PRODUCT MONOGRAPH

PrESTRADOT®25
Transdermal Therapeutic System
25µg/24 hours of estradiol
PrESTRADOT®37.5
37.5µg/24 hours of estradiol
PrESTRADOT®50
50µg/24 hours of estradiol
PrESTRADOT®75
75µg/24 hours of estradiol
PrESTRADOT®100
100 µg/24 hours of estradiol

Estradiol-17ß

Estrogen

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Date of Initial Approval:
DEC 6, 2022

Control # 269091

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Patch 25, 37.5, 50, 75 and 100 µg	Cellulose compounds, ethanol, ethylene-vinyl acetate copolymer, light mineral oil, polyester and polyisobutylene.

INDICATIONS AND CLINICAL USE

ESTRADOT® (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 ESTRADOT may retard further bone loss. ESTRADOT 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 intact uteri, ESTRADOT 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 ESTRADOT on women more than 65 years old.

Pediatrics:
ESTRADOT is not indicated for use in children

CONTRAINDICATIONS

- Known or suspected hypersensitivity to this drug or to any ingredient in the formulation or to any component of the patch. For a complete listing, see Dosage Forms, Composition and Packaging section.
- Known or suspected estrogen-dependent malignant neoplasia such as endometrial cancer.
- Endometrial hyperplasia
- Known , suspected or past history of breast cancer
- Known or suspected pregnancy
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis
- Known thrombophilic disorders
- Liver dysfunction or disease as long as liver function tests have failed to return to normal.
- Undiagnosed abnormal genital bleeding
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease)
- Porphyria
- Partial or complete loss of vision from ophthalmic vascular disease
- Classical Migraine
- Breast feeding

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

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. Epidemiologic evidence from a meta-analysis suggests that while the risk of ovarian cancer diminishes over time after discontinuation, the risk is still significantly increased more than five years (median time of 10 years since last use) after stopping long duration hormone therapy (median duration of treatment of nine years) for serous or endometrioid tumours.

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

Cardiovascular
The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women. [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 or porphyria 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 Tests 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 ESTRADOT 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

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

Estrogens may induce or exacerbate symptoms of angioedema, in particular in women with hereditary angioedema. Angioedema requiring medical intervention involving eye/eyelid, face, larynx, pharynx, tongue and extremity (hands, legs, ankles, and fingers) with or without urticaria has occurred in the post marketing experience of using estradiol. If angioedema involves the tongue, glottis, or larynx, airway obstruction may occur. Patients who develop angioedema after treatment with estradiol should not receive ESTRADOT again.

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.
Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be reevaluated.

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 ESTRADOT.

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

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

Pediatrics: ESTRADOT is not indicated for use in children.

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

Monitoring and Laboratory Tests

Before ESTRADOT (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.

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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 and DRUG INTERACTIONS**- Drug-Laboratory Tests Interactions**)

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

Endocrine disorders
Increased blood sugar levels; decreased glucose tolerance.

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

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

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

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

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

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

Psychiatric disorders
Mental depression; nervousness; irritability.

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

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

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

Vascular disorders
Isolated cases of thrombophlebitis; thromboembolic disorders and cerebrovascular accident.

Clinical Trial Adverse Drug Reactions with ESTRADOT

This section summarizes adverse drug reaction data pooled from multiple sources including clinical trials and published investigations.

Because clinical trials are conducted under very specific conditions the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The most commonly reported adverse reaction to VIVELLE® (estradiol-17ß), another matrix patch, in clinical trials in patients treated for post-menopausal symptoms was redness and irritation at the application site. This caused approximately 0.8% of patients to discontinue

therapy. In a comparative clinical trial, ESTRADOT was found to be less irritating than VIVELLE®.

In a 2-year controlled trial in patients with post-menopausal osteoporosis, back pain was reported in 13% of patients treated with the VIVELLE® patch and 4.5% of patients treated with placebo. Local application site reactions (patch site erythema, itching, rash, burning, irritation) were reported in approximately 9% of patients treated with active patch and 10% of patients treated with placebo. In most cases the local application site reactions were considered mild; none was considered severe. Two patients out of 259 were discontinued from the trial due to local application site reactions.

