESTRADERM* 50 and ESTRAGEST* 250/50 resulted in estradiol-17ß plasma concentrations raised to levels similar to those in the early to mid-follicular phase of the menstrual cycle 110-147 pM/L (30-40 pg/mL) above baseline, which is typically 37 pM/L (10 pg/mL)). The E_2/E_1 ratio was observed to undergo a corresponding shift from between 0.2 and 0.5 to approximately 1. ESTRAGEST* 250/50 provides pharmacologic replacement of estrogen in the same way as ESTRADERM* 50.

Metabolism: Norethindrone acetate (NETA) released by the ESTRAGEST* 250/50 patch is extensively hydrolysed by esterases during diffusion through the skin. Hydrolysis also occurs in whole blood and most other organs. The product of cleavage, norethindrone (NET), is the active hormone circulating in the body.

NET is primarily metabolized in the liver by reduction of the α,β-unsaturated ketone structure in ring A of the molecule. Among the four possible stereoisomeric tetrahydrosteroids, the 5β,3-hydroxy-derivative is the main metabolite in plasma. These compounds are predominantly excreted in urine or feces as sulphate and glucuronide conjugates.

Excretion: NET is eliminated from plasma with a mean half-life of 6 to 8 hours. The total plasma clearance of NET averages 340 L/(day•m^2) after oral administration of NETA. The pharmacokinetics of NET are not altered during long-term administration.

Special Populations and Conditions

Pediatrics: ESTRACOMB* should not be used 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: ESTRACOMB* 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 with estrogen for protection against endometrial hyperplasia during long-term therapy of women with intact uteri.

STORAGE AND STABILITY

Store patches in a cool dry place (not below 25°C) . Do not freeze.

Store in the original package
Each patch is individually sealed in a separate pouch. Do not store out of the pouch. Apply immediately upon removal from the protective pouch. Patches should be applied in whole

Keep ESTRADERM* 50 and ESTRAGEST* 250/50 patches out of the reach and sight of children and pets both before use and when disposing of used patches.

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

Do not use any ESTRACOMB* pack that is damaged or shows signs of tampering.

SPECIAL HANDLING INSTRUCTIONS
See DOSAGE AND ADMINISTRATION- Patch Application section.

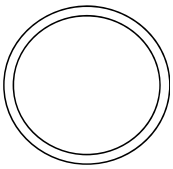
DOSAGE FORMS, COMPOSITION AND PACKAGING

The first type of transdermal system to be applied on the skin to initiate a 28-day treatment cycle is ESTRADERM* 50. ESTRADERM* 50 is a thin, round, multilayer, transparent transdermal therapeutic system, i.e., an adhesive patch, containing estradiol-17ß that is designed for application to an area of intact skin.

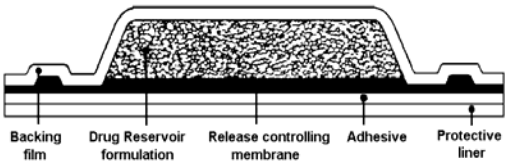
The ESTRADERM* 50 patch comprises five layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are:

1. a transparent polyester **backing film**
2. a drug **reservoir** of estradiol-17ß and ethanol gelled with hydroxypropyl cellulose
3. an ethylene vinyl acetate copolymer **release-controlling membrane**
4. an **adhesive** formulation of light mineral oil and polyisobutylene
5. a **protective liner** of siliconized polyethylene terephthalate film that is attached to the adhesive surface and must be removed before the patch can be used.

The active component of the patch is estradiol-17ß. The nonmedicinal ingredients of the patches are: cellulose compounds, ethanol, ethylene-vinyl acetate copolymer, light mineral oil, polyester and polyisobutylene.
The drug reservoir provides a source for continuous delivery of drug for up to 4 days.



Shape

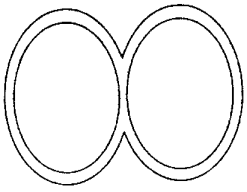


Cross section

ESTRADERM* 50 (the round patch)

The second type of transdermal therapeutic system to be applied on the skin during the last 14 days of a 28-day treatment cycle is ESTRAGEST* 250/50. ESTRAGEST* 250/50 is a thin, twin-shaped, multilayer, transparent patch, with two separate drug reservoir chambers and an adhesive surface for application to an area of intact skin. ESTRAGEST* 250/50 is comprised of the same 5 layers as ESTRADERM* 50. The active substances are released from the drug reservoirs, penetrate the skin and pass directly into the bloodstream (see PHARMACEUTICAL INFORMATION).

ESTRAGEST* 250/50 contains a fixed combination of norethindrone acetate (NETA) and estradiol-17ß. ESTRAGEST* 250/50 releases controlled amounts of NETA and estradiol-17ß simultaneously through the skin for up to 4 days.



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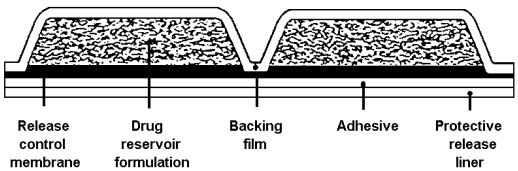


Cross section

ESTRAGEST* 250/50 (the twin-shaped patch)

The ESTRACOMB* (estradiol-17β and NETA/estradiol-17β) package consists of the following systems and releases estradiol and NETA at the following rate over a period of 4 days:

	ESTRADERM* 50	ESTRAGEST* 250/50
Estradiol-17ß Dosage Nominal *in vivo* delivery	50 µg/day	50 µg/day
NETA Dosage Nominal *in vivo* delivery	-	250 µg/day
Total Estradiol-17ß Content	4 mg	10 mg$^{\Delta}$
Total NETA Content	-	30 mg
Drug-Releasing Area	10 cm^2	20 cm^2
Shape of patch	Round	Twin
Printed (backing side)	-	CG FNF

$^{\Delta}$In order to achieve the same delivery rate of estradiol-17ß for the ESTRAGEST* 250/50 patch as the ESTRADERM* 50 patch, the content of estradiol-17ß had to be increased.

One ESTRACOMB* package contains four ESTRADERM* 50 patches (two patches per week) and four ESTRAGEST* 250/50 patches (two patches per week) for a 28-day treatment cycle.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

ESTRADERM* 50

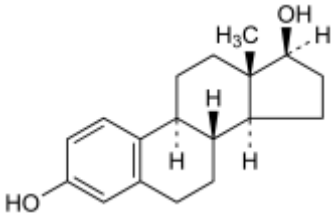
Proper name Estradiol-17β (i.e., E_2)

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

Molecular formula $C_{18}H_{24}0_2$

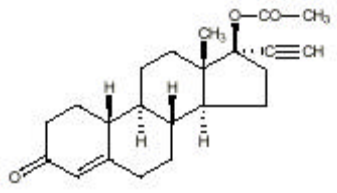
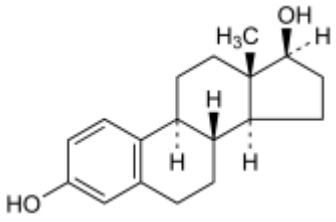
Molecular mass 272.39

Structural formula



Physicochemical properties Estradiol is a white crystalline powder.

ESTRAGEST* 250/50

Proper name	Norethindrone acetate (i.e., NETA)	Estradiol-17β (i.e., E_2)
Chemical name	17-hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one-acetate	estra-1,3,5 (10)-triene-3,17ß-diol
Molecular formula	$C_{22}H_{28}O_3$	$C_{18}H_{24}0_2$
Molecular mass	340.46	272.39
Structural formula		

Physicochemical properties	White to yellowish white crystalline powder.	Estradiol is a white crystalline powder.

CLINICAL TRIALS

Efficacy and Tolerability studies

Three pivotal studies (SP/NE 1, SP/NE 2, SP/NE 4) were conducted with ESTRACOMB* for 12 or 13 cycles (1 year) to assess endometrial response by biopsy. The overall incidence of endometrial hyperplasia after 1 year was below 2% (3 of the 296 patients). It was comparable to the pre-trial incidence, and much lower than the published incidence of about 40% endometrial hyperplasia with unopposed estrogen treatment for the same period of treatment.

Table 4: Summary of patient demographics for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N= population treated)	Mean age
SP/NE 1	Open, non-comparative within patient comparison of tolerability and efficacy	ESTRADERM* 50 twice weekly, week 1 and 2 ; NETA/E2-TTS twice weekly, week 3 and 4 Duration: 12 to 13 cycles of 4 weeks	72 patients evaluated for efficacy 94 patients evaluated for tolerability	54.0 54.1
SP/NE 2	Open, non-comparative		367 patients evaluated for efficacy and for tolerability	52.1
SP/NE 4	Open, non-comparative, multi-center		136 patients evaluated for efficacy 139 patients evaluated for tolerability	53.0
SP/NE 3	Open comparative, parallel randomized	-ESTRADERM* 50 twice weekly, week 1 and 2 ; NETA/E2-TTS twice weekly, week 3 and 4 -conjugated estrogens 0.625 mg o.d. and norgestrel 0.15 mg o.d. 12 days/cycle Duration: 6 cycles of 4 weeks	61 patients evaluated for efficacy 60 patients evaluated for tolerability	

Bleeding patterns were studied in 4 pivotal trials (SP/NE 1, SP/NE 2, SP/NE 3, SP/NE 4) with ESTRACOMB* (over 5300 treatment cycles).

Bleeding was generally well controlled. It occurred in 89.9% of all cycles for patients who completed the studies. Irregular bleeding occurred in 6.9 % of all cycles. The mean onset of

bleeding (including irregular bleeding) was between 12.1 and 12.4 days of the combined treatment and lasted for 5.9 to 6.5 days.

Although it was not the primary objective, every pivotal clinical trial with ESTRACOMB* showed that the efficacy of ESTRADERM*, in the relief of menopausal and postmenopausal symptoms and in the prevention of osteoporosis, is maintained when administered in combination with ESTRAGEST*.

As shown by endometrial biopsies, the administration of ESTRADERM* 50 for 2 weeks in sequence with ESTRAGEST* 250/50 for 2 weeks, resulted in the transformation of the estrogen-primed endometrium to a secretory state, and was effective in protecting against endometrial hyperplasia. In addition, control of menopausal symptoms and of cyclic bleeding was achieved. NETA administered by the transdermal route was effective at doses lower than those used orally, owing to the absence of first-pass metabolism.

DETAILED PHARMACOLOGY

See Action and Clinical Pharmacology (Part I)

TOXICOLOGY

Preclinical safety data

The toxicity profile of estradiol has been 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.

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

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PART III: CONSUMER INFORMATION

ESTRACOMB * contains two types of transdermal therapeutic systems (patches):

ESTRADERM* 50 (estradiol-17β)
ESTRAGEST *250/50 (estradiol-17β + Norethindrone Acetate)

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

ABOUT THIS MEDICATION

What the medication is used for:

ESTRACOMB* should only be used if you have a uterus (it has not been surgically removed)

- To reduce moderate or severe menopausal symptoms.
- To prevent osteoporosis

Some women are more likely to develop osteoporosis after menopause than others. If you have been prescribed ESTRACOMB* only for the prevention of osteoporosis you should discuss other alternative therapies with your doctor. . In addition, you should discuss adequate diet, calcium and vitamin D intake, cessation of smoking and regular physical weight-bearing exercise with your doctor or pharmacist.

ESTRACOMB* 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:

Uses of Estrogens

The main estrogen produced by your ovaries prior to menopause is estradiol, and this is the same estrogen that is in ESTRADERM* and ESTRAGEST*. When applied to the skin, the ESTRADERM* and ESTRAGEST* 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.

Treatment with ESTRACOMB* offers relief from menopausal symptoms for women with uteri. With ESTRACOMB*, you receive estradiol throughout the entire 28-day cycle, and norethindrone acetate (NETA), a progestin, during the last 2 weeks of the 28-day cycle. The progestin provides important protection for your uterus **(See Uses Of Progestins)**.

