PRODUCT MONOGRAPH

Pr DIVIGEL®

Estradiol Gel 0.1%

0.25 mg, 0.5 mg, 1 mg per packet

Estrogen

Transdermal Gel

Manufactured for:
Teva Canada Innovation
Montreal, Quebec H2Z 1S8

Distributed by:
Teva Canada Limited
Toronto, Ontario M1B 2K9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Transdermal	Gel 0.1%	Carbomer, ethanol, propylene glycol, purified water and triethanolamine

INDICATIONS AND CLINICAL USE

Divigel® (estradiol gel) 0.1% is indicated in the treatment of moderate to severe vasomotor symptoms associated with menopause.

Divigel should be prescribed with an appropriate dosage of progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma.

Geriatrics: No clinical studies were conducted to evaluate the effect of Divigel on women more than 65 years old.

Pediatrics: Divigel should not be used in children

CONTRAINDICATIONS

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph
- Liver dysfunction or disease as long as liver function tests have failed to return to normal
- Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer)
- Endometrial hyperplasia
- Known, suspected, or past history of breast cancer
- Undiagnosed abnormal genital bleeding
- Known or suspected pregnancy
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease [CHD])

- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis
- Partial or complete loss of vision due to ophthalmic vascular disease
- Breast feeding
- Classic migraine

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 70 years.[5, 38, 39]

The *estrogen plus progestin* arm of the WHI trial (mean age 63.3 years) indicated an increased risk of *myocardial infarction* (MI), *stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis* in postmenopausal women receiving treatment with combined conjugated equine estrogens (CEE, 0.625 mg/day) and medroxyprogesterone acetate (MPA, 2.5 mg/day) for 5.2 years compared to those receiving placebo.[39]

The estrogen-alone arm of the WHI trial (mean age 63.6 years) indicated an increased risk of stroke and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.[38]

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases
- Estrogens with or without progestins should be prescribed at the **lowest effective dose** for the approved indication
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the recognized indication

Carcinogenesis and Mutagenesis

Breast cancer

Available epidemiological data indicate that the use of combined estrogen plus progestin by postmenopausal women is associated with an increased risk of invasive breast cancer.

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of invasive breast cancer (38 on combined 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 not be given to women with existing breast cancer or those with a previous history of the disease (see **Contraindications**).

There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (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-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

Endometrial hyperplasia & endometrial carcinoma

The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer. Estrogen should be prescribed with an appropriate dosage of a progestin for women with intact uteri in order to prevent endometrial hyperplasia/carcinoma. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users, and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with increased risk of 15- to 24-fold for 5 to 10 years or more. This risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women taking estrogen/progestin combinations 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 the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Cardiovascular

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women.[39, 16, 14] The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.[39, 38]

WHI Trial Findings

In the combined estrogen plus progestin arm of the WHI trial, among 10,000 women over a one-year period, there were:

- 8 more cases of stroke (29 on combined HRT versus 21 on placebo)
- 7 more cases of CHD (37 on combined HRT versus 30 on placebo)[39]

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- No statistically significant difference in the rate of CHD[38]

HERS and HERS II Findings

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg 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 predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Women with familial hyperlipidemias or porphyria need special surveillance. Lipid-lowering measures are recommended additionally, before treatment is started.

Calcium and phosphorus metabolism

Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Hypothyroidism

Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see **Drug-Laboratory Test Interactions).**

Geritourinary

Vaginal bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Uterine leiomyomata

Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Endometriosis

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

Hematologic

Venous thromboembolism

Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen plus progestin* arm of the WHI trial, among 10,000 women on combined HRT over a one-year period, there were 18 more cases of venous thromboembolism, including 8 more cases of pulmonary embolism.[39]

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.[38]

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m^2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

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]

When data from the *estrogen plus progestin* arm of the WHIMS and the estrogen-alone arm of the WHIMS were combined, as per the original WHIMS protocol, in 10,000 women over a one-year period, there were:

- 18 more cases of probable dementia (41 on *estrogen plus progestin* or *estrogen-alone* versus 23 on placebo).[31]

Renal

Fluid retention

Estrogens may cause fluid retention.

Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

Special Populations

Pregnant Women: Estrogen products, including Divigel, should not be used in pregnancy. (see CONTRAINDICATIONS.)

Nursing Mothers: Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving estrogen therapy. Caution should be exercised when estrogen products, including Divigel, are administered to a nursing woman.

Pediatric Use: Safety and efficacy of Divigel in pediatric patients have not been established.

Geriatric Use: There have not been sufficient numbers of geriatric patients involved in studies utilizing Divigel® to determine whether those over 65 years of age differ from younger subjects in their response to Divigel.

Monitoring and Laboratory Tests

Before Divigel is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

Miscellaneous

Alcohol based gels are flammable. Avoid fire, flame, or smoking until the gel has dried.

Occlusion of the area where the topical drug product is applied, with clothing or other barriers, is not recommended until the gel is completely dried.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

The following adverse reactions have been reported with estrogen/progestin combination in general:

Blood and lymphatic system disorders	Altered coagulation tests (see **Warnings and Precautions, Drug-Laboratory Tests Interactions**).
Cardiac disorders	Palpitations; increase in blood pressure (see **Warnings and Precautions**); coronary thrombosis.
Endocrine disorders	Increased blood sugar levels; decreased glucose tolerance.
Eye disorders	Neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.
Gastrointestinal disorders	Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).
General disorders and administration site conditions	Fatigue; changes in appetite; changes in body weight; change in libido.
Hepatobiliary disorders	Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.
Musculoskeletal and connective tissue disorders	Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

Nervous system disorders	Aggravation of migraine episodes; headaches; dizziness; neuritis.
Psychiatric disorders	Mental depression; nervousness; irritability.
Renal and urinary disorders	Cystitis; dysuria; sodium retention; edema.
Reproductive system and breast disorders	Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.
Skin and subcutaneous tissue disorders	Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.
Vascular disorders	Isolated cases of: thrombophlebitis; thromboembolic disorders.