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

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

Psychiatric disorders	
Common:	Depression
Nervous system disorders	
Common:	Headache, Migraine, Dizziness
Gastrointestinal disorders	
Common:	Nausea, Abdominal pain, Abdominal distension
Reproductive system and breast disorders	
Very common:	Breast tenderness
Common:	Menstrual disorders, Metrorrhagia, Cervical discharge, Breast enlargement
General disorders and administration site conditions	
Very common:	Application site reaction*
Common:	Weight fluctuation, Oedema, Pruritus and rash

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

Less Common Adverse Drug Reactions (<1%)

Gastrointestinal disorders:
Uncommon: Vomiting
General disorders and administration site conditions:
Uncommon: Libido increased or decreased
Neoplasms benign, malignant and unspecified (including cysts and polyps):
Uncommon: Breast cancer

Reproductive system and breast disorders:
Uncommon: Genital candidiasis, Uterine leiomyoma
Skin and subcutaneous tissue disorders:
Uncommon: Alopecia, Hirsutism

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	↑
Partial tromboplastin time	↓
Sex-hormone binding globulin (SHBG)	SHBG↑ in serum due to increased circulating estrogen
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.

Post-Market Adverse Drug Reactions

Adverse Drug Reactions with unknown frequency

Cardiac disorders:	Embolism, hypertension
Gastrointestinal disorders:	Cholelithiasis, liver function tests abnormal, diarrhoea
Immune system disorders:	Anaphylactic reaction, anaphylactoid reaction, hypersensitivity
Musculoskeletal and connective tissue disorder	Back pain, pain in extremities
Reproductive system and breast disorders:	Endometrial hyperplasia, breast discomfort, breast pain, dysmenorrhea, fibrocystic breast disease, breast discharge
Skin and subcutaneous tissue disorders:	Angioedema, erythema nodosum, erythema multiforme, rash generalised, pruritus generalized, urticaria, contact dermatitis, chloasma. Hypersensitivity, including allergic contact dermatitis and isolated cases of anaphylactoid reactions (some of the patients had a history of previous allergy or allergic disorders). Reversible post-inflammatory pigmentation and precipitation or aggravation of porphyria cutanea tarda in predisposed individuals

Nervous system disorders	chorea.
Psychiatric disorders	Nervousness, affect liability
Vascular disorders	varicose veins

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 rifampicin, rifabutin, nevirapine and efavirenz) may interfere with the activity of orally administered estrogens.
- Estradiol is predominantly metabolized by CYP3A4; concomitant administration of inhibitors of CYP3A4 such as ketoconazole, erythromycin or ritonavir may therefore result in an increase of approximately 50% in estradiol exposure.

Drug-Drug Interactions

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

Table 3- Established or Potential Drug-Drug Interactions

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

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

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

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

Drug-Food Interactions

The interaction of ESTRADOT 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 Tests Interactions

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

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

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

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

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

Drug-Lifestyle Interactions:

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

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 ESTRADOT (estradiol-17ß) can be initiated at once. In women who are currently taking oral estrogens, treatment with ESTRADOT can be initiated on reappearance of menopausal symptoms, following discontinuation of oral therapy.
- ESTRADOT is administered as continuous therapy (uninterrupted application). ESTRADOT 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**).
- ESTRADOT 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 ESTRADOT 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. ESTRADOT 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.

2. Prevention of post-menopausal 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 183 pM/L (50 picogram/mL).

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

Special Populations

Patients with renal and / or hepatic impairment

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

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

Pediatric population

ESTRADOT is not indicated for use in children.

Missed Dose

Patients who miss applying a patch of ESTRADOT, 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 ESTRADOT 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. The patch should be placed consistently on the same area of the body with each application (i.e., either the buttocks, lower abdomen, hip, 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 ESTRADOT 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.

ESTRADOT must not never be applied to, or near, 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

ESTRADOT 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 (see Pharmacology).

ESTRADOT delivers estradiol-17ß via the 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 transdermal 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.

