PRODUCT MONOGRAPH

Pr DIVIGEL®

Estradiol Gel 0.1%

0.25 mg, 0.5 mg, 1 mg per packet

Estrogen

Transdermal Gel

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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 Hormone Replacement Therapy (HRT) versus 30 on placebo).¹

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.⁵

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.³⁸

It is recommended that estrogens <u>not</u> 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 (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 the 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.

Ovarian cancer:

Some recent epidemiological studies have found that the use of hormone replacement therapy (estrogen-

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 placebocontrolled 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 oral 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.¹⁶

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.¹⁴

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.

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

Geritourinary

Vaginal bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy

Hepatic/Biliary/Pancreatic

Gallbladder diseases

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

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**.

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 substudy 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.^{30, 31}

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).³⁰

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.³¹

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 a0 g0 G[* EMC /P <</MCII

		Divigel®		
SYSTEM ORGAN CLASS Preferred Term	0.25 g/day N=122 n (%)	0.5 g/day N=123 n (%)	1.0 g/day N=125 n (%)	N=125 n (%)
INFECTIONS & INFESTATIONS				
Nasopharyngitis	7 (5.7)	5 (4.1)	6 (4.8)	5 (4.0)
Upper Respiratory Tract Infection				

Table 1: Number (%) of Subjects with Common Adverse Events* in a 12-Week Placebo-Controlled Study of Divigel[®]

Table 2Number (%) of Subjects with AEs Occurring in
Week Placebo Controlled Study of Divigel1% of Subjects in A 12-
Week Placebo Controlled Study of Divigel

	Placebo	USL-221			
AE ^a System Organ Class	Gel (N=125)	0.25 g/day (N=122)	0.5 g/day (N=123)	1.0 g/day (N=125)	Combined (N=370)
Preferred Term	n (%) ^b	n (%) ^b	n (%) ^b	n (%) ^b	n (%) ^b
Any AE	57 (46)				

AE^a System Organ Class

If adverse symptoms persist, the prescription of HRT should be reconsidered.

DRUG INTERACTIONS

Overview

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

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

Drug-Drug Interactions

The metabolism of estrogens (and progestagens) may be increased by concomitant use of substances known to induced drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g., phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones (see Table 3 and 4 for further information as reported in the literature).

Wort (Hypericum perforatum) may induce the metabolism of estrogens (see section on Drug-Herb Interactions). At transdermal administration, the first pass

Drug-Food Interactions

Interaction of DIVIGEL® with food has not been established.

Drug-Herb Interactions

-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin.

Physicians and other healthcare providers should be made aware of other non-prescription products concomitantly used by the patient, including herbal and natural products obtained from the widespread health stores.

Drug-Laboratory Test Interactions

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

increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;

increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T_4) as measured by column or radioimmunoassay; T_3 resin uptake is decreased, reflecting the elevated TBG; free T_4 concentration is unaltered;

other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged;

increased plasma HDL and HDL₂ cholesterol sub-fraction concentrations, reduced LDL cholesterol concentration;

impaired glucose tolerance;

increased serum triglycerides and phospholipids concentration;

reduced response to metyrapone test.

In clinical trials with Divigel, there have been no known effects on fibrinogen, antithrombin III, TBG, CBG, SHBG, protein C system (protein C/S) or activated protein C resistance (APC resistance) due to factor V Leiden mutation.

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 hormone replacement therapy (HRT) when relevant specimens are submitted.

Divigel does not contain progestins. However, in the case where a progestin is co-administered, progestin overdosage has been characterized by depressed mood, tiredness, acne and hirtsuitism.

Treatment of Overdosage:

Symptomatic treatment should be given.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Divigel is a transdermal preparation comprised of a gel (0.1%) available in three doses of 0.25 mg, 0.5 mg and 1.0 mg estradiol respectively.

Upon application to intact skin, Divigel provides continuous systemic delivery of estrogen by releasing estradiol, the major estrogenic hormone secreted by the human ovary.

In comparison, orally administered estrogens are rapidly metabolized by the liver to estrone and its conjugates, giving rise to higher circulating levels of estrogen and estradiol. Therefore, transdermal administration of estradiol produces therapeutic plasma levels with lower circulating levels of

Pharmacokinetics

A. Absorption

Estradiol diffuses across intact skin and into the systemic circulation by a passive absorption process, with diffusion across the stratum corneum being the rate-limiting factor.

In a 14-day, Phase 1, multiple-dose study, Divigel[®] demonstrated linear and approximately doseproportional estradiol pharmacokinetics at steady state for both AUC₀₋₂₄ and C_{max} following once daily dosing to the skin of either the right or left upper thigh (Table 5).).

 Table 5: Mean (%CV) Pharmacokinetic Parameters for Estradiol (uncorrected for baseline) on Day 14 Following Multiple Daily Doses of Divigel[®] 0.1%

Parameter (units)Divigel® 0.25 gDivigel® 0.5 gDivigel®

The effect of sunscreens and other topical lotions on the systemic exposure of Divigel[®] has not been evaluated. Studies conducted using topical estrogen gel approved products have shown that sunscreens have the potential for changing the systemic exposure of topically applied estrogen gels.