Clinical Trial Adverse Drug Reaction:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Divigel was studied at doses of 0.25, 0.5 and 1.0 g/day in a 12-week, double-blind, placebo-controlled study that included a total of 495 postmenopausal women (86.5% Caucasian). The adverse events that occurred at a rate equal or greater than 5% in any of the treatment groups are summarized in Table 1.

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

	Divigel®			Placebo
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	7 (5.7)	3 (2.4)	2 (1.6)	2 (1.6)
Vaginal mycosis	1 (0.8)	3 (2.4)	8 (6.4)	4(3.2)
REPRODUCTIVE SYSTEM & BREAST DISORDERS				
Breast Tenderness	3 (2.5)	7 (5.7)	11 (8.8)	2 (1.6)
Metrorrhagia	5 (4.1)	7 (5.7)	12 (9.6)	2 (1.6)
Vaginal Hemorrrhage	4 (3.3)	3 (2.4)	10 (8.0)	0

* Adverse events reported by ≥5% of patients in any treatment group.

In a 12-week placebo-controlled study of Divigel, application site reactions at least possibly related were seen in <1% of subjects.

Table 2 Number (%) of Subjects with AEs Occurring in ≥1% of Subjects in A 12-Week Placebo Controlled Study of Divigel

AE[a] System Organ Class Preferred Term	Placebo Gel (N=125)	USL-221			
		0.25 g/day (N=122)	0.5 g/day (N=123)	1.0 g/day (N=125)	Combined (N=370)
	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]
Any AE	57 (46)	75 (61)	69 (56)	76 (61)	220 (59)
Ear and Labyrinth Disorders					
Vertigo	0	1 (<1)	0	2 (2)	3 (<1)
Tinnitus	0	0	0	2 (2)	2 (<1)
Gastrointestinal Disorders					
Abdominal Pain	0	2 (2)	4 (3)	0	6 (2)
Nausea	0	4 (3)	1 (<1)	1 (<1)	6 (2)
Abdominal Distension	1 (<1)	3 (2)	1 (<1)	1 (<1)	5 (1)
Constipation	1 (<1)	1 (<1)	3 (2)	1 (<1)	5 (1)
Dyspepsia	1 (<1)	0	3 (2)	1 (<1)	4 (1)
Vomiting	1 (<1)	2 (2)	1 (<1)	0	3 (<1)
Toothache	0	0	2 (2)	0	2 (<1)
Periodontitis	2 (2)	0	0	0	0
General Disorders and Administration Site Conditions					
Fatigue	1 (<1)	2 (2)	2 (2)	0	4 (1)
Edema Peripheral	2 (2)	1 (<1)	1 (<1)	1 (<1)	3 (<1)
Non-cardiac Chest Pain	0	1 (<1)	0	2 (2)	3 (<1)
Pain	0	2 (2)	0	1 (<1)	3 (<1)
Infections and Infestations					
Nasopharyngitis	5 (4)	7 (6)	5 (4)	6 (5)	18 (5)
Upper Respiratory Tract Infection	2 (2)	7 (6)	3 (2)	2 (2)	12 (3)
Sinusitis	2 (2)	5 (4)	3 (2)	2 (2)	10 (3)
Influenza	0	3 (2)	5 (4)	3 (2)	11 (3)
Fungal Infection	1 (<1)	1 (<1)	1 (<1)	7 (6)	9 (2)
Urinary Tract Infection	2 (2)	1 (<1)	3 (2)	2 (2)	6 (2)
Bronchitis	1 (<1)	3 (2)	2 (2)	1 (<1)	6 (2)
Vaginal Mycosis	3 (2)	0	2 (2)	2 (2)	4 (1)
Gastroenteritis Viral	0	2 (2)	1 (<1)	3 (2)	6 (2)
Pharyngitis	2 (2)	1 (<1)	0	2 (2)	3 (<1)
Injury, Poisoning and Procedural Complications					
Joint Sprain	1 (<1)	2 (2)	0	1 (<1)	3 (<1)
Contusion	0	1 (<1)	2 (2)	0	3 (<1)
Back Injury	2 (2)	2 (2)	0	0	2 (<1)
Investigations					
Weight Increased	2 (2)	4 (3)	4 (3)	1 (<1)	9 (2)