Pharmacodynamics

Estradiol
The active substance in ESTRADOT, 17beta-estradiol, is chemically and biologically identical to the endogenous human 17beta-estradiol and is classified as a natural estrogen. It compensates for the decreasing estrogen production in menopausal women and alleviates menopausal symptoms. Estradiol prevents bone loss after the menopause or after an ovariectomy.

Hormone Replacement Therapy
ESTRADOT (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**). ESTRADOT thus alleviate the symptoms of estradiol-17ß deficiency in menopausal women.

Pharmacokinetics

Absorption: Studies in postmenopausal women using other estradiol-17ß matrix patches (VIVELLE®) which provide 37.5, 50, 75 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 92, 173, 217 and 308 pM/L (25, 47, 59 and 84 picogram/mL) above baseline (typically 37 pM/L). At the same time, increases in estrone serum concentration averaged only 44, 111, 81 and 207 pM/L (12, 30, 22 and 56 picogram/mL) above baseline, respectively, providing an average E_2/E_1 ratio between 1.6 and 2.7, well within the premenopausal 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 VIVELLE®, for women with a body surface area of 1.4-1.9 m^2, (weight, 48-86 kg; average height 157 cm) VIVELLE® patches which provide 37.5, 50, 75 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 (pM/L) Above Baseline (typically 37 pM/L)
VIVELLE 37.5	37.5	66-106
VIVELLE 50	50	88-147
VIVELLE 75	75	132-228
VIVELLE 100	100	176-312

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. Only 2% is free and biologically active.

Biotransformation/Metabolism: Metabolism and plasma levels of estradiol-17ß delivered transdermally are similar to those of endogenous hormone in premenopausal women. Estradiol-17ß is metabolised primarily in the liver to estrone, then later to estriol, epiestriol and catechol estrogens, which are then conjugated to sulphates and glucuronides, which are far less active than estradiol-17ß. Cytochrome 450 isoforms CYP1A2 and CYP3A4 catalyze the hydroxylation of estradiol-17ß forming estriol. Estriol is glucuronidated by UGT1A1 and UGT2B7 in humans.

Estrogen metabolites are excreted by the kidneys but 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. The bulk of the metabolites is excreted in the urine as glucuronides and sulphates.

Special Populations and Conditions

Pediatrics: ESTRADOT is not indicated for use in children

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

Gender: ESTRADOT 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; 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 ESTRADOT patches between 2°C-30°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 ESTRADOT out of the reach and sight of children and pets both before use and when disposing of used patches.

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

SPECIAL HANDLING INSTRUCTIONS

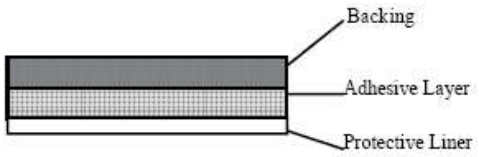
See DOSAGE AND ADMINISTRATION- Patch Application section.

DOSAGE FORMS, COMPOSITION AND PACKAGING

The ESTRADOT patch is thin, rounded rectangular, multilayer, transparent transdermal therapeutic system, i.e., an adhesive patch, containing estradiol 17ß that is designed for application to an area of intact skin.

Proceeding from the visible surface toward the surface attached to the skin, the ESTRADOT patch is comprised of three layers:

1. a translucent polyolefin film
2. an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, povidone and dipropylene glycol
3. a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used.



The active component of the patches is estradiol 17ß.
The nonmedicinal ingredients of the patches are: cellulose compounds, ethanol, ethylene-vinyl acetate copolymer, light mineral oil, polyester and polyisobutylene.

The matrix provides a source for continuous delivery of drug for up to 4 days. ESTRADOT is available in 5 strengths; the composition per unit area in each strength is identical. (see DOSAGE AND ADMINISTRATIONS section).