B. 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. Estrogens circulate in the blood largely bound to sex hormone binding globulin (SHBG) and albumin.

C. Metabolism

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 intestine followed by reabsorption. In postmenopausal women, a significant proportion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Estradiol from Divigel[®] avoids first pass metabolism and provides estradiol/estrone ratios at steady state in the range of 0.42 to 0.65.

D. Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates. The apparent terminal half-life for estradiol was about 10 hours following administration of Divigel.

E. Special Populations

Divigel has been studied only in postmenopausal women. No pharmacokinetic studies were conducted in special populations, including patients with renal or hepatic impairment.

F.

G. Potential for Estradiol Transfer and Effects of Washing

As with most topical products, there is a potential for estradiol transfer following physical contact with Divigel application sites. The effect of estradiol transfer was evaluated in healthy postmenopausal women who topically applied 1.0 g of Divigel (single dose) on one thigh. One and 8 hours after gel application, they engaged in direct thigh to arm contact with a partner for 15 minutes. While some elevation of estradiol levels over baseline was seen in the male subjects, the degree of transferability in this study was inconclusive.

The effect of application site washing on skin surface levels and serum concentrations of estradiol was determined in 16 healthy postmenopausal women after application of 1.0 g of Divigel to a 200 cm² area on the thigh. Washing the application site with soap and water 1 hour after application removed all detectable amounts of estradiol from the surface of the skin, and resulted in a 30-38% decrease in the mean total 24-hour exposure to estradiol.

STORAGE AND STABILITY

Store at controlled room temperature of 15 to 30°C.

Keep out of the reach of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Divigel (estradiol gel) 0.1% is a clear, colorless, smooth, opalescent gel supplied in single-dose foil packets of 0.25, 0.5, and 1.0 g, corresponding to 0.25, 0.5, and 1.0 mg estradiol, respectively.

Non-medicinal ingredients: Carbomer, ethanol, propylene glycol, purified water and triethanolamine

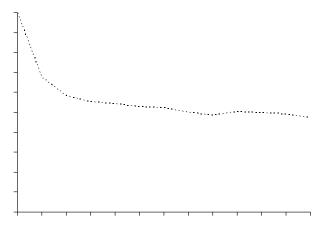
Supplied in cartons, packets of 7 or 30 foil pouches.

CLINICAL TRIALS

Effects on Vasomotor Symptoms

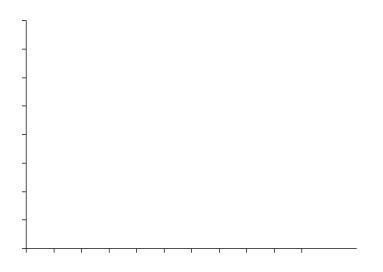
A randomized, double-blind, placebo-controlled trial evaluated the efficacy of 12-week treatment with three different daily doses of Divigel for vasomotor symptoms in 495 postmenopausal women (86.5% White; 10.1% Black) between 34 and 89 years of age (mean age 54.6) who had at least 50 moderate to severe hot flushes per week at baseline (2 week period prior to treatment). Subjects applied placebo, Divigel 0.25 g (0.25 mg estradiol), Divigel 0.5 g (0.5 mg estradiol) or Divigel 1.0 g (1.0 mg estradiol) once daily to the thigh. Reductions in both the mean daily frequency and the mean daily severity of moderate to severe hot flushes were stati

Figure 2 Change from Baseline in Mean Daily <u>Frequency</u> of MSVS by Week Using LOCF (ITT Population) – USL Study P04-001



, * Statistically significant compared to placebo at the 0.001, 0.01, and 0.05 levels, respectively.

Figure 3 Change from Baseline in Mean Daily <u>Severity</u> of MSVS by Week Using LOCF (ITT Population) – USL Study P04-001



, * Statistically significant compared to placebo at the 0.001, 0.01, and 0.05 levels, respectively.

Table 8: Relative and Absolute Risk Seen in the Estrogen-Plus Progestin Substudy of WHI at an Average of 5.6

	Years ^a	
Event ^c	Relative Risk CE/MPA vs. Placebo (95% nCl ^b)	Placebo

Research, Center for Biologics Evaluation and Research; October 2005.

- 12. Gambrell RD. The menopause: benefits and risks of estrogen-progestin replacement therapy. Fertil Steril. 1982;37:457-74.
- 13. Girdler SS, Hinderliter AL, Wells EC, Sherwood A, Grewen KM, Light KC. Transdermal versus oral estrogen therapy in postmenopausal smokers: hemodynamic and endothelial

if you are immobilized for long periods of time and following major surgery. You should discuss risk factors for blood clots with your doctor since blood clots can be life-threatening or cause serious disability.

Gallbladder Disease

The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease requiring surgery.

Dementia

The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in postmenopausal 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 **DIVIGEL**, talk to your doctor or pharmacist if you:

- have a history of allergy or intolerance to any medications or other substances
- have a personal history of breast disease (including breast





HOW TO STORE IT

Store at controlled room temperature of 15 to 30°C.

Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS