PRODUCT MONOGRAPH

[Pr]ESTRADERM*25
ESTRADERM*50
ESTRADERM*100

(Estradiol-17ß)

Transdermal Therapeutic System
25, 50, and 100 µg/24 hours of estradiol

Estrogen

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* ESTRADERM is a registered trademark

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(Estradiol-17ß)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Patch 25, 50 and 100 µg	Cellulose compounds, ethanol, ethylene-vinyl acetate copolymer, light mineral oil, polyester and polyisobutylene.

INDICATIONS AND CLINICAL USE

ESTRADERM* (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. In postmenopausal women already diagnosed as having osteoporosis and vertebral fractures, treatment with ESTRADERM* may retard further bone loss. ESTRADERM* is to be considered in the 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)

In women with an intact uteri, ESTRADERM* should always be supplemented by sequential administration of 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 ESTRADERM* on women more than 65 years old.

Pediatrics :
ESTRADERM* 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 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, ESTRADERM* treatment 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* HRT 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 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 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.

Estrogen-only hormonal therapy in postmenopause is recommended for women without uteri only to avoid unnecessary exposure to progestins. The focus of the clinical program with VIVELLE*/ESTRADOT* was the demonstration of efficacy in the treatment of postmenopausal symptoms and in the prevention of postmenopausal osteoporosis. Some clinical trials included non-hysterectomized patients who were treated with concomitant progestogen therapy according to the best medical practice at the time, with different dosages, regimens and types of progestin. In addition, endometrial sampling after treatment was not consistently performed and in most cases no baseline data were available to assess the relationship and the effects of the progestogen treatment on the endometrium.

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 hyperlipidemias need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Calcium and phosphorus metabolism
Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens 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 ESTRADERM* 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 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 sub-study of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.[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 ESTRADERM*.

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

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

Pediatrics: ESTRADERM* should not be used in children.

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

Monitoring and Laboratory Tests

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

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

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

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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

Blood and lymphatic system disorders
Altered coagulation tests (see 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 ESTRADERM*

This section summarizes adverse drug reaction data pooled from clinical trials, published investigations and post-marketing experience.

The most commonly reported adverse reaction to ESTRADERM* (estradiol-17ß) 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.

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

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

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

Vascular disorders	
Common:	Varicose veins
Nervous system disorders	
Common:	Dizziness, headache
Gastrointestinal disorders	
Common:	Nausea, abdominal pain, abdominal distension
Skin and subcutaneous tissue disorders	
Common:	Rash
Reproductive system and breast disorders	
Very common:	Breast discomfort
Common:	Menstrual disorder
Investigations	
Common:	Weight fluctuation
General disorders and administration site disorders	
Very common:	Application site reaction,
Common:	Oedema

Less Common Adverse Drug Reactions (<1%)

Cardiovascular disorders:

Rare: Embolism

Very rare: Hypertension

Hepatobiliary disorders:

Very rare: Jaundice cholestatic, liver function test abnormal

Immune system disorders:

Very rare: Anaphylactoid reactions

Musculoskeletal and connective tissue disorders:

Rare: Pain in extremity

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Rare: Breast cancer

Skin and subcutaneous tissue disorders:

Very rare: Generalised pruritus, pigmentation disorders

Adverse Drug Reactions with unknown frequency

Immune system disorders:

Not Known: Hypersensitivity

Skin and subcutaneous tissue disorders:

Not Known: Erythema nodosum, Erythema multiforme

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 ESTRADERM* 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 ESTRADERM*, no effect on fibrinogen, antithrombin III, TBG, CBG or SHBG and decreases in serum triglycerides 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 estrogen therapy when relevant specimens are submitted.