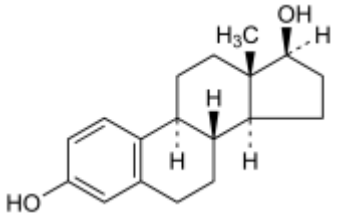
ESTRADOT (estradiol-17ß) is available in the following strengths in patient packs containing 8 patches:

	ESTRADOT 25	ESTRADOT 37.5	ESTRADOT 50	ESTRADOT 75	ESTRADOT 100
Estradiol-17ß Dosage nominal *in vivo* delivery	25 µg/day	37.5 µg/day	50 µg/day	75 µg/day	100 µg/day
Total Estradiol-17ß content	0.39 mg	0.585 mg	0.78 mg	1.17 mg	1.56
Drug-Releasing Area	2.5 cm^2	3.75 cm^2	5 cm^2	7.5 cm^2	10 cm^2
Shape of Patch	Rounded rectangle	Rounded rectangle	Rounded rectangle	Rounded rectangle	Rounded rectangle

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	290.4 g/Mol
Structural formula	
Physicochemical properties	Estradiol is a white crystalline powder. Estradiol is practically insoluble in water; soluble 1 in 28 of alcohol and soluble 1 in 17 of acetone

CLINICAL TRIALS

<u>Relief of menopausal symptoms</u>

Study demographics and trial design

Efficacy and safety of another estradiol-17ß matrix patch (VIVELLE®) in the relief of menopausal and postmenopausal symptoms have been studied in two multicenter, double-blind, placebo-controlled pivotal studies. A total of 356 healthy menopausal women aged 30-65 years (mean 50.5 years) with moderate to severe vasomotor symptoms, a minimum of 6 hot flushes/day, plasma estradiol levels ≤20 picogram/mL and plasma FSH levels ≥50 mU/mL were enrolled in the studies. A total of 266 women were randomized to VIVELLE® patches (37.5, 50, 75 or 100 µg/day) and 90 were randomized to placebo patches. Over 3 months (3 cycles), the patches were applied to a clear, non-oily area of the abdomen below the waist and were changed twice a week. The evaluable groups consisted of 239 active and 80 placebo patients.

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=356)	Mean age (Range)	Gender
Studies 1003-A and 1003-B combined	two multicenter, double-blind, placebo-controlled pivotal safety and efficacy trials	-patch 37.5 µg/day (n=79), twice a week for 3 months - patch 50 µg/day (n=44), twice a week for 3 months - patch 75 µg/day (n=40), twice a week for 3 months - patch 100 µg/day (n=76), twice a week for 3 months	ESTRADOT: 266 women randomised to VIVELLE® patches (37.5,50,75 or 100 µg/day)	30-65 years (mean 50.5 years)	Women
		Patch placebo (n=80), twice a week for 3 months	Placebo: 80 women randomized to placebo patches		

Study results

The primary efficacy variable for both studies was the change in the number of hot flushes at the end of the third treatment cycle compared to baseline values. VIVELLE® was found to be statistically and clinically superior to placebo at all four doses (Table 5). In addition, VIVELLE® significantly reduced the severity of hot flushes, sweating and insomnia compared to placebo.

Table 5 Mean reduction in number of hot flushes - Studies 1003-A and 1003-B combined

Treatment	N	Baseline	N	Cycle 3
37.5 µg/day	79	10.3	77	-7.1*
50 µg/day	44	12.5	43	-7.6*
75 µg/day	40	13.0	37	-9.1*
100 µg/day	76	11.2	68	-9.0*
Placebo	80	10.8	72	-3.0

*$p<0.0001$

Prevention of osteoporosis

Study demographics and trial design

Efficacy and safety of another estradiol-17ß matrix patch (VIVELLE®) in the prevention of postmenopausal osteoporosis have been studied in a 2-year double-blind, randomized, placebo-controlled, parallel group study. A total of 261 hysterectomized (161) and non-hysterectomized (100), surgically or naturally menopausal women (within 5 years of menopause), with no evidence of osteoporosis (lumbar spine bone mineral density within 2 standard deviation of average peak bone mass, i.e., ≥0.827 g/cm2) were enrolled in this study; 194 patients were randomized to one of the four doses of VIVELLE® (100, 50, 37.5 or 25 µg/day) and 67 patients to placebo. Over 2 years, study systems were applied to the buttock or the abdomen twice a week. Non-hysterectomized women received oral medroxy progesterone acetate (2.5 mg/day) throughout the study.

