

ESCLIM®**estradiol transdermal system**

Continuous delivery for twice-weekly application

Prescribing information**1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA IN POSTMENOPAUSAL WOMEN.**

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that “natural” estrogens are more or less hazardous than “synthetic” estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

There is no indication for estrogen therapy during pregnancy or during the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Estrogens are not indicated for the prevention of postpartum breast engorgement.

Estrogen therapy during pregnancy is associated with an increased risk of congenital defects in the reproductive organs of the fetus, and possibly other birth defects. Studies of women who received diethylstilbestrol (DES) during pregnancy have shown that female offspring have an increased risk of vaginal adenosis, squamous cell dysplasia of the uterine cervix, and clear cell vaginal cancer later in life; male offspring have an increased risk of urogenital abnormalities and possibly testicular cancer later in life. The 1985 DES Task Force concluded that use of DES during pregnancy is associated with a subsequent increased risk of breast cancer in the mothers, although a causal relationship remains unproven and the observed level of excess risk is similar to that for a number of other breast cancer risk factors.

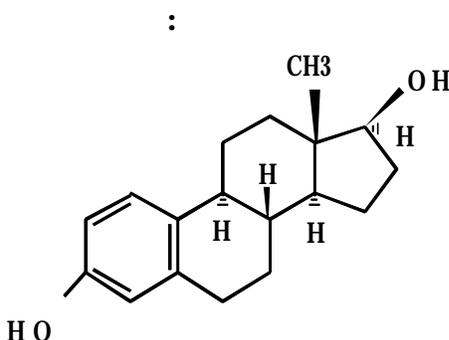
DESCRIPTION

The Esclim estradiol transdermal system contains estradiol in a polymeric adhesive. The system is designed to release 17 β -estradiol continuously upon application to intact skin.

Five systems are available to provide nominal *in vivo* delivery of 0.025, 0.0375, 0.05, 0.075 or 0.1 mg of estradiol per day via skin of average permeability. Each corresponding system having an active surface area of 11, 16.5, 22, 33 or 44 cm² contains 5, 7.5, 10, 15 or 20 mg of estradiol USP, respectively.

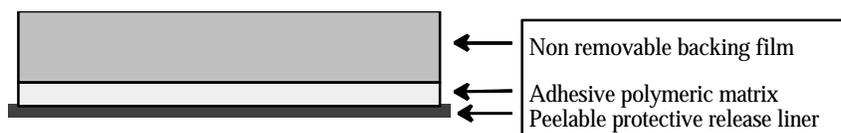
The composition of the systems per unit area is identical.

Estradiol USP (17 β -estradiol) is a white, crystalline powder, chemically described as estra-1, 3, 5 (10)



The molecular formula of estradiol is C₁₈ H₂₄ O₂. The molecular weight is 272.39.

Esclim transdermal systems are composed of a soft, flexible, rectangular foam backing material with rounded corners, covered on one side with a self-adhesive polymer matrix which contains estradiol and pharmacologically inactive components. The adhesive surface is covered by a transparent protective release liner as shown in the diagram below.



The active component of the system is estradiol. The remaining components of the system (EVA copolymers, ethylcellulose, octyldodecanol, dipropylene glycol, polyester protective release liner) are pharmacologically inactive.

CLINICAL PHARMACOLOGY

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sexual characteristics. Although circulating estrogens exist in a dynamic

equilibrium of metabolic interconversions, estradiol is the principal intracellular human estrogen and is substantially more potent than its metabolites, estrone and estriol at the receptor level. The primary source of estrogen in normally cycling adult women is the ovarian follicle, which secretes 70 to 500 µg of estradiol daily, depending on the phase of the menstrual cycle. After menopause, most endogenous estrogen is produced by conversion of androstenedione, secreted by the adrenal cortex, to estrone by peripheral tissues. Thus, estrone and the sulfate conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women.

Circulating estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH) through a negative feedback mechanism and estrogen replacement therapy acts to reduce the elevated levels of these hormones seen in postmenopausal women.

Pharmacokinetics

The pharmacokinetics of transdermally administered estradiol using Esclim have been evaluated in a total of 138 healthy postmenopausal women in nine clinical pharmacology and biopharmaceutic studies.