Drug-Lifestyle Interactions:

Specific drug-lifestyle interaction studies have not been conducted with ESTRADERM*.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

- For all therapeutic indications, the lowest effective dose should be used for maintenance therapy (see **Coadministration of Progestins**).
- Hormone replacement therapy (HRT) involving either estrogen alone or estrogen-progestogen combined therapy should only be continued as long as the benefits outweigh the risks for the individual.
- In women who are not currently taking oral estrogens, treatment with ESTRADERM* (estradiol-17ß) can be initiated at once. In women who are currently taking oral estrogens, treatment with ESTRADERM* can be initiated on reappearance of menopausal symptoms, following discontinuation of oral therapy.
- ESTRADERM* is administered as continuous therapy (uninterrupted application). ESTRADERM* should be applied twice weekly i.e., the patch should be changed once every 3-4 days.

- In women with intact uteri, a progestin should be sequentially coadministered for 12 to 14 days per cycle to avoid overstimulation of the endometrium. The addition of sufficient progestin to induce secretory transformation of the endometrium during estrogen replacement therapy is mandatory.
- 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 progestin coadministration may include vaginal bleeding during or after progestin 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**).
- ESTRADERM* should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. Progestin therapy is not required as part of hormone replacement therapy in women who have had a previous hysterectomy.

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

Recommended Dose and Dosage Adjustment

1. Menopausal symptoms

Treatment of menopausal symptoms is usually initiated with a patch that releases 50 µg estradiol-17ß per day i.e. ESTRADERM* 50. 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 may be considered.

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.

The doses of ESTRADERM* and conjugated estrogens which have been shown to produce the same clinical effect on postmenopausal symptomatology are:

ESTRADERM* 25: conjugated estrogens 0.3 MG

ESTRADERM* 50: conjugated estrogens 0.625 MG

ESTRADERM* 100: conjugated estrogens 1.25 MG

2. Prevention of Osteoporosis

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. Ideally, plasma estradiol-17ß levels should be maintained at 184 pM/L (50 pg/mL). To treat patients with established osteoporosis, therapy should be initiated with ESTRADERM* 100.

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

Missed Dose

Patients who miss applying a patch of ESTRADERM*, 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* 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* 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.

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

Coadministration of Progestins

Studies have reported that the addition of a progestin for 10 or more days of a cycle of estrogen administration greatly lowers the incidence of endometrial hyperplasia, and thereby irregular bleeding and endometrial carcinoma, compared to estrogen treatment alone. This applies to women with intact uteri and not to those who have had hysterectomies.

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.

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
ESTRADERM* is designed to deliver daily 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 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 .

ESTRADERM* delivers estradiol-17ß via skin, which metabolizes estradiol only to a small extent. In comparison, orally administered estrogens are rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrogens than estradiol. Therefore, transdermal administration of estradiol produces therapeutic plasma levels with lower circulating levels of estrone conjugates and requires smaller total doses than does oral therapy.

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

Estradiol
Like all steroid hormones, estrogens exert their metabolic effects intracellularly. In the cells of the target organs, estrogens interact with a specific receptor to form a complex which modulates gene transcription and subsequent protein synthesis. Such receptors have been identified in various organs, e.g. hypothalamus, pituitary, vagina, urethra, uterus, breast and liver, and in osteoblasts.

Estradiol, which from the menarche to the menopause is produced mainly by the ovarian follicles, is the most active estrogen. It is largely responsible for the development and maintenance of the female urogenital system and of secondary sexual characteristics. After the menopause, when the ovaries have ceased to function, only small amounts of estradiol are still

produced, from aromatisation of androstenedione and to a lesser extent testosterone, by the aromatase enzyme, yielding estrone and estradiol, respectively. Estrone is further transformed to estradiol by the enzyme 17beta-hydroxysteroid-dehydrogenase. Both enzymes occur in fat, liver, and muscle tissue.

In many women, the cessation of ovarian estradiol production results in vasomotor symptoms (hot flushes), sleep disturbances, and progressive atrophy of the urogenital system.

Hormone Replacement Therapy
ESTRADERM* (estradiol-17ß) provide continuous, controlled transdermal delivery of estradiol-17ß such that estradiol-17ß levels as well as the E_2/E_1 ratio in postmenopausal women are restored to those seen in the earlier follicular phase of the premenopausal range (see **Pharmacokinetics**). ESTRADERM* thus alleviate the symptoms of estradiol-17ß deficiency in menopausal women.

Placebo-controlled clinical studies have demonstrated that treatment with ESTRADERM* 50 or 100 (50 µg or 100 µg per day, respectively) prevents bone loss in postmenopausal women. In recently post-menopausal women, prophylactic treatment with ESTRADERM* 100 for 2 years led to a significant increase (3.7% above baseline), in vertebral bone density. Treatment with ESTRADERM* 50 showed maintenance of bone density. Initiating treatment with ESTRADERM* 100/medroxyprogesterone acetate (MPA) 10-15 years after menopause, prevented further loss of bone density in osteoporotic women with vertebral fractures. Vertebral bone density increased by 7.5% after 1 year.

Pharmacokinetics

Absorption: Studies in postmenopausal women using ESTRADERM* patches which provide 25, 50, and 100 µg of exogenous estradiol-17ß per day, showed increased blood levels within 4 hours. These levels were linearly proportional to the size of the dose and maintained respective mean serum estradiol-17ß levels of 59, 117 and 246 pM/L (16, 32, and 67 pg/mL) above baseline (typically 37 pM/L (10 pg/mL)). At the same time, increases in estrone serum concentration averaged only 1.1, 33, and 100 pM/L (0.3, 9, and 27 pg/mL) above baseline, respectively, providing an average E_2/E_1 ratio between 0.9-1.4, well within the pre-menopausal range. Serum concentrations of estradiol-17ß and estrone returned to pre-application levels within 24 hours after removal of the patch.

Distribution: Mean plasma clearance rates of estradiol-17ß and estrone in women have been estimated to be 735 L/day per m^2 and 1213 L/day per m^2, respectively. Hence, based on studies with ESTRADERM*, for women with a body surface area of 1.4-1.9 m^2, (weight, 48-86 kg; average height 157 cm) ESTRADERM* patches which provide 25, 50 and 100 µg/day should maintain mean steady state serum concentrations as follows:

Patch	Estradiol Dosage (µg per day)	Expected Increase in Serum Levels of Estradiol (pg/mL) Above Baseline (typically 10 pg/mL)

ESTRADERM* 25	25	12-18
ESTRADERM* 50	50	24-40
ESTRADERM* 100	100	48-85

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 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. Multiple-application studies yielded similar results, with urinary output of estradiol-17ß conjugates returning to baseline within 3 days of patch removal.

The plasma elimination half-life of estradiol-17ß is approximately 1 hour. The short half-life and rapid clearance of estradiol-17ß permit a rapid cessation of estrogen therapy when cycling is desirable.

Special Populations and Conditions

Pediatrics: ESTRADERM* 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: ESTRADERM* 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.

STORAGE AND STABILITY

Store patches below 25°C. Do not freeze.

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

Do not use any ESTRADERM* patch that is damaged or shows signs of tampering.

SPECIAL HANDLING INSTRUCTIONS

See DOSAGE AND ADMINISTRATION- Patch Application section.

DOSAGE FORMS, COMPOSITION AND PACKAGING

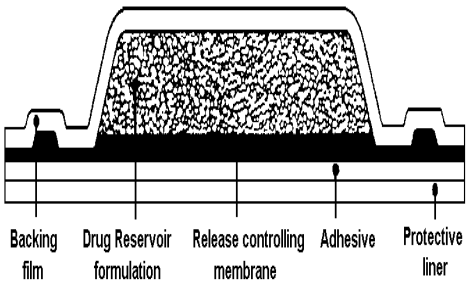
ESTRADERM* (estradiol-17ß) is a thin, round, multilayer, transparent transdermal therapeutic system, i.e., an adhesive patch, containing estradiol-17ß that is designed for application to an area of intact skin.

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

- a transparent polyester **backing film**
- a drug **reservoir** of estradiol-17ß and ethanol gelled with hydroxypropyl cellulose
- an ethylene vinyl acetate copolymer **release-controlling membrane**
- an **adhesive** formulation of light mineral oil and polyisobutylene
- 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. ESTRADERM* is available in 3 strengths; the composition per unit area is identical.



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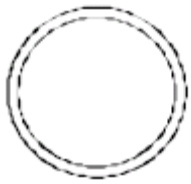


Shape

ESTRADERM* 50 (the round patch)

ESTRADERM* (estradiol-17ß) is available in the following strengths in patient packs containing 8 patches:

	ESTRADERM* 25	ESTRADERM* 50	ESTRADERM* 100
Estradiol-17ß Dosage nominal *in vivo* delivery	25 µg/day	50 µg/day	100 µg/day
Total Estradiol-17ß content	2 mg	4 mg	8 mg
Drug-Releasing Area	5 cm^2	10 cm^2	20 cm^2
Shape of Patch	Round	Round	Oblong
Printed (backing side)	CG DND	-	-

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

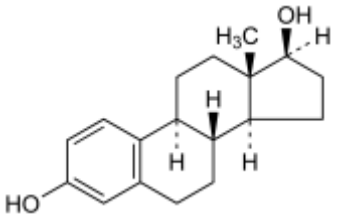
Proper name Estradiol-17β

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.

CLINICAL TRIALS

Relief of menopausal symptoms

Study demographics and trial design

Efficacy and safety of ESTRADERM* in the prevention of postmenopausal symptoms have been studied in two large 3-month comparative pivotal trials.

Table 4- Summary of patient demographics for clinical trials in Relief of menopausal symptoms

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=337)
Protocol 01	Open-label 3 weeks	Previously effective dose of conjugated estrogens (0.3 mg; 0.625 mg; 1.25 mg)	337 symptomatic postmenauposal women
	Washout period 10 days to 21 days	No treatment	

	Double-blind, randomized, stratified,
	parallel design,
	11 weeks period
		• Fixed dose of conjugated estrogens which they had previously taken + titrated ESTRADERM* TTS placebo
		  • Stratum I: 0.3 mg of conjugated estrogens
		  • Stratum II: 0.625 mg of conjugated estrogens
		  • Stratum III : 1.25 mg of conjugated estrogens
		• Titrated ESTRADERM* TTS (twice a week) + fixed dose conjugated estrogens placebo
		  • ESTRADERM* TTS 25 µg/day initiated
		  • After 1 week; ESTRADERM* TTS 50 µg/ day (if symptom were not adequately controlled)
		  • After 1 week; ESTRADERM* TTS 100 µg/day if symptoms were still present.
			240
			symptomatic postmenauposal women

Study results

Patient assessment for hot flushes, other menopausal symptoms, the effect on vaginal cytology, blood and urine hormonal levels, and global patient evaluation constituted the efficacy measures in this study.

A total of 203 patients were analyzable for efficacy. Analysis of the results revealed no statistically significant difference between the number of vasomotor flushes experienced by patients treated with ESTRADERM* and conjugated estrogens (0.3 mg; 0.625 mg; 1.25 mg). The doses of ESTRADERM* required to control symptoms varied between strata. Patients who had been controlled on conjugated estrogens 1.25 mg/day generally required the largest dose of ESTRADERM* (100 µg/day patch).

Another pivotal study, a double-blind, placebo-controlled, comparative study, 8 weeks period was conducted to evaluate the efficacy of ESTRADERM* TTS and conjugated estrogens in the treatment of menopausal symptoms.

Table 5- Summary of patient demographics for clinical trials in Relief of menopausal symptoms

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=166)

Protocol C-83-004	Double-blind, placebo-controlled, comparative study, 8 weeks period	Week 1-3	1 capsule of conjugated estrogens (0.625 or 1.25 mg ,the dose that he had been used for 3-24 months prior to enrolment for control of hot flushes) + 2 TTS placebo systems (replaced twice a week)	166 postmenopausal women who had obtained satisfactory control of hot flushes with either 0.625 or 1.25 mg of conjugated estrogens
		Week 4	Therapy-free week: ESTRADERM* TTS placebo (twice a week) + 1 capsule conjugated estrogens placebo	
		Week 5-7	1/3 of patients were randomly assigned to continue conjugated estrogens (0.625 or 1.25 mg, the dose used in weeks 1-3) 2/3 of patients received active treatment with ESTRADERM* 100µg / day	
		Week 8	Therapy-free week ESTRADERM* TTS placebo (twice a week) + 1 capsule conjugated estrogens placebo	