The study population comprised naturally (82%) or surgically (18%) menopausal, hysterectomized (61%) or nonhysterectomized (39%) women with a mean age of 52.0 years (range 27 to 62 years; the mean duration of menopause was 31.7 months (range 2 to 72 months). Two hundred thirty nine (92%) of randomized subjects (178 on active drug, 61 on placebo) contributed data to the analysis of percent change from baseline in bone mineral density (BMD) of the AP lumbar spine, the primary efficacy variable.

Table 6- Summary of patient demographics for clinical trials in Prevention of osteoporosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=261)	Mean age (Range)	Gender
035	2-year double-blind, randomized, placebo-controlled, parallel group study	-patch 25 µg/day twice a week for 2 years - patch 37.5 µg/day twice a week for 2 years - patch 50 µg/day twice a week for 2 years - patch 100 µg/day twice a week for 2 years	ESTRADOT: 194 patients were randomized to one of the four doses of VIVELLE® (100, 50, 37.5 or 25 µg/day)	27-62 years (mean 52.0 years)	Women
		Patch placebo twice a week for 2 years	Placebo: 67 women randomized to placebo patches		

Study results

There was an increase in BMD of the AP lumbar spine in all VIVELLE® dose groups; in contrast to this a decrease in AP lumbar spine BMD was observed in placebo patients. All VIVELLE® doses were significantly superior to placebo ($p<0.05$) at all time points with the exception of VIVELLE® 50 µg/day at 6 months, implying bone preservation for all treatment groups, as opposed to bone loss for placebo.

Analysis of percent change from baseline in femoral neck BMD also showed similar results; all doses of VIVELLE® were significantly superior to placebo ($p<0.05$) at 24 months.

Serum osteocalcin (a marker of bone formation) and urinary excretion of cross-link N-telopeptides of type 1 collagen (a marker of bone resorption) generally decreased in active treatment groups, suggesting a decrease in bone turnover. However, the differences were not statistically significant.

Bioequivalence Study

A comparative, multiple dose, cross-over pharmacokinetic study in 30 healthy postmenopausal women demonstrated that the ESTRADOT 5 cm^2 (50 µg/day) and the VIVELLE® 14.5 cm^2 (50 µg/day) patches produced comparable serum concentrations of estradiol at steady state. Each patch was administered for four 84-hour dosing periods with a 7-day washout period between treatments. Statistical analyses also demonstrated equivalence between the two patches for estradiol pharmacokinetic parameters.

Table 7- Mean Observed Pharmacokinetic Parameters for Estradiol (E_2) Obtained After Treatments with Two Different Transdermal Estradiol Systems (n=30)

Parameter	ESTRADOT 5.0 cm^2 patch Mean (SD)	VIVELLE® 14.5 cm^2 patch Mean (SD)
C_{max} (pg/mL)	56.7 (30.7)	52.7 (20.0)
T_{max} (h)	30.7 (15.6)	22.0 (13.5)
C_{trough} (pg/mL)	28.1 (19.5)	29.4 (12.3)
% Fluctuation	158.0 (190.8)	89.2 (59.4)
AUC_{0-84} (pg·h/mL)	3088 (1721)	2886 (1147)
AUC_{0-96} (pg·h/mL)	3268 (1865)	3051 (1191)
k_e (h^{-1})	0.138 (0.079)	0.132 (0.056)
$t_{½}$ (h)	7.7 (7.1)	6.3 (2.7)

DETAILED PHARMACOLOGY

See Action and Clinical Pharmacology (Part I)

TOXICOLOGY

Preclinical safety data

The toxicity profile of estradiol is 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 ESTRADOT), 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.

REFERENCES

1. Adami S, Suppi R, Bertoldo F, Rossini M, Residori M, Maresca V, et al. Transdermal estradiol in the treatment of postmenopausal bone loss. Bone and Mineral, Elsevier1989; 7:79-86.

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

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

4. Bergkvist L, Adami HO, Persson I, Hoover R, Schairer C. The risk of breast cancer after estrogen and estrogen-progestin replacement. N Engl J Med 1989; 321(5):293-7.

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

6. CGS 15885 ESTRADERM TTS Single case file of spontaneous reports on adverse reactions. Ciba-Geigy Ltd., Basel, (data available on request).

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

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

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

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

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

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

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

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

15. Daly E, Vessey MP, Hawkins MM, Carson JL, Gough P, Marsh S. Risk of Venous thromboembolism in users of hormone replacement therapy. Lancet 1996; 348:977-80.

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

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

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

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

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

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

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

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

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

25. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. JAMA 1998; 280(7):605-13.

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

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

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

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

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

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

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

33. Naessén T, Persson I, Adami HO, Bergström R, Bergkvist L. Hormone replacement therapy and the risk for first hip fracture. Ann Int Med 1990; 113(2):95-103.

34. Padwick ML, Endacott J, Whitehead MI. Efficacy, acceptability, and metabolic effects of transdermal estradiol in the management of postmenopausal women. Am J Obstet Gynecol 1985; 152 (8): 1085-1091 postmenopausal women. Am J Obstet Gynecol 1985; 152(8):1085-91.

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

36. Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal oestrogen therapy and hip fractures. Ann Int Med 1981;95(1):28-31.

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

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

39. Place VA, Powers M, Darley PE, Schenkel L, Good WR. A double-blind comparative study of Estraderm and Premarin in the amelioration of postmenopausal symptoms. Am J Obstet Gynecol 1985; 152(8):1092-9.

40. Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17ß-estradiol: Comparison with conventional oral estrogens used for hormone replacement. Am J Obstet Gynecol 1985; 152(8):1099-106.

41. Ribot C, Tremollieres F, Pouilles JM, Louvet JP, Peyron R. Preventive effects of transdermal administration of 17ß-estradiol on postmenopausal bone loss: A 2-year prospective study. Gynecol Endocrinol 1989; 3:259-67.

42. Selby PL, Peacock M. Dose dependent response of symptoms, pituitary, and bone to transdermal oestrogen in post menopausal women. Br Med J 1986; 293:1337-9.

43. Selby PL, Peacock M. The effect of transdermal oestrogen on bone, calcium regulating hormones and liver in postmenopausal women. Clin Endocrinol 1986; 25(5):543-7.

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

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

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

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

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

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

50. Stevenson JC, Cust MP, Gangar KF, Hillard TC, Lees B, Whitehead MI. Effects of transdermal versus oral hormone replacement therapy on bone density in spine and proximal femur in postmenopausal women. Lancet 1990; 336:265-9.

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

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

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

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

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

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

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

PART III: CONSUMER INFORMATION

PrESTRADOT®25
PrESTRADOT®37.5
PrESTRADOT®50
PrESTRADOT®75
PrESTRADOT®100
estradiol-17β

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

ABOUT THIS MEDICATION

What the medication is used for:
ESTRADOT 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,
- The prevention of osteoporosis due to a lack of estrogens occurring naturally or caused by a surgery (removal of uterus). In postmenopausal women already diagnosed as having osteoporosis and vertebral fractures, treatment with ESTRADOT may retard further-bone loss. For the prevention of osteoporosis, you should also consider alternative therapies with your doctor.

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

ESTRADOT 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 ESTRADOT. When applied to the skin, the ESTRADOT 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, ESTRADOT 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: 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.

ESTRADOT 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, 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 genital bleeding
- if you have active thrombophlebitis (inflamed varicose veins)

- if you currently have a problem with blood clots forming in your blood vessels or have ever had such a problem in the past. This may cause painful inflammation of the veins (thrombophlebitis) or blockage of a blood vessel in the legs (deep vein thrombosis), lungs (pulmonary embolism) or other organs
- if you have ever had a heart attack, stroke or coronary heart disease
- 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 estradiol or any other component of the patch (see **What the medicinal ingredient is** and **What the nonmedicinal ingredients are**).