AE[a] System Organ Class Preferred Term	Placebo Gel (N=125)	USL-221			
		0.25 g/day (N=122)	0.5 g/day (N=123)	1.0 g/day (N=125)	Combined (N=370)
	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	1 (<1)	3 (2)	4 (3)	1 (<1)	8 (2)
Back Pain	5 (4)	3 (2)	3 (2)	0	6 (2)
Muscle Cramp	0	4 (3)	1 (<1)	1 (<1)	6 (2)
Myalgia	0	3 (2)	1 (<1)	1 (<1)	5 (1)
Musculoskeletal Pain	1 (<1)	0	2 (2)	0	2 (<1)
Pain in Extremity	3 (2)	0	0	0	0
Neoplasms Benign, Malignant and Unspecified					
Uterine Leiomyoma	1 (<1) [2]	3 (2) [5]	2 (2) [3]	3 (2) [5]	8 (2) [4]
Nervous System Disorders					
Headache	6 (5)	5 (4)	5 (4)	5 (4)	15 (4)
Dizziness	2 (2)	3 (2)	2 (2)	3 (2)	8 (2)
Migraine	1 (<1)	1 (<1)	1 (<1)	2 (2)	4 (1)
Paraesthesia	2 (2)	0	0	0	0
Psychiatric Disorders					
Anxiety	0	1 (<1)	2 (2)	0	3 (<1)
Insomnia	2 (2)	1 (<1)	0	1 (<1)	2 (<1)
Irritability	2 (2)	0	0	0	0
Reproductive System and Breast Disorders					
Breast Tenderness	2 (2)	3 (2)	7 (6)	11 (9)	21 (6)
Vaginal Hemorrhage	0	4 (3) [6]	3 (2) [5]	10 (8) [18]	17 (5) [9]
Vaginal Discharge	2 (2)	1 (<1)	4 (3)	4 (3)	9 (2)
Metrorrhagia	2 (2) [4]	1 (<1) [2]	4 (3) [7]	2 (2) [4]	7 (2) [4]
Nipple Pain	1 (<1)	1 (<1)	1 (<1)	5 (4)	7 (2)
Genital Pruritus Female	0	1 (<1)	3 (2)	1 (<1)	5 (1)
Ovarian Cyst	0	3 (2)	0	2 (2)	5 (1)
Dysmenorrhea	0	0	0	2 (2) [4]	2 (<1) [1]
Menorrhagia	0	0	2 (2) [3]	0	2 (<1) [1]
Uterine Hemorrhage	0	0	1 (<1) [2]	1 (<1) [2]	2 (<1) [1]
Endometrial Hyperplasia	1 (<1) [2]	1 (<1) [2]	0	0	1 (<1) [1]
Adnexa Uteri Pain	0	0	0	1 (<1) [2]	1 (<1) [1]
Menstruation Irregular	0	0	0	1 (<1) [2]	1 (<1) [1]
Uterine Spasm	0	1 (<1) [2]	0	0	1 (<1) [1]

AE[a] System Organ Class Preferred Term	Placebo Gel (N=125)	USL-221			
		0.25 g/day (N=122)	0.5 g/day (N=123)	1.0 g/day (N=125)	Combined (N=370)
	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]	n (%)[b]
Respiratory, Thoracic and Mediastinal Disorders					
Pharyngolaryngeal Pain	0	2 (2)	1 (<1)	2 (2)	5 (1)
Cough	0	2 (2)	2 (2)	0	4 (1)
Sinus Congestion	1 (<1)	0	2 (2)	0	2 (<1)
Skin and Subcutaneous Tissue Disorders					
Pruritus	1 (<1)	3 (2)	0	2 (2)	5 (1)
Rash	1 (<1)	2 (2)	0	1 (<1)	3 (<1)
Vascular Disorders					
Hypertension	2 (2)	1 (<1)	1 (<1)	2 (2)	4 (1)

a. Subjects may be counted in more than one AE category.

b. Value in [ ] is percentage of subjects based on N for subjects with intact uterus in the Phase 3 Placebo-Controlled Study: 53 for placebo; 64 for Estradiol Gel, 0.1%, 0.25 g/day; 60 for Estradiol Gel, 0.1%, 0.5 g/day; 56 for Estradiol Gel, 0.1%, 1.0 g/day; and 180 for all Estradiol Gel, 0.1% combined.

Less Common [< 1%] Clinical Trial Adverse Reactions:

Cardiac Disorders

Palpitations, Angina Pectoris, Arrhythmia

Gastrointestinal Disorders

Dyspepsia, Vomiting, Abdominal Pain Lower

General Disorders & Administration Site Conditions

Fatigue, Non-cardiac Chest Pain, Oedema Peripheral Pain

Hepatobiliary Disorders

Cholelithiasis

Immune System Disorders

Hypersensitivity

Infections and Infestations

Pharyngitis, Viral Infection

Injury, Poisoning and Procedural Complications

Joint Sprain, Back Injury

Musculoskeletal and Connective Tissue Disorders

Myalgia, Musculoskeletal Pain, Pain in Extremity

Nervous System Disorders
Migraine

Psychiatric Disorders
Insomnia, Anxiety, Nervousness, Irritability

Reproductive System and Breast Disorders
Genital Pruritus Female, Menstruation Irregular, Ovarian Cyst, Dysmenorrhoea, Menorrhagia

Respiratory, Thoracic and Mediastinal Disorders
Cough, Pharyngolaryngeal Pain, Sinus Congestion

Skin and Subcutaneous Tissue Disorders
Rash

The following additional adverse reactions have been reported with estrogen and/or progestin therapy.

1. **Genitourinary system:** Changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea; increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer; vaginal discharge.

2. **Breasts:** Tenderness; enlargement; pain; nipple discharge; galactorrhea, fibrocystic breast changes; breast cancer; nipple pain.

3. **Cardiovascular:** Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

4. **Gastrointestinal:** Nausea; vomiting; abdominal cramps; bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis; enlargement of hepatic hemangiomas; abdominal pain.

5. **Skin:** Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus; rash.

6. **Eyes:** Retinal vascular thrombosis; intolerance to contact lenses.

7. **Central Nervous System:** Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy; dementia.

8. **Miscellaneous:** Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthralgias; leg cramps; changes in libido; urticaria; angioedema; anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides; muscle cramps.

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).