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.

Osteoporosis is a thinning of the bones that makes them weaker and allows them to break more easily. In osteoporosis, the bones of the spine, wrists and hips break most often. The bones of both men and women start to thin after about age 40, but women lose bone faster after menopause.

Using estrogens after menopause slows down bone thinning and may prevent bones from breaking.

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 ESTRACOMB* 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. Each cycle of progestin administration should induce a periodic bleeding, during which time the inner lining of the uterus is shed., This protects against 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.

ESTRACOMB* should not be used under these 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 cancer which is sensitive to estrogens
- if you have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus)
- if you have unexplained changes in unexpected or unusual genital bleeding that has not been investigated.
- if you have active thrombophlebitis (inflamed varicose veins)
- if you currently have a problem with abnormal 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 a heart attack, coronary heart disease or stroke
- if you currently have a 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 ever had any unusual allergic reaction to estrogens or any other component of ESTRACOMB* (see **What the medicinal ingredient are and What the nonmedicinal ingredients are**).

ESTRACOMB* is not a contraceptive, nor will it restore fertility.

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 ingredient are:
ESTRACOMB* contains two types of transdermal therapeutic systems (patches) that are used in sequence. The round patch is called ESTRADERM* 50 (ESTRADERM*) and the twin patch is called ESTRAGEST* 250/50 (ESTRAGEST*).

ESTRADERM* contains a natural estrogen hormone, **estradiol**, while ESTRAGEST* contains **estradiol** as well as a progestin, **norethindrone acetate (NETA).**

What the nonmedicinal ingredients are:
cellulose compounds, ethanol, ethylene-vinyl acetate copolymer, light mineral oil, polyester and polyisobutylene.

What dosage forms it comes in:
One ESTRACOMB* package contains four ESTRADERM* 50 patches (two patches per week) and four ESTRAGEST* 250/50 patches (two patches per week) for a 28-day treatment cycle.

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 lump, 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-examination 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 ESTRACOMB* talk to your doctor or pharmacist if you:

- have a history of allergy 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 a history of kidney disease, asthma or epilepsy (seizures)
- 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
- have a history of high cholesterol or high

triglycerides
- o are pregnant or may be pregnant
- o are breastfeeding
- o have had a hysterectomy (surgical removal of the uterus)
- o smoke
- o are undergoing surgery or need long bed rest.

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

INTERACTION WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines. Remember also those not prescribed by a doctor.

This particularly includes the following: anti-anxiety medicines (e.g.barbiturates, meprobamate), anti-epileptic medicines (e.g. pheno barbital, phenytoin or carbamazepine), an anti-inflammatory medicine called phenylbutazone, antibiotics and other anti-infective medicines (e.g. rifampicin, rifabutin, nevirapine, efavirenz), and herbal medicines (e.g. St John's wort).

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

PROPER USE OF THIS MEDICATION

Usual dose:

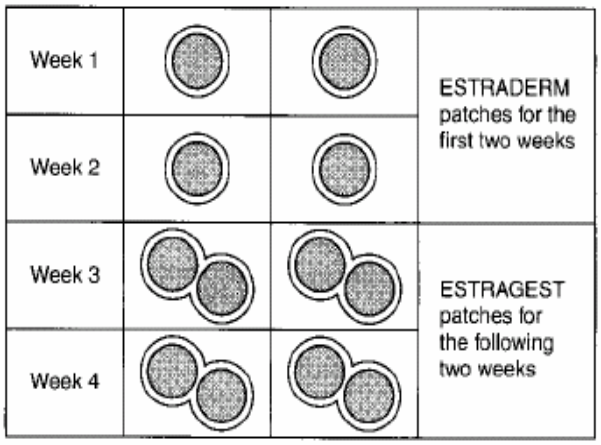
Each ESTRACOMB* pack contains four ESTRADERM* and four ESTRAGEST* patches. The round ESTRADERM* patch provides the estrogen, estradiol. The twin ESTRAGEST* patch provides estradiol and the progestin, norethindrone acetate (NETA). These patches contain and release different amounts of active ingredient, as follows:

- ESTRADERM*: 10 cm^2 round patch, containing 4 mg estradiol and releasing about 50 µg estradiol a day
- ESTRAGEST*: 20 cm^2 goggle-shaped patch, containing 10 mg estradiol and 30 mg norethindrone acetate, and releasing about 50 µg estradiol and 250 µg NETA a day

When ESTRACOMB* is applied to the skin, the patches release small amounts of estradiol and NETA, which pass directly through the skin into your bloodstream.