Study results

Results of the within subject comparison of hot flush frequency in weeks 1-3 (all patients on conjugated estrogens compared with weeks 5-7 (1/3 on conjugated estrogens and 2/3 on ESTRADERM*) showed no statistically significant difference in the mean number of weekly hot flushes between the two treatment periods for any treatment groups. During the course of the study, 51 patients terminated enrollment prior to the end of week 8, with 37 dropping out in weeks 1-4 while receiving conjugated estrogens or placebo. Only six patients discontinued treatment during ESTRADERM* use.

Prevention of osteoporosis

The efficacy and safety of ESTRADERM* in the prevention of postmenopausal osteoporosis showed that ESTRADERM* patches are a well tolerated and effective means to prevent bone loss in recently postmenopausal women

Study demographics and trial design

Table 7- Summary of patient demographics for clinical trials in prevention of osteoporosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=127)
Protocol Number 05	Double-blind,	• 80 patients were	127 postmenopausal

	randomized, parallel group, prospective trial, stratified by age (40-49, > 50 years) placebo controlled, 2 years	randomized to receive either ESTRADERM* 25, 50 or 100 µg/ day patches • 43 patients were randomized to placebo	women who were ≥ 40 years of age (average age 47 years)

A total of 127 patients were randomized to receive either ESTRADERM* 25, 50 or 100 µg/day patches (80 patients) or placebo (43 patients), of which 93 completed the 2 year study and were acceptable for the efficacy analysis. The primary measure of efficacy was bone mineral density of the lumbar spine (L2-L4). After 2 years of treatment, loss of vertebral bone density was prevented by ESTRADERM* 50 and 100 µg/day used on a daily basis. The higher daily dosage (100 µg/day) showed a significant gain in bone density (+3.7 % vs. baseline) after 2 years. In contrast, the placebo group lost 6.4% of their bone mass. ESTRADERM* 25 µg/day also significantly diminished the amount of bone lost from lumbar spine after 2 years ($p<0.05$) but did not completely eliminate net bone loss.

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.

At low physiological doses of estradiol (similar to those delivered by ESTRADERM*), neoplastic potential is negligible in experimental animals. Most of the documented effects of exogenously administered estradiol in animal studies have been consequences of the administration of supraphysiological doses and are consistent with an exaggerated pharmacological response (most notably the promotion of tumours in oestrogen-responsive tissues). However, long-term unopposed treatment with physiological doses of estradiol may lead to hyperplastic changes in oestrogen-dependent reproductive organs like the uterus.

In local tolerability studies in rabbits, some skin irritation was observed.

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PART III: CONSUMER INFORMATION

ESTRADERM*25
ESTRADERM*50
ESTRADERM*100

estradiol-17β

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

ABOUT THIS MEDICATION

What the medication is used for:

ESTRADERM* should not be used by women with intact uteri unless taken with an appropriate dosage of a progestin.

- The relief of menopausal and postmenopausal symptoms
- To prevent osteoporosis

Some women are more likely to develop osteoporosis after menopause than others. If you have been prescribed ESTRADERM* 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.

If you have not had a hysterectomy (operation to remove the womb), estrogens should be prescribed in association with a progestin

ESTRADERM* 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:

The main estrogen produced by your ovaries prior to menopause is estradiol, and this is the same estrogen that is in ESTRADERM*. When applied to the skin, the ESTRADERM* patch continually releases 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. Your doctor may adjust the amount you get by prescribing another (different) patch size.

By providing estradiol, ESTRADERM* offers relief from menopausal symptoms, slows down bone loss and may prevent bones from breaking.

Your body normally makes estrogens and progesterone (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.

When it should not be used

Certain medical conditions may be aggravated by estrogens, therefore estrogens should not be used at all under these conditions.
ESTRADERM* 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
- 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 coronary heart disease, a heart attack 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 the patch (see **What the medicinal ingredient is and What the nonmedicinal ingredients are**)

ESTRADERM* 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 is:
Estradiol-17 ß

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

What dosage forms it comes in:
ESTRADERM* is a transdermal patch available in three strengths: ESTRADERM* 25, ESTRADERM* 50 and ESTRADERM* 100, containing respectively 2, 4 and 8 mg of estradiol.

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 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).

If you still have your uterus, you should take a progestin medication (another hormone drug) regularly for a certain number of days of each month 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 ESTRADERM* 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
- are pregnant or may be pregnant
- are breastfeeding
- have had a hysterectomy (surgical removal of the uterus)
- smoke
- are undergoing surgery or need long bed rest.

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

INTERACTIONS WITH THIS MEDICATION

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

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 ESTRADERM* or, conversely, they may affect how well ESTRADERM* works. Your doctor may need to adjust the dose of your treatment.

PROPER USE OF THIS MEDICATION

Usual dose:

Follow all instructions given to you by your doctor or pharmacist carefully. Your doctor will explain when to start using ESTRADERM*. ESTRADERM* is used as continuous therapy. You will need to wear a patch all the time. The ESTRADERM* patches are applied twice weekly on the same days of each week. Each patch should be worn continuously for 3 to 4 days.

Each box contains eight ESTRADERM* patches. If your treatment is for less than 28 days of estrogen (cyclical therapy), you will have one or two patches left over which can be used for the next month.

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 ESTRADERM*

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).

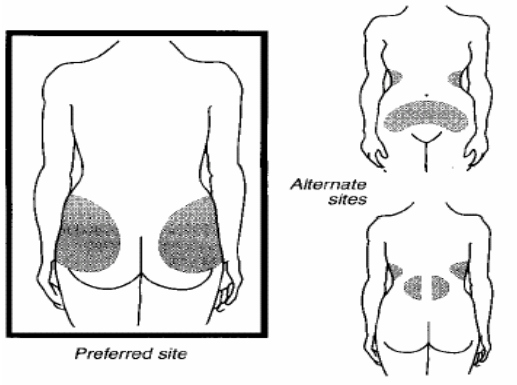
1. Preparing The Skin

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* patch

The buttock is the preferred place to apply the patch. Other suitable application sites are the sides, hip, 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.

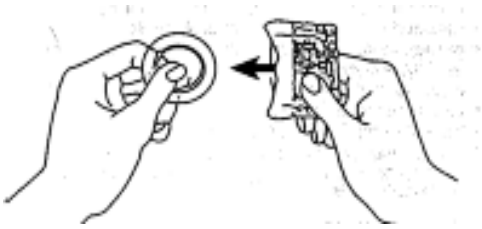
DO NOT APPLY ESTRADERM* TO YOUR BREAST, since this may cause unwanted effects and discomfort.

3. Opening the Pouch

Each ESTRADERM* 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.

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 (see 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* Patch

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

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

Any adhesive left on your skin should rub off easily. You can also use mineral oil, baby oil or rubbing alcohol to remove adhesive from the skin. Apply a new ESTRADERM* 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 (to a different 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* patch 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* 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.

Overdose:
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.

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.

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 bleedspainful and/or heavy periods (may be signs of growth of fibroids in the uterus), 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, spotty darkening of the skin, particularly on the face or abdomen (chloasma), rash, itching, acne, dryness or discoloration of the skin, purple skin patches, decline of memory or mental ability, 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 pharmacist
		Only if severe	In all cases	
Common	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 or excessively heavy vaginal 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 ESTRADERM*, contact your doctor or pharmacist.

HOW TO STORE IT

ESTRADERM* should be stored at room temperature (below 25°C) and away from direct sunlight. Do not freeze. **Store in the original package.**

ESTRADERM* patches should be kept out of the reach and sight of children and pets.

Do not use ESTRADERM* after the expiry date shown on the pack.

Do not use ESTRADERM* 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 provide. 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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