Herbal preparations containing St. John's Wort (Hypericum perforatum) may induce the metabolism of estrogens (see section on Drug-Herb Interactions). At transdermal administration, the first pass effect in the liver is avoided and thus, transdermally applied estrogens (and progestagens) might be less affected than oral hormones by enzyme inducers.)

Clinically, an increased metabolism of estrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

Table 3 – Drugs which may affect the Concentrations of Ethinyl Estradiol

Drug	Ref	Proposed Mechanism	Effect
Acetaminophen	Literature		Increased AUC and/or plasma concentrations of ethinyl estradiol
Anticonvulsants Phenobarbital Phenytoin Carbamazepine	Literature	Increased metabolism of ethinyl estradiol	Decreased plasma concentrations of estradiol
Ascorbic acid	Literature		Increased AUC and/or plasma concentrations of ethinyl estradiol
Atorvastatin	Literature		When co-administered with certain ethinyl estradiol containing drug products (e.g. oral contraceptives containing ethinyl estradiol), the AUC values of ethinyl estradiol increase by 20%.
Rifampin	Literature	Increased metabolism of ethinyl estradiol	Decreased plasma concentrations of estradiol. Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.
Troglitazone	Literature		When co-administered with certain ethinyl estradiol containing drug products (e.g. oral contraceptives containing ethinyl estradiol), the plasma concentrations of ethinyl estradiol reduce by 30%.

Table 4 – Modification of Other Drug Action by Co-administration with Certain Drugs Containing Ethinyl Estradiol (e.g. oral contraceptives containing ethinyl estradiol)

Drug	Ref	Effect
Acetaminophen	Literature	Decreased plasma concentrations of acetaminophen
Clofibric Acid	Literature	Increased clearance of clofibric acid
Cyclosporin	Literature	Increased plasma concentrations of cyclosporine
Morphine	Literature	Increased clearance of morphine
Prednisolone	Literature	Increased plasma concentrations of prednisolone
Salicylic Acid	Literature	Increased clearance of salicylic acid
Temazepam	Literature	Increased clearance of temazepam
Theophylline	Literature	Increased plasma concentrations of theophylline

Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds or induce the conjugation of other compounds.

Drug-Food Interactions
Interaction of DIVIGEL® with food has not been established.

Drug-Herb Interactions
It was found that some herbal products (e.g. St. John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin.

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 HDL_2 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.

Drug-Lifestyle Interactions

Divigel is an alcohol based gel. Alcohol based gels are flammable. Avoid fire, flame or smoking until the gel has dried.

Occlusion of the area where the topical gel product is applied with clothing or other barriers, is not recommended until the gel is completely dry.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Patients should be re-evaluated periodically as clinically appropriate (e.g., 3-month to 6-month intervals) to determine if treatment is still necessary (see **BOXED WARNINGS** and **WARNINGS**). For women who have a uterus, adequate diagnostic measures, such as endometrial sampling, when indicated, should be undertaken to rule out malignancy in cases of undiagnosed persistent or recurring abnormal vaginal bleeding.

Divigel (estradiol gel) 0.1%, at doses of 0.25, 0.5, and 1.0 g/day, is indicated for transdermal use in the treatment of moderate to severe vasomotor symptoms associated with menopause. Each gram of Divigel contains 1 mg of estradiol.

Patients should be treated with the lowest effective dose of Divigel. Generally, women should be started at 0.25 grams Divigel daily. Subsequent dosage adjustments may be made based upon the individual patient response. This dose should be periodically reassessed by the healthcare provider.

Divigel should be applied once daily on the skin of either the right or left upper thigh. The application surface area should be about 5 by 7 inches (approximately the size of two palm prints). The entire contents of a unit dose packet should be applied each day. To avoid potential skin irritation, Divigel should be applied to the right or left upper thigh on alternating days. Divigel should not be applied on the face, breasts, or irritated skin or in or around the vagina. After application, the gel should be allowed to dry before dressing. The application site should not be washed within 1 hour after applying Divigel. Contact of the gel with eyes should be avoided. Hands should be washed after application.

OVERDOSAGE

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

Symptoms of Overdosage:
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.

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 estrone conjugates and requires smaller total doses than does oral therapy.

Pharmacodynamics

Divigel provides estrogen therapy by delivering estradiol, the major estrogenic hormone secreted by the human ovary, to the systemic circulation following topical application.
Endogenous 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 mcg 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.

Estrogens act through binding to nuclear receptors in estrogen-responsive tissues. To date, two estrogen receptors have been identified. These vary in proportion from tissue to tissue.

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

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 dose-proportional estradiol pharmacokinetics at steady state for both AUC_{0-24} and C_{max} following once daily dosing to the skin of either the right or left upper thigh (Table 5).).