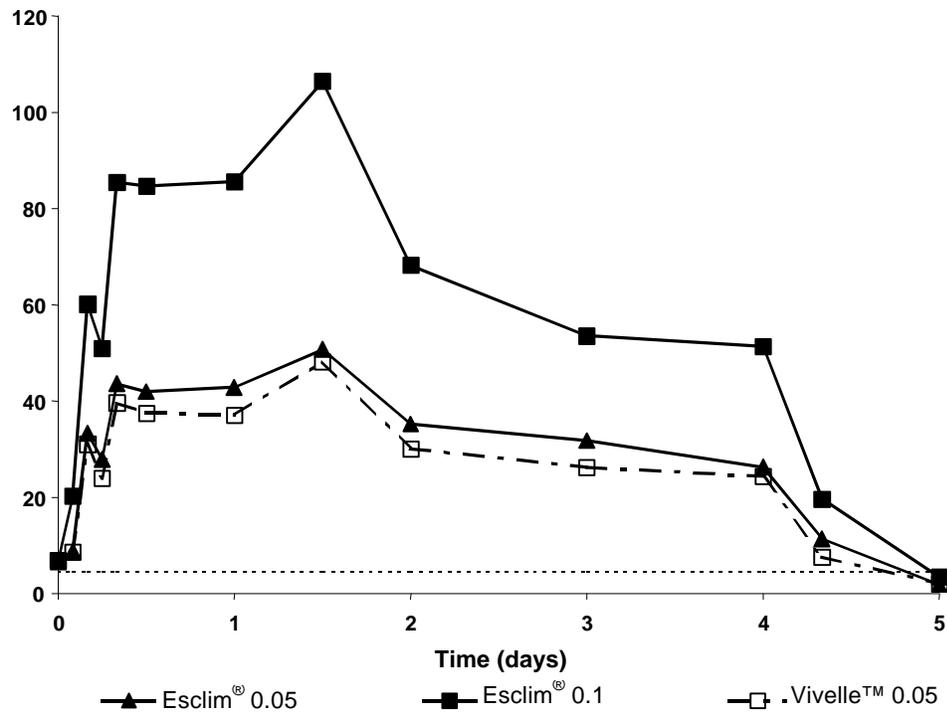
Absorption

Transdermal administration of estradiol produces therapeutic serum concentrations of estradiol with lower circulating concentrations of estrone and estrone conjugates and requires smaller total doses than does oral therapy.

The *in vivo* estradiol daily delivery rate from Esclim was estimated using the baseline adjusted average serum concentrations determined from pharmacokinetic studies and an estradiol clearance value of 1600 L/day. The estimated mean *in vivo* transdermal delivery rates of estradiol are 0.020 mg/day, 0.051 mg/day, and 0.101 mg/day for the 11 cm², 22 cm² and 44 cm² Esclim systems, respectively.

The bioavailability of estradiol from Esclim was compared with Vivelle™ in a 4-day single application randomized crossover study of Esclim 0.05 (22 cm²), Esclim 0.1 (44 cm²) and Vivelle 0.05 in 23 postmenopausal women. The mean maximum serum estradiol concentrations of 62 pg/ml and 124 pg/ml were obtained at a mean T_{max} of 27 hours following application of Esclim 0.05 and Esclim 0.1, respectively. In this study, serum estradiol concentration profiles (Figure 1) and pharmacokinetic parameters (C_{max} and AUC) obtained with the Esclim 0.1 system were twice as high as those produced by the Esclim 0.05 system.

Figure 1: Mean Uncorrected Serum Estradiol Concentrations After Application of Esclim 0.05, Esclim 0.1 and Vivelle 0.05 for 4 Days



In a 3-week multiple application study in 18 postmenopausal women, Esclim 0.05 (22 cm²) applied to the buttocks increased serum estradiol concentrations within 4 hours and maintained an average serum estradiol concentration of approximately 51 pg/mL above baseline. Trough values of approximately 27 to 35 pg/mL above the baseline were observed at the end of each application interval (3 or 4 days). Nearly identical serum estradiol concentration profiles were seen during each successive week, indicating little or no accumulation of estradiol in the body.

In a 3-day, single-application, crossover study in 12 postmenopausal women, estradiol serum concentrations were compared following application of the Esclim 0.05 system to sites on the buttocks (site used in clinical trials), the femoral triangle, and the upper arm. The profiles of serum estradiol concentrations from these different application sites are shown in Figure 2, and the pharmacokinetic results derived from each site are presented in Table 1.

Figure 2: Mean Uncorrected Serum Estradiol Concentrations After Application of ESCLIM 0.05 to Different Body Sites for 3 Days