All eight patches are to be used in a 28-day treatment cycle.

Therapy is started with the ESTRADERM* patches which are used for the first 2 weeks followed by the ESTRAGEST* patches for the next 2 weeks (See Figure 1). The ESTRADERM* and ESTRAGEST* patches are applied twice weekly on the same days of each week. Each patch should be worn continuously for 3-4 days.



Regular cyclical bleeding usually starts towards the end of the ESTRAGEST* application phase (i.e., while you are wearing the 4th ESTRAGEST* patch of that cycle). The duration of bleeding is around 6 days. Bleeding is of light intensity or spotting for 60-70% of this time. Tell your doctor if you have heavy or irregular bleeding after a few months of treatment.

As therapy with ESTRACOMB* is continuous, the next treatment cycle is started with ESTRADERM* immediately after removal of the last ESTRAGEST* patch, and regardless of whether there is still bleeding (i.e., you will have a patch on at all times).

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 ESTRACOMB*

It is recommended that you change the site of application each time the patch is applied.

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).

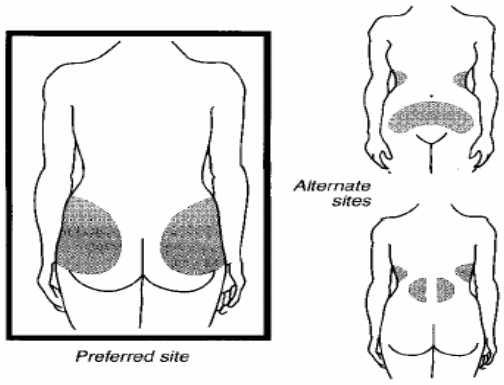
1. Preparing The Skin

In order for the patch to stick, the skin should be clean, dry and free of creams, 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) won't affect the patch, although very hot water or steam may loosen it and therefore should be avoided **(see Helpful Hints)**.

2. Where To Apply The ESTRADERM* Or ESTRAGEST* Patches

The buttock is the preferred place to apply the patches. Other suitable application sites are the side, lower back or lower abdomen (see Figure 1). Change the site of application each time you put a patch on. You can use the same spot more than once but **not twice in a row**.

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.

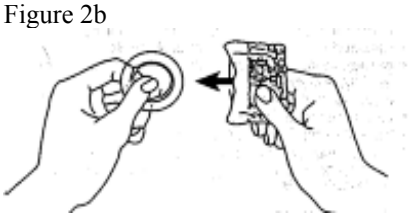
DO NOT APPLY THE PATCHES TO YOUR BREAST, since this may cause unwanted effects and discomfort.

3. Opening The Pouch

Each ESTRADERM* or ESTRAGEST* patch is individually sealed in a protective pouch. **Tear** open this pouch at the indented notch and remove the patch (see Figures 2a and 2b). Do not use scissors, as you may accidentally cut and destroy the patch. There may or may not be bubbles in the patch, but this is normal. Do not cut the twin ESTRAGEST* patch in half.

Figure 2a

Figure 2b

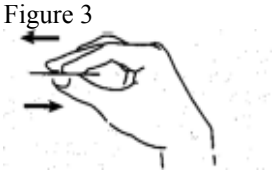


4. Removing The Liner

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 your thumb on the smooth liner, your other fingers on the patch. See positioning in Figure 3. Press your thumb against your other fingers by using the motion of snapping your fingers slowly.

Figure 3



This will allow you to easily separate the patch and liner. Holding the **edge** of the patch you can now peel away the liner (Figure 4). Avoid touching the adhesive.

Figure 4

Don't worry if the patch buckles slightly because you can flatten it out after the liner has been removed. Apply the patch soon after opening the pouch and removing the liner.

5. Applying The ESTRADERM* And ESTRAGEST* 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.

6. When And How To Remove The Patch

The ESTRADERM* and ESTRAGEST* patches 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 ESTRADERM* or ESTRAGEST* patch on a different spot of clean, dry skin.

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 new area of skin) and continue your regular schedule. Make sure you choose a clean, lotion-free area of the 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 the 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 ESTRADERM* and ESTRAGEST* 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, there are some things that you may do:

- choose the buttock as the site of application
- change the site of application of the ESTRADERM* or ESTRAGEST* patch every time a new patch is applied, usually twice weekly

Experience with ESTRADERM* 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.

<u>Overdose</u>:

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 more medication has been taken than what has been prescribed, remove the patch and contact either your doctor, hospital, or emergency department immediately.

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

Treatment
Owing to the mode of administration (transdermal), plasma levels of estradiol-17ß and norethindrone acetate can be rapidly reduced by removal of the patch.

Missed Dose:
If you miss applying a patch, apply a new patch as soon as you remember. No matter what day that happens, go back to changing this patch on the same day as your initial schedule.

Always Remember

Your doctor has prescribed ESTRACOMB* for you after a careful review of your medical needs. Use it only as directed and do not give it to anyone else. Your doctor should re-examine you at least once a year.

If you have any questions, contact your doctor or pharmacist.

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:, swelling of the lower legs, ankles, fingers or abdomen due to fluid retention (oedema) persisting for more than 6 weeks, change in weight, change in your sex drive, easy bruising, excessive nose bleeds, painful and/or heavy periods (may be signs of growth of fibroids in uterus), back pain or menstrual period-like pain, breast tenderness and excessive vaginal secretions (may be a sign that too much estrogen is taken), change in vaginal discharge (may be a sign that too much estrogen is taken), vaginal thrush (vaginal fungal infection with severe itching, vaginal discharge), intolerable breast tenderness, persistent or severe skin irritation, itching under the patch, reddening of the skin after the patch has been removed; hair loss, excessive hairiness, rash, itching, dryness or discoloration of the skin, spotty darkening of the skin, particularly on the face or abdomen (chloasma), acne, purple skin patches, decline of memory or mental ability, headache, nervousness, rapid change in mood, contact lens discomfort, gall bladder disease (tendency to form gall stones).

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Frequency	**Symptom/possible side effect**	**Talk to your doctor or pharmacist**		**Stop taking drug and call your doctor or pharma-cist**
		Only if severe	**In all cases**	
Commo	Abdominal pain, nausea or vomiting		**x**	
Uncommon	Breast lump		**x**	
	Crushing chest pain or chest heaviness			**x**
	Pain or swelling in the leg			**x**
	Persistent sad mood			**x**
	Sharp pain in the chest, coughing blood or sudden shortness of breath			**x**
	Sudden partial or complete loss of vision			**x**
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			**x**
	Migraine			**x**
	Unexpected vaginal bleeding or excessively heavy bleeding		**x**	
	Yellowing of the skin or eyes (jaundice)			**x**
	Signs of allergic reaction: sudden troubled breathing, tightness of the chest, general rash, swelling or itching			**x**
	Increase in blood pressure		**x**	

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

HOW TO STORE IT

ESTRADERM* and ESTRAGEST* should be stored in a cool dry place (not above 25°C). Do not freeze. **Store in the original package.**

ESTRADERM* and ESTRAGEST* patches should be kept out of the reach and sight of children and pets before and after use.

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

Do not use any ESTRACOMB* pack that is damaged or shows signs of tampering.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:
Online: www.healthcanada.gc.ca/medeffect
Toll-free telephone: 1-866-234-2345
toll-free fax 1-866-678-6789
Postage Paid mail:
Canada Vigilance Program
Health Canada
AL 0701C
Ottawa ON K1A 0K9

NOTE: *Should you require information related to the management of the side effect, please contact your health care provider. The Canada Vigilance Program does not provide medical advice.*

MORE INFORMATION

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

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

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