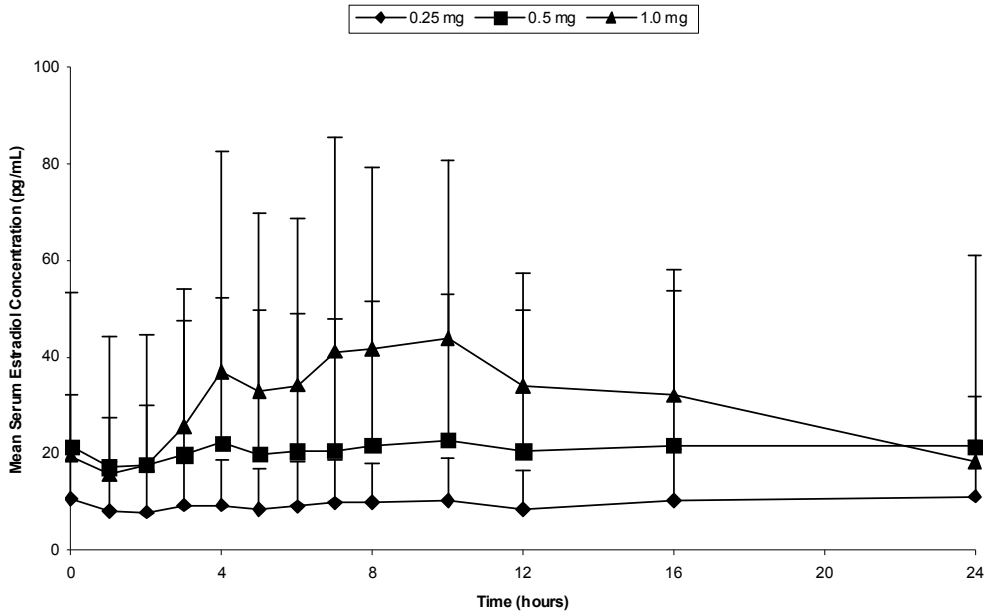
Table 5: Mean (%CV) Pharmacokinetic Parameters for Estradiol (uncorrected for baseline) on Day 14 Following Multiple Daily Doses of Divigel® 0.1%

Parameter (units)	Divigel® 0.25 g	Divigel® 0.5 g	Divigel® 1.0 g
AUC_{0-24} (pg•h/mL)	236 (94)	504 (149)	732 (81)
C_{max} (pg/mL)	14.7 (84)	28.4 (139)	51.5 (86)
C_{avg} (pg/mL)	9.8 (92)	21 (148)	30.5 (81)
t_{max}* (h)	16 (0, 72)	10 (0, 72)	8 (0, 48)
E2:E1 ratio	0.42	0.65	0.65

*Median (Min, Max).

Steady-state serum concentrations of estradiol are achieved by day 12 following daily application of Divigel® to the skin of the upper thigh. The mean (SD) serum estradiol levels following once daily dosing at day 14 are shown in Figure 1.

Figure 1: Mean (SD) Serum Estradiol Concentrations (Values Uncorrected for Baseline) on Day 14 Following Multiple Daily Doses of Divigel 0.1%



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. Drug Interactions

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4, such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin, may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4, such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir, and grapefruit juice, may increase plasma concentrations of estrogens and result in side effects.

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 cm^2 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 30 foil pouches.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

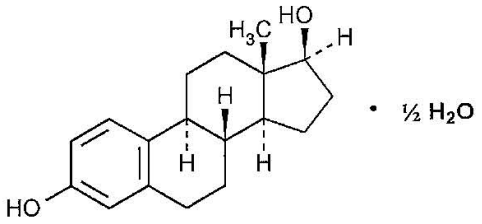
Proper name: Estradiol

Chemical name: Estra-1,3,5(10)-triene-3, 17β-diol

Molecular mass: 281.39 (hemihydrate)
272.38 (anhydrous)

Molecular formula: $C_{18}H_{24}O_2 \cdot ½ H_20$

Structural formula:



Physicochemical properties:

Physical Form: White or creamy white hygroscopic crystals or crystalline powder

Solubility: Practically insoluble in water; 1 in 28 in alcohol (40 mg/mL); 1 in 17 in acetone (60 mg/mL); 1 in 435 in chloroform (2 mg/mL); soluble in dioxane and solutions of alkali hydroxides; sparingly soluble in fixed oils; soluble in propylene glycol, 74 mg/g (80 mg/mL)

Melting Point: 173-179° C

CLINICAL TRIALS

Effects on Vasomotor Symptoms

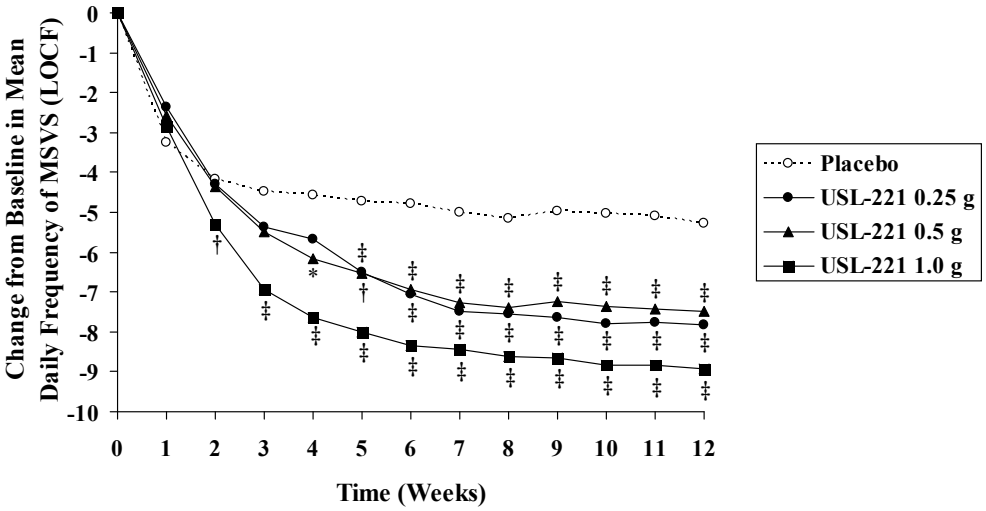
A randomized, double-blind, placebo-controlled trial evaluated the efficacy of 12-week treatment with three different daily doses of Divigel for vasomotor symptoms in 495 postmenopausal women (86.5% White; 10.1% Black) between 34 and 89 years of age (mean age 54.6) who had at least 50 moderate to severe 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 statistically significant for the 0.5 g/day and the 1.0 g/day Divigel doses when compared to placebo at week 4. Statistically significant reductions in both the mean daily frequency and the mean daily severity of moderate to severe hot flushes for the Divigel 0.25 g/day dose when compared to placebo were delayed to week 7. There were statistically significant reductions in mean daily frequency and severity of hot flushes for all three Divigel doses (0.25 g/day, 0.5 g/day and 1.0 g/day) compared to placebo at week 12. See Table 6 for results.