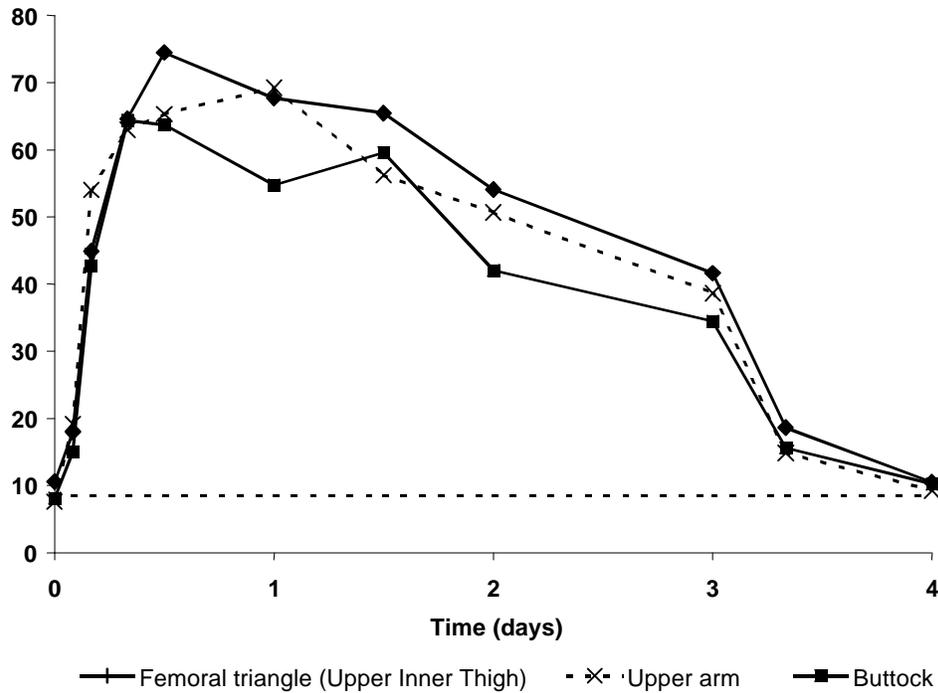


Table 1: Mean Uncorrected Estradiol Pharmacokinetic Parameters after Application of ESCLIM 0.05 Patches to Different Body Sites

Parameter	Femoral Triangle	Upper Arm	Buttock
C_{max} (pg/mL)	80.1 ± 34.9	80.2 ± 44.1	72.6 ± 36.2
C_{min72} (pg/mL)	41.6 ± 18.3	38.7 ± 15.2	34.5 ± 18.8
C_{av72} (pg/mL)	49.0 ± 24.6	47.4 ± 24.3	42.8 ± 20.7
C_{av96} (pg/mL)	42.8 ± 20.5	40.8 ± 19.7	37.3 ± 17.1
$AUC_{(0-72)}$ (pg•hr/mL)	4106 ± 1826	3825 ± 1897	3477 ± 1530
$AUC_{(0-96)}$ (pg•hr/mL)	4578 ± 1938	4306 ± 1925	3885 ± 1622

Linear pharmacokinetics have been demonstrated for the Esclim transdermal system. Serum estradiol concentrations following a 4-day application of the Esclim 0.025, 0.05, and 0.1 systems are shown in Figure 3, while the mean values for pharmacokinetic parameters from these applications are summarized in Table 2. Results for the Esclim 0.025 system are from one study, while results for Esclim 0.05 and 0.1 systems are from a separate study. C_{max} occurred at approximately 30 hours.

Figure 3: Mean Uncorrected Serum Estradiol Concentrations After Application of ESCLIM 0.025, ESCLIM 0.05 and ESCLIM 0.1 for 4 Days

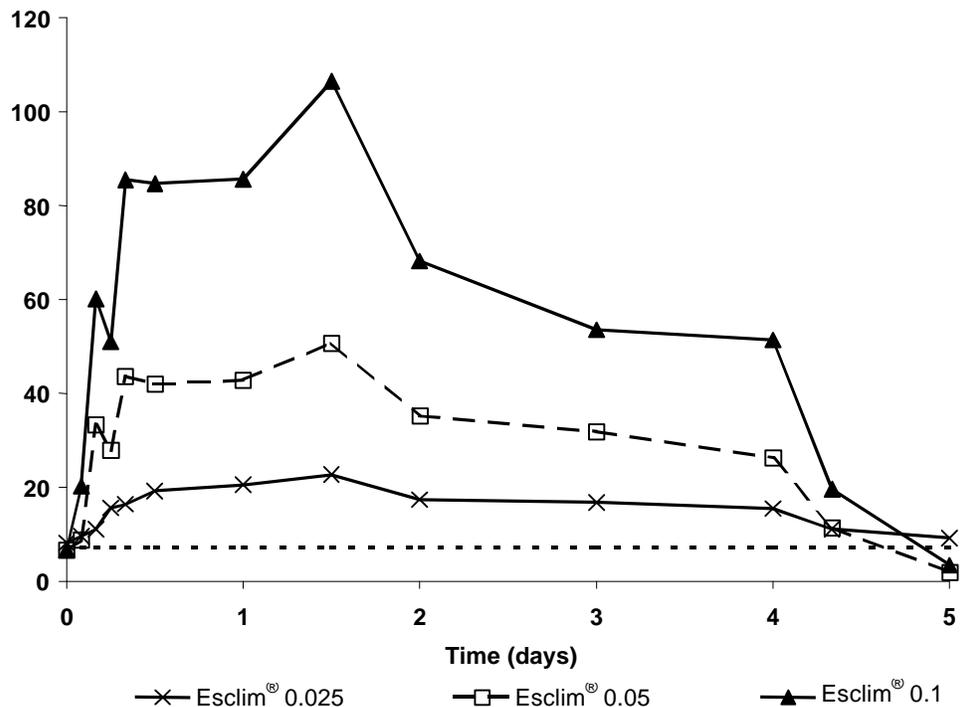


Table 2: Mean ± SD Uncorrected Estradiol Pharmacokinetic Parameters for Esclim Transdermal Systems Applied to the Buttocks (N = 23)