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

What the medicinal 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:
ESTRADOT is a patch that is applied to the skin. It is available in five sizes, each containing and releasing different amounts of estradiol, as follows:

- ESTRADOT 25: 2.5 cm^2 patch, containing 0.39 mg estradiol (as hemihydrate) and releasing around 25 µg estradiol per day.
- ESTRADOT 37.5: 3.75 cm^2 patch, containing 0.585 mg estradiol (as hemihydrate) and releasing around 37.5 µg estradiol per day.
- ESTRADOT 50: 5 cm^2 patch, containing 0.78 mg estradiol (as hemihydrate) and releasing around 50 µg estradiol per day.
- ESTRADOT 75: 7.5 cm^2 patch, containing 1.17 mg estradiol (as hemihydrate) and releasing around 75 µg estradiol per day.
- ESTRADOT 100: 10 cm^2 patch, containing 1.56 mg estradiol (as hemihydrate) and releasing around 100 µg estradiol per day.

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 the 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 ESTRADOT talk to your doctor or pharmacist if you:

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

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

INTERACTIONS WITH THIS MEDICATION

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

This particularly includes the following: 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, ketoconazole, erythromycin, rifabutin, nevirapine, efavirenz), and herbal medicines (e.g. St John's wort).

The following interactions with ethinyl estradiol-containing products (specifically, oral contraceptives) have been reported in the public literature. It is unknown whether such interactions occur with drug products containing other types of estrogens (like hormone replacement therapy): acetaminophen, vitamin C, aminoglutethimide with medroxyprogesterone acetate (MPA), atorvastatin, clofibric acid, cyclosporin, morphine, prednisolone, salicylic acid, temazepam, theophylline, and troglitazone.

These medicines may be affected by ESTRADOT or, conversely, they may affect how well ESTRADOT 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 ESTRADOT. ESTRADOT is used as continuous therapy. You will need to wear a patch all the time. The ESTRADOT 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 ESTRADOT 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 ESTRADOT
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).

Patches should be applied whole.

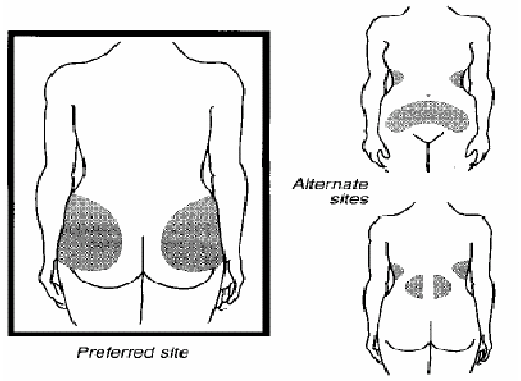
1. Preparing the Skin
In order for the patch to stick, the skin should be clean, dry and free of creams, lotions or oils. If you wish, you may use body lotion after the patch has been properly applied to the skin. The skin should not be irritated or broken, since this may alter the amount of hormone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

The ESTRADOT patch is rounded rectangular.

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



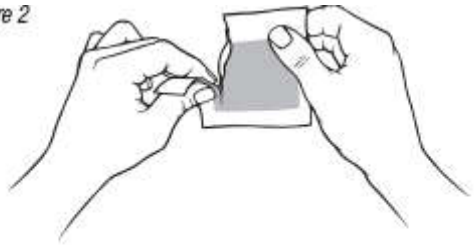
Avoid areas of the skin where clothing may rub the patch off or areas where the skin is very hairy or folded. Also avoid areas where the patch is likely to be exposed to the sun since this may affect how the patch works.

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

3. Opening the Pouch

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

Figure 2



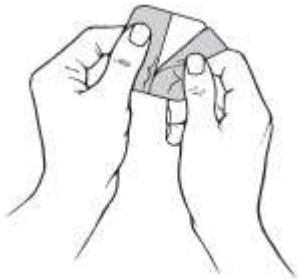
4. Removing the Liner

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

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

To separate the patch from the liner, hold the patch with the protective liner facing you. Peel off one half of the protective liner and discard it (see Figure 3). Try to avoid touching the sticky side of the patch with your fingers.