Table 6: Summary of Changes From Baseline in the Mean Daily Frequency and Severity of Hot Flushes during Divigel® Treatment (ITT Population)

	Divigel®			**Placebo**
Evaluation	0.25 g/day N=121	0.5 g/day N=119	1.0 g/day N=124	N=124
Frequency of Daily Hot Flushes				
Baseline Mean	12.11	10.86	10.69	10.79
Mean Change: Week 4	-5.66	-6.17	-7.63	-4.56
p-value†	0.132	0.011	<0.001	
Mean Change: Week 7	-7.47	-7.26	-8.44	-4.99
p-value†	<0.001	<0.001	<0.001	
Mean Change: Week 12	-7.83	-7.48	-8.92	-5.27
p-value†	<0.001	<0.001	<0.001	
Severity of Daily Hot Flushes				
Baseline Mean	2.53	2.52	2.52	2.53
Mean Change: Week 4	-0.34	-0.65	-0.87	-0.25
p-value†	0.283	<0.001	<0.001	
Mean Change: Week 7	-0.68	-0.86	-1.20	-0.36
p-value†	<0.001	<0.001	<0.001	
Mean Change: Week 12	-0.84	-1.00	-1.39	-0.47
p-value†	0.021	0.002	<0.001	

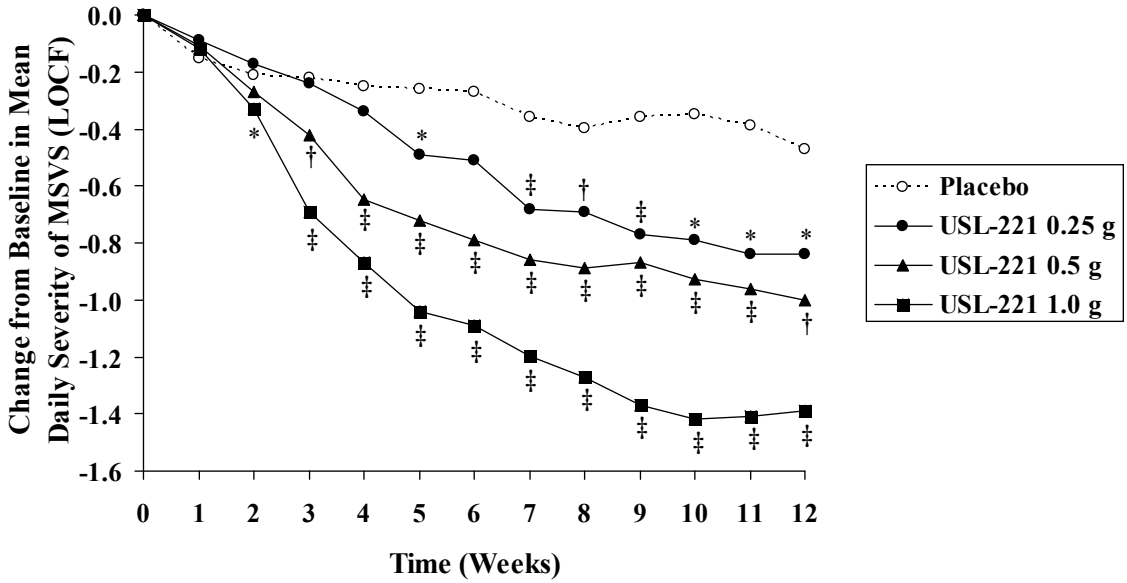
†P-value for comparison versus placebo from a van Elteren's test stratified by pooled centre.

Figure 2 Change from Baseline in Mean Daily Frequency 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 Severity 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.

Women's Health Initiative Studies

The Women's Health Initiative (WHI) enrolled a total of 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of either the use of oral conjugated estrogens (CE 0.625 mg) alone per day or in combination with medroxyprogesterone acetate (CE 0.625 mg/MPA 2.5 mg) per day compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of coronary heart disease (CHD) (nonfatal myocardial infarction (MI), silent MI and CHD death), with invasive breast cancer as the primary adverse outcome studied. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, pulmonary embolism (PE), endometrial cancer (only in the estrogen-plus-progestin substudy), colorectal cancer, hip fracture, or death due to other cause. The study did not evaluate the effects of CE or CE/MPA on menopausal symptoms.

The estrogen-alone substudy was stopped early because an increased risk of stroke was observed and it was deemed that no further information would be obtained regarding the risks and benefits of estrogen alone in predetermined primary endpoints. Results of the estrogen-alone substudy, which included 10,739 women (average age of 63 years, range 50 to 79; 75.3% White, 15.1% Black, 6.1% Hispanic, 3.6% Other), after an average follow-up of 6.8 years are presented in Table 7.