Surface area (cm ²)	Estradiol Dose (mg/day)	C_{max} (pg/mL)	C_{min}^a (pg/mL)	C_{avg} (pg/mL)
11	0.025	24.5 ± 11 ^b	15.5 ± 6.1 ^b	17.8 ± 6.6 ^b
22	0.05	61.6 ± 33	26.3 ± 14	38.6 ± 21
44	0.1	124 ± 66	51.4 ± 29	74.0 ± 43

^a C_{min} =Serum estradiol concentration at 96 hours following application. ^bN = 17

Distribution

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs. Estradiol and other naturally occurring estrogens are bound mainly to sex hormone binding globulin (SHBG), and to lesser degree to albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Since transdermally absorbed estradiol is not subject to first pass liver metabolism, the ratio of serum concentrations of estradiol to either of its major metabolites, estrone or estrone sulfate, is closer to those observed in premenopausal women than when administered by the oral route of administration. The clinical relevance of the estradiol to estrone ratio is presently unknown.

In a double-blind, parallel-group placebo-controlled clinical trial using Esclim, the steady-state serum concentrations of estradiol, estrone and estrone sulfate were measured between 24 and 72 hours after application of patch at week 13 and are presented in Table 3.

Table 3: Mean ± SD Steady State Serum Concentration of Estradiol and Its Metabolites at Week 13 Following the Application of Esclim

Patch	Steady State Serum Concentration		
	Estradiol (pg/mL)	Estrone (pg/mL)	Estrone Sulfate (ng/dL)
Placebo	19.6 ± 14.0 31 ^a	29.7 ± 11.7 31	42.9 ± 24.0 30
0.025 mg/day	48.2 ± 27.4 22	38.7 ± 21.5 22	152.6 ± 129.7 22
0.05 mg/day	102.8 ± 63.6 24	49.0 ± 28.0 24	236.1 ± 147.1 22
0.1 mg/day	165.3 ± 116.1 28	64.9 ± 31.7 28	373.6 ± 272.0 28

^anumber of subjects**Excretion**

Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Serum concentrations of estradiol and estrone returned to baseline values within 12 to 24 hours after removal of Esclim.

Special Populations

No specific studies have been conducted using Esclim in any special populations.

Drug Interactions

No specific drug interaction studies have been conducted using Esclim.

Clinical Trials

In a 12-week, double-blind study evaluating the efficacy and safety of Esclim 0.025, 0.05, and 0.1 versus placebo, in symptomatic women (average of 8 or more moderate to severe hot flashes per day), reduction in the frequency of these vasomotor symptoms was demonstrated within 4 weeks. Results from this trial are presented in Table 4 and Figure 4.

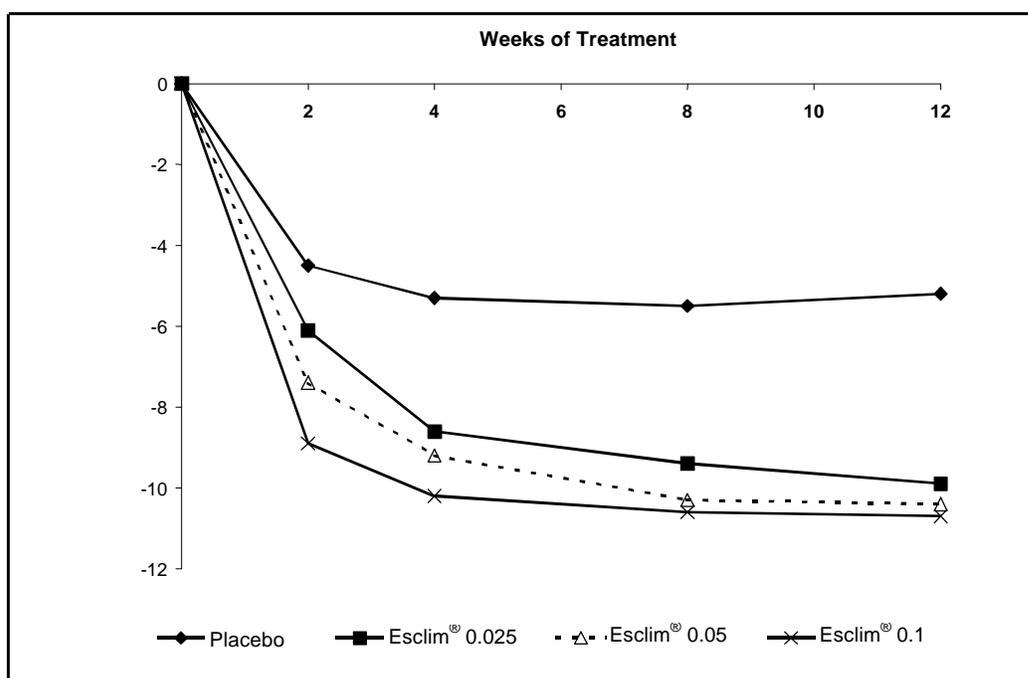
After 4 weeks of treatment, the mean reduction in the moderate to severe vasomotor symptoms (MSVS) was up to 8.6 MSVS per day in the Esclim 0.025 group, 9.2 and 10.2 in the Esclim 0.05 and Esclim 0.1 groups respectively, compared with 5.3 in the placebo group. After 12 weeks of treatment, this increased to 9.9 in the Esclim 0.025 group, 10.4 in the Esclim 0.05 group and 10.7 in the Esclim 0.1 group and remained stable at 5.2 in the placebo group.