Figure 3



Using the other half of the liner as a handle, apply the sticky side of the system to a dry area of intact skin on the trunk of the body. Press the sticky side on the skin and smooth down. Fold back the remaining side of the edge of the protective linerand pull it across the skin (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 ESTRADOT 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 ESTRADOT 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 ESTRADOT 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 ESTRADOT 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 ESTRADOT patch every time a new patch is applied, usually twice weekly

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

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

Overdose:
If more medication has been taken than what has been prescribed, remove the patch and contact either your doctor, hospital, or emergency department or poison control centre immediately.

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:
The most common adverse drug reactions (≥1%) are: swelling of the lower legs, ankles, fingers or abdomen due to fluid retention (oedema), change in weight, vaginal bleeding or spotting and changes in vaginal discharge**,** headache, depression, migraine, dizziness, nausea, abdominal pain and swelling, tender breasts and breast enlargement, and persistent or severe skin irritation, redness, rash or itching of the skin after the patch has been removed (signs of application site reaction includes bleeding, bruising, burning, discomfort, dryness, skin boils, edema, erythema, inflammation, irritation, pain, tiny solid skin bumps, rash, skin discolouration, skin pigmentation, swelling, hives, and blisters.

The less common adverse drug reactions (<1%) are: change in your sex drive, hair loss, excessive hairiness, vomiting, lump or mass in the breast (possible signs of breast cancer), fibroids (benign growths in the uterus) vaginal thrush (vaginal fungal infection with severe itching, vaginal discharge).

The adverse drug reactions with unknown frequency are:
easy bruising, excessive nose bleeds, spotty darkening of the skin, particularly on the face or abdomen (chloasma), purple skin patches, acne, decline of memory or mental ability, rapid mood changes, contact lens discomfort, dry eyes, gall bladder disease (tendency to form gall stones), nervousness, back pain and pain in extremity, signs or symptoms that blood clots may have formed in your body (pains in the calves, thighs or chest, sudden shortness of breath, coughing blood or dizziness), increase in blood pressure, yellowing of the eyes or the skin, diarrhea, signs of an allergic reactions **(**sudden troubled breathing, tightness of the chest, general rash or itching), uncontrollable jerky movements **(**chorea), skin inflammation and rash (rash with painful red lumps, pain in joints and muscles swelling, blistering of lips, eyes, skin peeling) breast pain, irregular heavy vaginal bleeding or constant spotting (possible signs of endometrial hyperplasia), menstrual cramps, breast discharge, lumps in the breast (non-cancerous), hives, worsening of porphyria (a condition affecting the liver), and varicose veins.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Abdominal pain and nausea		√	
	Migraine			√
	Persistent sad mood (depression)			√
Uncommon	Breast lump		√	
	Crushing chest pain or chest heaviness			√
	Pain or swelling in the leg			√
	Sharp pain in the chest, coughing blood or sudden shortness of breath			√
	Sudden partial or complete loss of vision			√
	Sudden severe headache or worsening of headache, vomiting, dizziness, fainting, disturbance of vision or speech or weakness or numbness in an arm or leg			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Frequency	Symptom / possible side effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
	Unexpected vaginal bleeding		√	
	Yellowing of the skin or eyes (jaundice)			√
	Signs of allergic reaction: may include rash, itching, hives, breathlessness or difficult breathing, wheezing or coughing, light-headedness, dizziness, changes in levels of consciousness, hypotension, with or without mild generalized itching, skin reddening, swelling of the face, throat, lips, tongue, skin and periorbital edema.			√
	Increase in blood pressure		√	

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

HOW TO STORE IT

Store ESTRADOT patches between 2°C-30°C. Do not freeze. Store in the original package.

ESTRADOT patches should be kept out of the reach and sight of children and pets before use and when disposing of used patches.

Do not use ESTRADOT after the expiry date shown on the pack.

Do not use ESTRADOT pack that is damaged or shows signs of tampering.

REPORTING SUSPECTED SIDE EFFECTS

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

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

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

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
www.sandoz.ca
or by contacting the sponsor, Sandoz Canada Inc., at:
1-800-361-3062.

This leaflet was prepared by Sandoz Canada Inc.

Last revised: DEC 6, 2022

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