Table 7: Relative and Absolute Risk Seen In the Estrogen-Alone Substudy Of WHI[a]

Event	Relative Risk CE vs. Placebo (95% nCI[a])	Placebo n = 5,429	CE n = 5,310
		Absolute Risk per 10,000 Women-Years	
CHD events[b]	0.95 (0.79- 1.16)	56	53
Nonfatal MI[b]	*0.91 (0.73-1.14)*	*43*	*40*
CHD death[b]	*1.01 (0.71- 1.43)*	*16*	*16*
Stroke[c]	1.39 (1.10-1.77)	32	44
Deep vein thrombosis[b,d]	1.47 (1.06-2.06)	15	23
Pulmonary embolism[b]	1.37 (0.90-2.07)	10	14
Invasive breast cancer[b]	0.80 (0.62-1.04)	34	28
Colorectal cancer[c]	1.08 (0.75-1.55)	16	17
Hip fracture[c]	0.61 (0.41-0.91)	17	11
Vertebral fractures[c,d]	0.62 (0.42-0.93)	17	11
Total fractures[c,d]	0.70 (0.63-0.79)	195	139
Death due to other causes[c,e]	1.08 (0.88-1.32)	50	53
Overall mortality[c,d]	1.04 (0.88-1.32)	78	81
Global index[c,f]	1.01 (0.91-1.12)	190	192

[a] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons
[b] Results are based on centrally adjudicated data for an average follow-up of 7.1 years
[c] Results are based on an average follow-up of 6.8 years
[d] Not included in Global Index
[e] All deaths, except from breast or colorectal cancer, definite/probable CHD, PE or cerebrovascular disease
[f] A subset of the events was combined in a "global index", defined as the earliest occurrence of CHD events, invasive breast cancer, stroke, pulmonary embolism, colorectal cancer, hip fracture, or death due to other causes

For those outcomes included in the WHI "global index" that reached statistical significance, the absolute excess risk per 10,000 women-years in the group treated with CE alone was 12 more strokes, while the absolute risk reduction per 10,000 women-years was 6 fewer hip fractures. The absolute excess risk of events included in the "global index" was a nonsignificant 2 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality. (see **BOXED WARNINGS**, **WARNINGS**, and **PRECAUTIONS**).

Final centrally adjudicated results for CHD events and centrally adjudicated results for invasive breast cancer incidence from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no overall difference for primary CHD events (nonfatal MI, silent MI and CHD death) and invasive breast cancer incidence in women receiving CE alone compared with placebo (see Table 7).

The estrogen-plus-progestin substudy was also stopped early, because according to the predefined stopping rule, after an average follow-up of 5.2 years of treatment, the increased risk of breast cancer and cardiovascular events exceeded the specified benefits included in the "global index." The absolute excess risk of events included in the "global index" was 19 per 10,000 women-years (RR 1.15, 95% nCI 1.03-1.28).

For those outcomes included in the WHI "global index" that reached statistical significance after 5.6 years of follow-up, the absolute excess risks per 10,000 women years in the group treated with CE/MPA were 6 more CHD events, 7 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 7 fewer colorectal cancers and 5 fewer hip fractures. (see **BOXED WARNINGS, WARNINGS**, and **PRECAUTIONS**).

Results of the estrogen-plus-progestin substudy, which included 16,608 women (average age of 63 years, range 50 to 79; 83.9% White, 6.8% Black, 5.4% Hispanic, 3.9% Other), are presented in Table 8 below. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.[2]

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% nCI[b])	Placebo n = 8102	CE/MPA n = 8506
		Absolute Risk per 10,000 women-years	
CHD events	1.24 (1.00-1.54)	33	39
Non-fatal MI	*1.28 (1.00-1.63)*	*25*	*31*
CHD death	*1.10 (0.70-1.75)*	*8*	*8*
All strokes	1.31 (1.02-1.68)	24	31
Ischemic stroke	*1.44 (1.09 -1.90)*	*18*	*26*
Deep vein thrombosis	1.95 (1.43 – 2.67)	13	26
Pulmonary embolism	2.13 (1.45-3.11)	8	18
Invasive breast cancer[c]	1.24 (1.01-1.54)	33	41
Invasive colorectal cancer	0.56 (0.38-0.81)	16	9
Endometrial cancer	0.81 (0.48-1.36)	7	6
Cervical cancer	1.44 (0.47-4.42)	1	2
Hip fracture	0.67 (0.47-0.96)	16	11
Vertebral fractures	0.65 (0.46-0.92)	17	11
Lower arm/wrist fractures	0.71 (0.59-0.85)	62	44
Total fractures	0.76 (0.69-0.83)	199	152

[a] Results are based on centrally adjudicated data. Mortality data was not part of the adjudicated data; however, data at 5.2 years of follow-up showed no difference between the groups in terms of all-cause mortality (RR 0.98, 95% nCI 0.82-1.18)
[b] Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
[c] Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer

Women's Health Initiative Memory Study

The estrogen-alone Women's Health Initiative Memory Study (WHIMS), a substudy of the WHI, enrolled 2,947 predominantly healthy postmenopausal women 65 years of age and older (45% were aged 65 to 69 years, 36% were 70 to 74 years, and 19% were 75 years of age and older) to evaluate the effects of conjugated estrogens (CE 0.625 mg) on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group (37 per 10,000 women-years) and 19 in the placebo group (25 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the estrogen-alone group was 1.49 (95% confidence interval (CI), 0.83-2.66) compared to placebo. It is unknown whether these findings apply to younger postmenopausal women. (see **BOXED WARNINGS, WARNINGS**, **Dementia,** and **PRECAUTIONS, Geriatric Use**).