Table 4: Changes from Baseline in Frequency of MSVS

Week	Placebo (N=54)	Esclim 0.025 mg/day (N=48)	Esclim 0.05 mg/day (N=47)	Esclim 0.1 mg/day (N=47)
Week 0 (Baseline) Mean ± SD	11.4 ± 3.7	11.6 ± 5.4	10.9 ± 4.2	11.2 ± 2.8
Week 4 Mean Reduction ± SD (% Reduction)	-5.3 ± 4.1 (-48.9%)	-8.6 ± 5.7* (-72.6%)	-9.2 ± 4.5* (-84.4%)	-10.2 ± 2.9* (-92.0%)
Week 8 Mean Reduction ± SD (% Reduction)	-5.5 ± 4.7 (-51.5%)	-9.4 ± 5.7* (-79.8%)	-10.3 ± 4.3* (-94.0%)	-10.6 ± 2.8* (-95.4%)
Week 12 Mean Reduction ± SD (% Reduction)	-5.2 ± 5.1 (-50.3%)	-9.9 ± 5.8* (-83.4%)	-10.4 ± 4.2* (-95.3%)	-10.7 ± 2.8* (-95.6%)

*Statistically different difference from placebo in mean reduction (Dunnett's test)

Figure 4: Reduction of MSVS During Double-Blind, Placebo-Controlled Study



Maintenance of the relief of VMS over a median period of 2 years was documented in two open-label trials.

INDICATIONS AND USAGE

Esclim (estradiol transdermal system) is indicated in the following:

1. Treatment of moderate to severe vasomotor symptoms associated with the menopause. There is no adequate evidence that estrogens are effective for nervous symptoms of depression that might occur during menopause and they should not be used to treat these conditions.
2. Treatment of vulval and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure.

CONTRAINDICATIONS

Patients with known hypersensitivity to any of the components of the therapeutic system should not use Esclim. Estrogens should not be used in individuals with any of the following conditions:

1. Known or suspected pregnancy (see Boxed Warning). Estrogen may cause fetal harm when administered to a pregnant woman.
2. Undiagnosed abnormal genital bleeding.
3. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease.
4. Known or suspected estrogen-dependent neoplasia.
5. Active thrombophlebitis or thromboembolic disorders.

WARNINGS

1. *Induction of Malignant Neoplasms.* Some studies have suggested a possible increased incidence of breast cancer in those women taking estrogen therapy at higher doses or for prolonged periods of time. The majority of studies, however, have not shown an association with the usual doses used for estrogen replacement therapy. Women on this therapy should have regular breast examinations and should be instructed in breast self-examination. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12-fold greater than in nonusers and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with the use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use with increased risks of 15 to 24-fold for 5 to 10 years or more. In three studies, persistence of risk was demonstrated for 8 to over 15 years after cessation of estrogen treatment. In one study, a significant decrease in the incidence of endometrial cancer occurred 6 months after

estrogen withdrawal. Concurrent progestin therapy may offset this risk, but the overall health impact in postmenopausal women is not known (see PRECAUTIONS).

Estrogen therapy during pregnancy is associated with an increased risk of fetal congenital reproductive tract disorders. In female offspring, there is an increased risk of vaginal adenosis, squamous cell dysplasia of the cervix, and clear cell vaginal cancer later in life; in males, urogenital and possibly testicular abnormalities. Although some of these changes are benign, it is not known whether they are precursors of malignancy.

2. *Gallbladder Disease.* Two studies have reported a 2 to 4-fold increase in the risk of surgically confirmed gallbladder disease in postmenopausal women receiving oral estrogen replacement therapy, similar to the 2-fold increase previously noted in users of oral contraceptives.
3. *Cardiovascular Disease.* Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.

