
PRESCRIBING INFORMATION

Product Monograph

Pr **ESTRADOT**®

(Estradiol-17 β)

Transdermal Therapeutic System

25, 37.5, 50, 75 and 100 μ g/24 hours of estradiol

Estrogen

Warning

As the Women's Health Initiative (WHI) study results indicated increased risk of myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep venous thrombosis in postmenopausal women receiving treatment with combined oral conjugated equine estrogens (CE 0.625 mg) and medroxyprogesterone acetate (MPA 2.5 mg) compared to those receiving placebo tablets, the following should be highly considered:

- 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 indications.
- For the prevention of osteoporosis, estrogen treatment should be considered in light of other available therapies.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the recognized indications.

Actions And Clinical Pharmacology

ESTRADOT is designed to deliver daily estradiol-17 β , a physiologic hormone, transdermally into the systemic circulation. Due to the transdermal route of administration, the estradiol-17 β does not undergo first-pass liver metabolism. Resultant estradiol-17 β plasma levels are comparable to those seen in premenopausal women in the early follicular phase of the menstrual cycle. Estradiol-17 β stimulates target tissues such as the uterus, breast and vagina (see Pharmacology).

ESTRADOT delivers estradiol-17 β 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.

Clinical Studies

Relief of menopausal symptoms

Efficacy and safety of another estradiol-17 β 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 \leq 20 pg/mL and plasma FSH levels \geq 50 mU/mL were enrolled in the studies. A total of 266 women were randomized to VIVELLE patches (37.5, 50, 75 or 100 μ g/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.

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 I). In addition, VIVELLE significantly reduced the severity of hot flushes, sweating and insomnia compared to placebo.

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

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

*p<0.0001

Prevention of osteoporosis

Efficacy and safety of another estradiol-17 β 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 μ g/day) and 67 patients to placebo. Over 2 years, study systems were applied to the buttock or the abdomen twice a week. Nonhysterectomized 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. 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 μ g/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 cm² (50 μ g/day) and the VIVELLE 14.5 cm² (50 μ g/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 II Mean Observed Pharmacokinetic Parameters for Estradiol (E₂) 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)

Indications And Clinical Use

ESTRADOT (estradiol-17β) is indicated for the relief of menopausal and postmenopausal symptoms occurring in naturally or surgically induced estrogen deficiency states.

ESTRADOT is also indicated for 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.

In patients with an intact uterus, ESTRADOT should always be supplemented by sequential administration of a progestin whose role is to prevent endometrial hyperplasia.

Contraindications

ESTRADOT (estradiol-17β) should not be administered to patients with any of the following conditions:

- Personal history of known or suspected estrogen-dependent neoplasia such as breast or endometrial cancer
- Known or suspected breast cancer
- Active hepatic dysfunction or disease, especially of the obstructive type

- Severe hepatic disease
- Endometrial hyperplasia
- Undiagnosed abnormal vaginal bleeding
- Active or past history of arterial thromboembolic disease (e.g. cerebrovascular accident, myocardial infarction, coronary heart disease)
- Active or past history of confirmed venous thromboembolism (such as deep venous thrombosis or pulmonary embolism) or active thrombophlebitis
- Porphyria
- Partial or complete loss of vision from ophthalmic vascular disease
- Classical Migraine
- Known or suspected pregnancy
- Breast feeding
- Known or suspected hypersensitivity to any component of the patch

Warnings

See **Boxed Warnings** at the front page

CARDIOVASCULAR DISORDERS

Available epidemiological disorders data indicate that use of estrogen with or without progestin is associated with an increased risk of stroke and coronary heart disease. WHI-trial's results concluded that there are more risks than benefits among women using combined oral Hormone Replacement Therapy (HRT), compared to the group using placebo. In 10,000 women on combined HRT (conjugated equine estrogens/medroxyprogesterone acetate) over one year period, there were seven more cases of coronary heart disease (37 on combined HRT versus 30 on placebo) and eight more cases of strokes (29 versus 21).

