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.

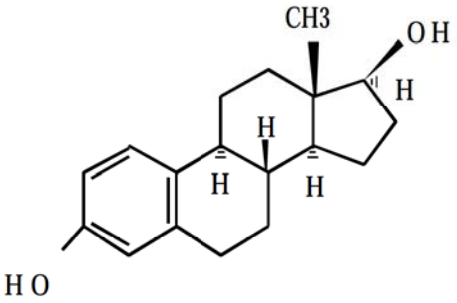
DESCRIPTION

The Esclim estradiol transdermal system contains estradiol in a polymeric adhesive. The system is designed to release 17ß–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 cm^2 contains 5, 7.5, 10, 15 or 20 mg of estradiol USP, respectively.

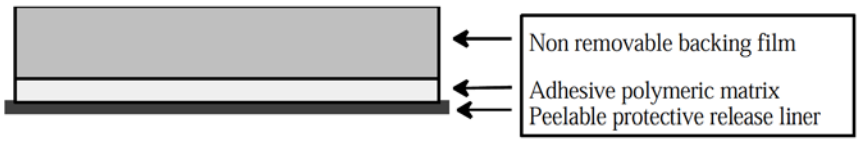
The composition of the systems per unit area is identical.

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



The molecular formula of estradiol is C_{18} H_{24} O_2. 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.

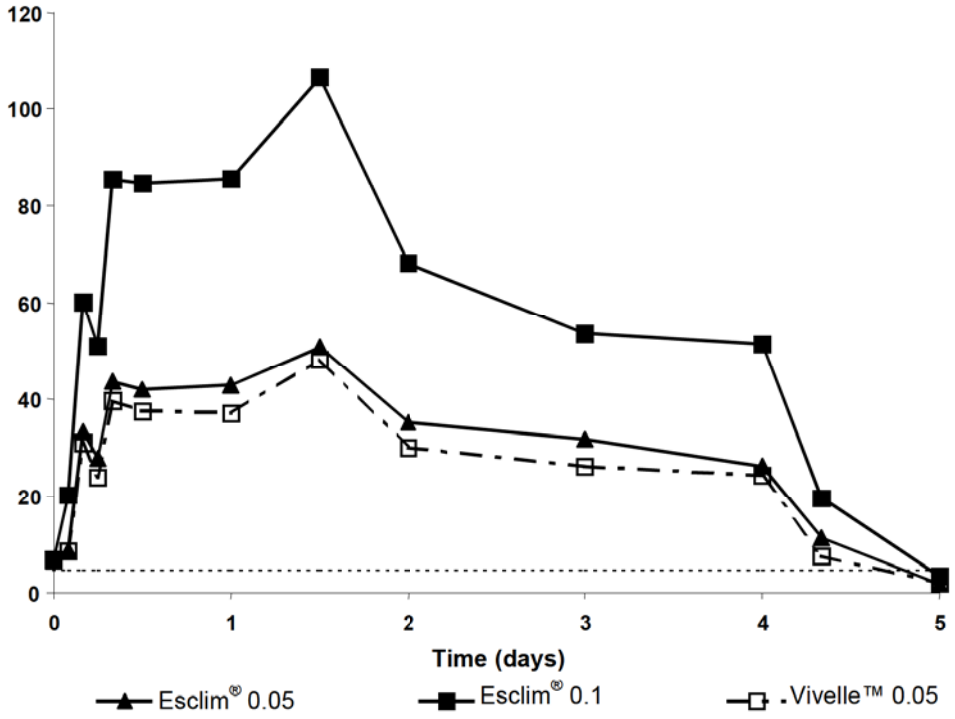
Absorption

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 cm^2, 22 cm^2 and 44 cm^2 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 cm^2), Esclim 0.1 (44 cm^2) 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 cm^2) 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

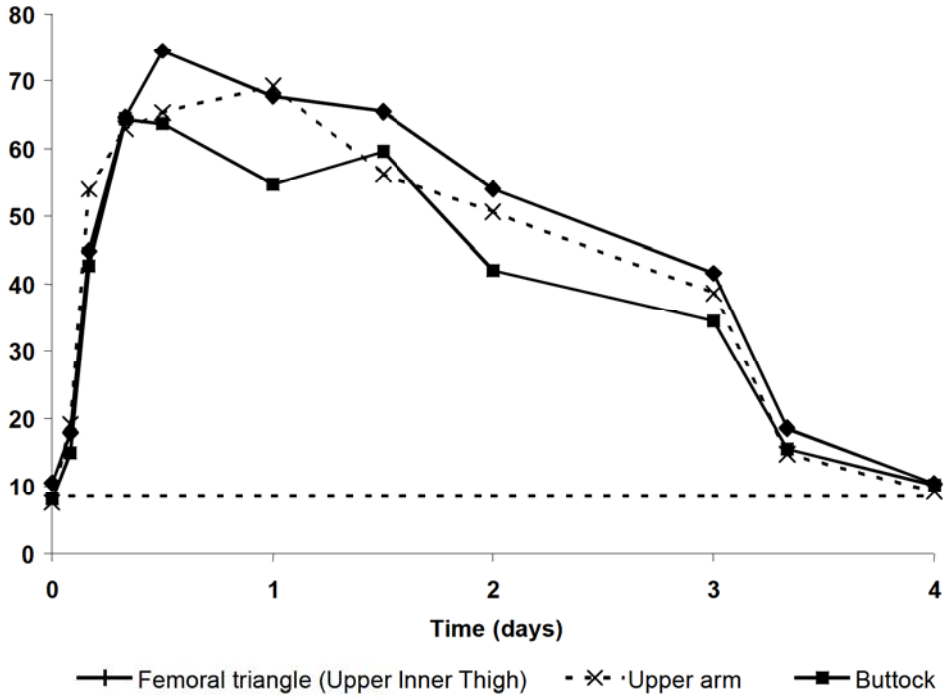


Table 1: Mean Uncorrected Estradiol Pharmacokinetic Parameters after Application of ESCLIM 0.05 Patches to Different Body Sites

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

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