These risks cannot necessarily be extrapolated from men to women. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

4. *Elevated Blood Pressure.* Occasional blood pressure increases during estrogen replacement therapy have been attributed to idiosyncratic reactions to estrogens. More often, blood pressure has remained the same or has dropped. Postmenopausal estrogen use does not increase the risk of stroke. Nonetheless, blood pressure should be monitored at regular intervals with estrogen use, especially if high doses are used. Ethinyl estradiol and conjugated estrogens have been shown to increase renin substrate. In contrast to these oral estrogens, transdermally-administered estradiol does not affect renin substrate.
5. *Hypercalcemia.* Administration of estrogen may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

PRECAUTIONS

General

1. *Addition of a Progestin.* Studies of the addition of a progestin for 10 or more days of a cycle of estrogen administration have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Morphological and biochemical studies of endometria

suggest that 10 to 14 days of progestin are needed to provide maximal maturation of the endometrium and to reduce the likelihood of hyperplastic changes.

There are however, possible risks that may be associated with the use of progestins in estrogen replacement regimens. These include:

- (1) adverse effects on lipoprotein metabolism (lowering HDL and raising LDL), which could diminish the purported cardioprotective effect of estrogen therapy (see PRECAUTIONS, below);
- (2) impairment of glucose tolerance; and
- (3) possible enhancement of mitotic activity in breast epithelial tissue, although few epidemiological data are available to address this point (see PRECAUTIONS, below).

The choice of progestin, its dose and its regimen may be important in minimizing these adverse effects, but these issues will require further study before they are clarified.

2. *Cardiovascular Risk.* A causal relationship between estrogen replacement therapy and reduction of cardiovascular disease in postmenopausal women has not been proven. Furthermore, the effect of added progestins on this putative benefit is not yet known.

In recent years, many published studies have suggested that there may be a cause-effect relationship between postmenopausal oral estrogen replacement therapy *without added progestins* and a decrease in cardiovascular disease in women. Although most of the observational studies which assessed this statistical association have reported a 20% to 50% reduction in coronary heart disease risk and associated mortality in estrogen takers, the following should be considered when interpreting these reports:

- (1) Because only one of these studies was randomized and it was too small to yield statistically significant results, all relevant studies were subject to selection bias. Thus, the apparently reduced risk of coronary artery disease cannot be attributed with certainty to estrogen replacement therapy. It may instead have been caused by life-style and medical characteristics of the women studied with the result that healthier women were selected for estrogen therapy. In general, treated women were of higher socio-economic and educational status, more slender, more physically active, more likely to have undergone surgical menopause, and less likely to have diabetes than the untreated women. Although some studies attempted to control for these selection factors, it is common for properly-designed randomized trials to fail to confirm benefits suggested by less rigorous study designs. Thus ongoing and future large-scale randomized trials may fail to confirm this apparent benefit.
- (2) Current medical practice often includes the use of concomitant progestin therapy in women with intact uteri (see PRECAUTIONS and WARNINGS). While the effects of added

progestins on the risk of ischemic heart disease are not known, all available progestins reverse at least some of the favorable effects of estrogens on HDL and LDL levels.

- (3) While the effects of added progestins on the risk of breast cancer are also unknown, available epidemiologic evidence suggests that progestins do not reduce, and may enhance, the moderately increased breast cancer incidence that has been reported with prolonged estrogen replacement therapy (see WARNINGS, above).

Because relatively long-term use of estrogens by a woman with a uterus has been shown to induce endometrial cancer, physicians often recommend that women who are deemed candidates for hormone replacement should take progestins as well as estrogens. When considering prescribing concomitant estrogens and progestins for hormone replacement therapy, physicians and patients are advised to carefully weigh the potential benefits and risks of the added progestin. Large-scale randomized, placebo-controlled, prospective clinical trials are required to clarify these issues.

3. *Physical Examination.* A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pre-treatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs and should include a Papanicolaou smear. As a general rule, estrogen should not be prescribed for longer than 1 year without re-examining the patient.
4. *Hypercoagulability.* Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity. This effect appears dose and duration dependent and is less pronounced than that associated with oral contraceptive use. Also, postmenopausal women tend to have increased coagulation parameters at baseline compared to premenopausal women. There is some suggestion that low-dose postmenopausal mestranol may increase the risk of thromboembolism, although the majority of studies (primarily of users of conjugated estrogens) report no such increase. There is insufficient information on hypercoagulability in women who have had previous thromboembolic disease.
5. *Familial Hyperlipoproteinemia.* Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.
6. *Fluid Retention.* Because estrogens may cause some degree of fluid retention, conditions that might be exacerbated by this factor, such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.
7. *Uterine Bleeding and Mastodynia.* Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.

8. *Impaired Liver Function.* Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution.