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit.

Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary

heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years.

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS, 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.

BREAST CANCER

Current epidemiological data indicate that the use of combined HRT is associated with an increased risk of invasive breast cancer. WHI-trial's results suggest that risks exceed benefits among women using combined HRT (conjugated equine estrogens/medroxyprogesterone acetate), compared to the group using placebo. In 10,000 women on combined HRT over one year period, there were eight more cases of invasive breast cancer (38 on combined HRT versus 30 on placebo).

The WHI study 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 WHI trial also reported that 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.

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease. 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 increased risk of being diagnosed with breast cancer after 4 years of treatment with HRT (as reported in the results of WHI-trial) be discussed with the patient and weighed against its known benefits.

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

VENOUS THROMBOEMBOLISM

Recent epidemiological data indicate that the use of estrogen with or without progestin is associated with an increased risk of developing venous thromboembolism (VTE). WHI-trial's results suggest that risks exceed benefits among women using combined HRT (conjugated equine estrogens/medroxyprogesterone acetate), compared to the group using placebo. In 10,000 women on combined HRT over a period of one year, there were eighteen more cases of total blood clots in the lungs and legs (34 on combined HRT versus 16 on placebo).

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) and severe obesity (body mass index > 30 kg/m²). 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 this diagnosis is confirmed, the use of HRT is viewed as contraindicated.

The risk of VTE may be temporarily increased with prolonged immobilization, major elective surgery or posttraumatic surgery, or major trauma (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. 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 although there is no consensus about the possible role of varicose veins in VTE. 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.

ENDOMETRIAL HYPERPLASIA & ENDOMETRIAL CARCINOMA

Estrogen-only HRT increases the risk of endometrial hyperplasia (if taken by women with intact uteri). Estrogen-only hormonal therapy in postmenopause is recommended for women without uterus 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 was available to assess the relationship and the effects of the progestogen treatment on the endometrium.

The risk of endometrial cancer in users of unopposed estrogens who have an intact uterus 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 Coadministration Of Progestins under Dosage And Administration and Pharmacology**).

OVARIAN CANCER

In some epidemiological studies, the long-term use of unopposed estrogens in hysterectomised women has been associated with an increased risk of ovarian cancer. It is uncertain whether long-term use of combined HRT (estrogens and progestogens) confers a different risk than estrogen-only HRT products.

GALLBLADDER DISEASES

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported with combined oral CE and MPA treatment.

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.

BENIGN HEPATIC ADENOMAS AND HEPATOCELLULAR CARCINOMAS

Benign hepatic adenomas have been associated with the use of combined estrogen and progestin oral contraceptives. Although benign and rare, these tumors 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. 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.

DEMENTIA

In a randomized placebo controlled ancillary study of the WHI, the Women's Health Initiative Memory Study (WHIMS), women aged 65 and older (average age 71) treated with oral CEE and MPA for an average follow-up of 4 years were reported to have a two-fold increase in the risk of developing probable dementia. The absolute excess risk of probable dementia was 23 additional cases per 10,000 person-years (45 versus 22) in CEE/MPA treated women and the relative risk was 2.05.

Since only women aged 65 and older were included in this study, it is unknown whether these findings apply to younger postmenopausal women.

The estrogen-only sub-study of the WHIMS is currently on-going and no data are available yet. It is therefore unknown whether these findings apply to estrogen-only therapy.

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.

Precautions

- Before ESTRADOT (estradiol-17 β) 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 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 and should include at least those procedures outlined above.

Women should be advised that changes in their breasts should be reported to their doctor or nurse. Investigations, including mammography, should be carried out in accordance with currently accepted screening practices and adapted to the clinical needs of the individual woman.

It is important that patients are encouraged to practice frequent self-examination of the breasts.