Information for the Patient

See text of Patient Package Insert, which appears after the HOW SUPPLIED section.

Laboratory Tests

Estrogen administration should generally be guided by clinical response at the smallest dose, rather than laboratory monitoring, for relief of symptoms for those indications in which symptoms are observable.

Drug/Laboratory Tests Interactions

Some of these drug/laboratory test interactions have been observed only with estrogen–progestin combinations (oral contraceptives):

1. Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII–X complex, II–VII–X complex; and beta–thromboglobulin; decreased levels of anti–factor Xa and antithrombin III; decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.
2. Increased thyroid–binding globulin (TBG) leading to increased circulating total thyroid hormone, as T_4 levels (by column or by radioimmunoassay) or T_3 levels by radioimmunoassay. T_3 resin uptake is decreased, reflecting the elevated TBG. Free T_4 and free T_3 concentrations are unaltered.
3. 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. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha–1–antitrypsin, ceruloplasmin).
4. Increased plasma HDL and HDL–2 subfraction concentrations, reduced LDL cholesterol concentration, increased triglyceride levels.
5. Impaired glucose tolerance.
6. Reduced response to metyrapone test.

7. Reduced serum folate concentration.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 (see CONTRAINDICATIONS and WARNINGS).

Pregnancy Category X

Estrogens should not be used during pregnancy (see CONTRAINDICATIONS and Boxed Warning).

Nursing Mothers

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk.

ADVERSE REACTIONS

See WARNINGS and Boxed Warning regarding the potential adverse effects on the fetus, the induction of malignant neoplasms, gallbladder disease, cardiovascular disease, elevated blood pressure and hypercalcemia.

Skin irritation: In controlled clinical studies with Esclim, the most commonly reported adverse events were topical reactions of erythema and/or pruritis at the application site. In general these reactions caused patients little or no discomfort, and led to premature discontinuation of treatment in 0.9% (3/317) of patients in these trials. The rate of application site reactions, based on 8,135 applications of the 0.025, 0.05, and 0.1 Esclim systems in these trials was 6.1 per 100 applications (4.9, 5.4, 10.7 for the three Esclim doses respectively) compared to 6.2 in the placebo treated patients (2,014 applications).

In a placebo-controlled trial of Esclim 0.025, 0.05, and 0.1 conducted in 196 patients in the US, the adverse events reported by at least 5% of patients in one or more of the treatment groups are shown in Table 5.

Table 5
Incidence of Adverse Events >5% in a
Placebo-Controlled Study of Esclim
Data are Expressed as % of Treatment Group

Adverse Event	Placebo (N=54)	Esclim 0.025 mg/day (N=48)	Esclim 0.05 mg/day (N=47)	Esclim 0.1 mg/day (N=47)
Breast Pain	3.7	25.0	44.7	46.8
Headache	22.2	18.8	8.5	6.4
Infection	7.4	10.4	10.6	8.5
Injury Accident	3.7	10.4	4.3	2.1
Anxiety	0	8.3	2.1	0
Emotional Lability	1.9	8.3	2.1	6.4
Arthralgia	1.9	6.3	2.1	4.3
Flu Syndrome	7.4	6.3	6.4	8.5
Joint Disorder	0	6.3	0	0
Pruritis	1.9	6.3	12.8	0
Rhinitis	1.9	6.3	4.3	4.3
Abdominal Pain	9.3	4.2	10.6	2.1
General Edema	1.9	4.2	6.4	6.4
Monilia Vagina	5.6	4.2	8.5	4.3
Nausea	1.9	4.2	10.6	8.5
Peripheral Edema	0	4.2	2.1	6.4
Sinusitis	7.4	4.2	2.1	4.3
Asthenia	1.9	2.1	10.6	6.4
Back Pain	3.7	2.1	2.1	6.4
Diarrhea	1.9	2.1	8.5	0
Dysmenorrhea	0	2.1	2.1	6.4
Enlarged Abdomen	0	2.1	2.1	6.4
Enlarged Breast	0	2.1	2.1	8.5
Rash	5.6	2.1	4.3	2.1
Anemia	0	0	6.4	4.3
Gastroenteritis	1.9	0	0	6.4
Hyperlipemia	5.6	0	0	2.1
Leukorrhea	0	0	12.8	0
Paresthesia	1.9	0	6.4	0

Urogenital Adverse Events: (See Precautions: Addition of a progestin): In the US placebo-controlled study, 72 patients were included who had intact uteri. As expected, after 12-13 weeks of continuous unopposed therapy, findings of endometrial hyperplasia (diagnosed either by endometrial biopsy and/or ultrasonography) were increased with increasing doses of estradiol (placebo: 0/18 patients; Esclim 0.025: 1/14 (7.1%); Esclim 0.05: 12/22 (54.5%); Esclim 0.1: 10/18 (55.6%). In the 86 patients who had not previously undergone a total hysterectomy, vaginal bleeding was also increased with increasing doses of estradiol (placebo: 2/21 patients (9.5%); Esclim 0.025: 6/19 (31.6%); Esclim 0.05: 14/25 (56.0%); Esclim 0.1: 12/21 (57.1%).

In two long-term studies involving a total of 488 patients treated for a mean duration of 618 days and up to 3.5 years, the nature and incidence of adverse events did not change with prolonged duration of treatment.

The following additional adverse reactions have been reported with estrogen therapy:

1. *Genitourinary System*. Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding, spotting; increase in size of uterine leiomyomata; vaginal candidiasis; change in amount of cervical secretion.
2. *Breasts*. Tenderness, enlargement.
3. *Gastrointestinal*. Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; gallbladder disease.
4. *Skin*. Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism.
5. *Eyes*. Steepening of corneal curvature; intolerance to contact lenses.
6. *Central Nervous System*. Headache, migraine, dizziness; mental depression; chorea.
7. *Miscellaneous*. Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

OVERDOSAGE

Serious ill effects have not been reported following acute ingestion of large doses of estrogen containing oral contraceptives by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION

The adhesive side of the Esclim system should be placed on a clean, dry area of the skin on buttocks, femoral triangle (upper inner thigh), or upper arm, but *Esclim should not be applied to the breasts or other parts of the body*. The Esclim transdermal system should be replaced every 3 to 4 days (twice a week). The sites of application must be rotated, with an interval of at least 1 week allowed between applications to a particular site. The area selected should not be oily, damaged or irritated. The waistline should be avoided, since tight clothing may rub the system off. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place with the palm of the hand for about 10 seconds, making sure there is good contact, especially around the edges. In the unlikely event that a system should fall off, the same system may be reapplied. If necessary, a new system may be applied. In either case, the original treatment schedule should be continued.

Initiation of Therapy

For the treatment of moderate to severe vasomotor symptoms, and vulval and vaginal atrophy associated with the menopause, and of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure, treatment is generally initiated with the Esclim 0.025 transdermal system applied to the skin twice weekly but the initial selection of the dose should be based on the evaluation of the severity of the patient's symptomatology and responsiveness to estrogen treatment. Depending upon the clinical response to treatment, the dosage can then be titrated up or down to individual needs. In order to use the lowest dosage necessary for the control of symptoms, decisions to increase dosage should not be made until after the first two or three weeks of therapy. Attempts to discontinue or taper medication should be made at 3-month to 6-month intervals.

In women not currently taking oral estrogens or in women switching from another estradiol transdermal therapy, treatment with the Esclim estradiol transdermal system may be initiated at once.

In women who are currently taking oral estrogens, treatment with the Esclim estradiol transdermal system should be initiated 1 week after withdrawal of oral hormone replacement therapy, or sooner if menopausal symptoms reappear in less than one week.

Therapeutic Regimen

Esclim may be given continuously in patients who do not have an intact uterus. In those patients with an intact uterus, Esclim may be given on a cyclic schedule (e.g., 3 weeks on drug followed by 1 week off drug).

HOW SUPPLIED

Esclim estradiol transdermal system 0.025 mg/day

(Each 11 cm² system contains 5 mg of estradiol USP)

Patient calendar Pack of 8 systems	NDC
Carton of 6 Patient Calendar Packs of 8 Systems	NDC
Carton of 24 systems	NDC

Esclim estradiol transdermal system 0.0375 mg/day

(Each 16.5 cm² system contains 7.5 mg of estradiol USP)

Patient calendar Pack of 8 systems	NDC
Carton of 6 Patient Calendar Packs of 8 Systems	NDC
Carton of 24 systems	NDC

Esclim estradiol transdermal system 0.05 mg/day

(Each 22 cm² system contains 10 mg of estradiol USP)

Patient Calendar Pack of 8 systems	NDC
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Carton of 6 Patient Calendar Packs of 8 Systems.....NDC

Carton of 24 systems.....NDC

Esclim estradiol transdermal system 0.075 mg/day

(Each 33 cm² system contains 15 mg of estradiol USP)

Patient Calendar Pack of 8 systems.....NDC

Carton of 6 Patient Calendar Packs of 8 systems.....NDC

Carton of 24 systems.....NDC

Esclim estradiol transdermal system 0.1 mg/day

(Each 44 cm² system contains 20 mg of estradiol USP)

Patient Calendar Pack of 8 systems.....NDC

Carton of 6 Patient Calendar Packs of 8 systems.....NDC

Carton of 24 systems.....NDC

Store at 25°C (77°F); excursion permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature]. Do not store unpouched. Apply immediately upon removal from the protective pouch.

Rx only

Manufactured for Serono Laboratories, Inc. Randolph, MA 02368 USA

By Laboratoires Fournier SA, 21000 Dijon, France

Made In France

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