- 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.
- Women using hormonal replacement therapy (HRT) 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 evaluated and HRT therapy may have to be discontinued.
- Abnormal vaginal bleeding due to its prolongation, irregularity or heaviness occurring during therapy should prompt diagnostic measures like hysteroscopy, endometrial biopsy or curettage to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.
- Pre-existing uterine leiomyoma may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyoma requires discontinuation of medication.
- Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.
- Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis, or loss of consciousness should discontinue medication.
- Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. Treatment should be stopped if there is an increase in epileptic seizures. 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.

- 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, in patients with renal insufficiency and in patients with otosclerosis.
- A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and post-menopausal patients on oral estrogen treatment. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.
- Women with familial hypertriglyceridemia need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.
- 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 **Laboratory Tests**.
- Caution is advised in patients with a history of estrogen-related jaundice and pruritus. If cholestatic jaundice develops during treatment, the treatment should be discontinued and appropriate investigations carried out.

Drug Interactions

Estrogens may diminish the effectiveness of anticoagulants, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes (e.g., barbiturates, hydantoin, carbamazepine, meprobamate, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

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.

1. The metabolism of ethinyl estradiol is increased by rifampicin and anticonvulsants such as phenobarbital, phenytoin and carbamazepine. Coadministration of troglitazone and certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduces the plasma concentrations of ethinyl estradiol by 30 percent.

Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol) increases AUC values for ethinyl estradiol by 20 percent.

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

2. Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral

contraceptives containing ethinyl estradiol). In addition, these drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased plasma concentrations of acetaminophen and increased clearance of temazepam, salicylic acid, morphine and clofibric acid have been noted when these drugs were administered with certain ethinyl estradiol containing drug products (e.g., oral contraceptives containing ethinyl estradiol).

Concomitant administration of aminoglutethimide with medroxyprogesterone acetate (MPA) may significantly reduce the bioavailability of MPA.

It was found that some herbal products (e.g., St. John's wort) which are available as OTC products might affect metabolism, and therefore, efficacy and safety of estrogen/progestin products.

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

Laboratory Tests

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

- increased sulfobromophthalein retention;
- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T_4) as measured by column or radioimmunoassay; free 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;
- reduced response to the METOPIRONE test;
- impaired glucose tolerance;
- reduced serum folate concentration;
- increased serum triglyceride and phospholipid concentration.

With transdermally administered estradiol- 17β , 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 months. The pathologist should be informed that the patient is receiving estrogen therapy when relevant specimens are submitted.

Information To Be Provided To The Patient

See Information For The Consumer.

Adverse Reactions

See **Warnings** and **Precautions** regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The most commonly reported adverse reaction to VIVELLE (estradiol-17 β), 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.

The following adverse reactions have been reported with estrogens in general.

Gastrointestinal

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain); bloating; gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

Genitourinary

Breakthrough bleeding; spotting and vaginal bleeding; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; dysuria; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; cystitis; changes in cervical erosion and amount of cervical secretion.

Skin

Allergic contact dermatitis; reversible post-inflammatory pigmentation; general pruritus and exanthema; loss of scalp hair; chloasma or melasma, which may persist when drug is discontinued; pigmentation of the skin; erythema nodosum; erythema multiforme; hemorrhagic skin eruptions; precipitation or aggravation of porphyria cutanea tarda in predisposed individuals; hirsutism.

Isolated cases of anaphylactoid reactions (some of the patients had a history of previous allergy or allergic disorders).

Endocrine

Breast swelling and tenderness; increased blood sugar levels; decreased glucose tolerance; sodium retention.

Cardiovascular/Hematologic

Palpitations; isolated cases of: thrombophlebitis; thromboembolic disorders; exacerbations of varicose veins; increase in blood pressure (see Warnings and Precautions); coronary thrombosis; altered coagulation tests (**see Laboratory Tests under Precautions**).

Central Nervous System

Aggravation of migraine episodes; headaches; mental depression; nervousness; dizziness; fatigue; irritability; neuro-ocular lesions (e.g., retinal thrombosis, optic neuritis).

Dementia has been reported in association with some estrogen-progesterone treatments.

Ophthalmic

Visual disturbances; steepening of the corneal curvature; intolerance to contact lenses; neuro-ocular lesions (see CNS above).

Miscellaneous

Changes in appetite; changes in body weight; edema; neuritis; change in libido; musculoskeletal pain [including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks). If symptoms persist, the dose of estrogen should be reduced.]

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

Symptoms And Treatment Of Overdosage**Symptoms**

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

Owing to the mode of administration (transdermal), plasma levels of estradiol-17 β can be rapidly reduced by removal of the patch.

Symptomatic treatment should be given.

Dosage And Administration

Dosage

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-17 β) 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 an intact uterus, 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**).

See the Precautions section on the examination of the patient before ESTRADOT administration.

Dose Adjustment

1. Menopausal symptoms

Treatment of menopausal symptoms is usually initiated with a patch that releases 50 μ g estradiol-17 β 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-17 β may require adjustment according to the patient's clinical status, the plasma estradiol-17 β levels and the results of bone mineral density studies. Ideally, plasma estradiol-17 β levels should be maintained at 183 pM/L (50 pg/mL).

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

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 be applied to the breasts to avoid potentially harmful effects on the breast tissue.

If a woman has forgotten to apply a patch, she 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.

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.

Wide interpatient variation in absorption occurs with progestins.

The following regimens have been shown, in general, to produce histological and biochemical changes consistent with a uniform secretory pattern in the endometrium.

- norethindrone 0.7 mg/day P.O. administered sequentially for 12 days each cycle.

- medroxyprogesterone acetate (MPA) 10 mg/day (P.O.) administered sequentially for 12 days each cycle.

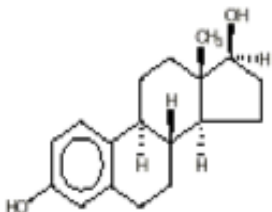
There are possible additional risks that may be associated with the inclusion of a progestin in estrogen replacement regimens. The potential risks include adverse effects on carbohydrate and lipid metabolism, mood changes and edema. The choice and dose of progestin may be important in minimizing these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

Children

ESTRADOT should not be used in children.

Pharmaceutical Information

Drug Substance:



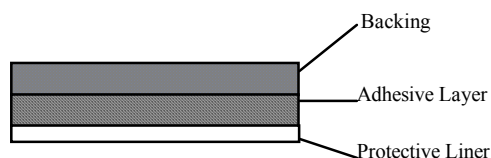
Estradiol-17β

Chemical Name:	estra-1,3,5 (10)-triene-3,17β-diol
Molecular Formula:	C ₁₈ H ₂₄ O ₂
Molecular Weight:	272.39
Description:	White crystalline powder
Solubilities:	Practically insoluble in water; Soluble 1 in 28 of alcohol Soluble 1 in 17 of acetone

Composition:

The ESTRADOT patch is thin, rounded rectangular, multilayer, transparent transdermal therapeutic system, i.e., an adhesive patch, containing estradiol-17β 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-17β. 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 Administration section**).

Stability And Storage Recommendations

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.

Availability Of Dosage Forms

^{Pr}ESTRADOT (estradiol-17 β) is available in the following strengths in patient packs containing 8 patches:

	ESTRADOT 25	ESTRADOT 37.5	ESTRADOT 50	ESTRADOT 75	ESTRADOT 100
Estradiol-17 β Dosage nominal <i>in vivo</i> delivery	25 μ g/day	37.5 μ g/day	50 μ g/day	75 μ g/day	100 μ g/day
Total Estradiol- 17 β content	0.390 mg	0.585 mg	0.780 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

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^{Pr}ESTRADOT[®] is a registered trademark.