The estrogen-plus-progestin WHIMS substudy enrolled 4,532 predominantly healthy postmenopausal women 65 years of age and older (47% were aged 65 to 69 years, 35% were 70 to 74 years, and 18% were 75 years of age and older) to evaluate the effects of conjugated estrogens (CE 0.625 mg) plus medroxyprogesterone acetate (MPA 2.5 mg) daily on the incidence of probable dementia (primary outcome) compared with placebo.

After an average follow-up of 4 years, 40 women in the estrogen-plus-progestin group (45 per 10,000 women-years) and 21 in the placebo group (22 per 10,000 women-years) were diagnosed with probable dementia. The relative risk of probable dementia in the hormone therapy group was 2.05 (95% CI, 1.21-3.48) compared to placebo.

When data from the two populations were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable dementia was 1.76 (95% CI 1.19-2.60). It is unknown whether these findings apply to younger postmenopausal women. (see **BOXED WARNING**, **WARNINGS**, **Dementia**, and **PRECAUTIONS, Geriatric Use**.)[2]

DETAILED PHARMACOLOGY

See Action and Clinical Pharmacology (Part 1).

TOXICOLOGY

Estradiol was shown to have low acute oral toxicity in mice when tested alone or in combination with medroxyprogesterone acetate (MPA). In repeat-dose dermal irritation studies of rabbits dosed for 28 days, no evidence of primary or cumulative skin irritancy was observed. Divigel was not a skin sensitizer when tested using the Buehler method in guinea pigs. A slight degree of ocular irritancy was observed in the rabbit following administration of Divigel and this irritancy was reduced with eye washing. Divigel showed no phototoxicity or photosensitivity in guinea pigs.

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PART III: CONSUMER INFORMATION

PrDIVIGEL®
(Estradiol gel 0.1%)

IMPORTANT: PLEASE READ

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

Please read this leaflet carefully before you start taking DIVIGEL and each time you have your prescription refilled. It contains information regarding possible risks of hormone replacement therapy obtained from the results of the Women's Health Initiative Study.

This information leaflet does not take the place of talking to your health professional about your medical condition or your treatment. If you have any questions or concerns, consult your doctor or your pharmacist.

ABOUT THIS MEDICATION

What the medication is used for:
DIVIGEL is approved for the replacement of estrogen in menopausal women with symptoms of menopause, which may include hot flushes, disturbed sleep and vaginal dryness.

DIVIGEL should not be used by women with an intact uterus unless it is prescribed in association with a progestin.

Divigel should be used only under the supervision of a doctor, with regular follow-up at least once a year to identify side effects associated with its use. Your first follow-up visit should be within 3 to 6 months of starting treatment. Your visit may include a blood pressure check, a breast exam, a Pap smear and pelvic exam. You should have a mammogram before starting treatment and at regular intervals as recommended by your doctor. Your doctor may recommend some blood tests.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your doctor. You should regularly talk with your doctor about whether you still need treatment with HRT.

What it does:

ABOUT MENOPAUSE
Menopause is not a disease. Menopause is a natural phase in a women's life when the ovaries decrease their production of the female hormones, estrogen and progesterone. In most women, this occurs between the ages of 45 and 55 or sooner if the ovaries have been removed by surgery.

The symptoms associated with menopause vary for every woman. The most common symptom is hot flushes/flashes. Other symptoms some women may develop during menopause include insomnia (reduced quality of sleep) and vaginal atrophy (dryness). Your doctor can provide you with further information about menopause.

The active ingredient is DIVIGEL is estradiol, a natural female hormone. In healthy women of childbearing age, estradiol is the main estrogen produced by the ovaries.

DIVIGEL does not contain progestins.

For information on the dose and how frequently it should be taken, please see PROPER USE OF THIS MEDICATION below.

When it should not be used:
Do not use DIVIGEL if you:
- have liver disease
- have a personal history of breast cancer or endometrial cancer (cancer of the uterus)
- have been diagnosed with endometrial hyperplasia (overgrowth of the lining of the uterus)
- have experienced undiagnosed or unexpected vaginal bleeding
- are pregnant or suspect you may be pregnant;
- are breast feeding
- have a history of coronary heart disease (including heart attack) or stroke
- experience migraine headaches
- have a history of blood clots
- have active thrombophlebitis (inflammation of the veins)
- have had partial or complete loss of vision due to blood vessel disease of the eye
- known or suspected hormone dependent cancer
- have had an allergic or unusual reaction to DIVIGEL or to an of its ingredients (see information below on medicinal and nonmedicinal ingredients)

What the medicinal ingredient is:
Estradiol 0.1%.

What the important nonmedicinal ingredients are:
Carbomer, ethanol, propylene glycol, purified water and triethanolamine.

What dosage forms it comes in:
DIVIGEL is packaged in single dose foil pouches.

Divigel is supplied:

Carton of 30 packets, 0.25 mg
Carton of 30 packets, 0.5 mg
Carton of 30 packets, 1.0 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial is a large clinical study that assessed the benefits and risks of oral combined *estrogen plus progestin* therapy and oral *estrogen-alone* therapy compared with placebo (a pill with no active ingredients) in postmenopausal women.

The WHI trial indicated an increased risk of myocardial infarction (heart attack), stroke, breast cancer, pulmonary emboli (blood clots in the lungs) and deep vein thrombosis (blood clots in the large veins) in postmenopausal women taking oral combined *estrogen plus progestin.*

The WHI trial indicated an increased risk of stroke and deep vein thrombosis in postmenopausal women with prior hysterectomy (surgical removal of the uterus) taking oral *estrogen-alone.*

Therefore, you should carefully consider the following:

- There is an increased risk of developing invasive breast cancer, heart attack, stroke and blood clots in both lungs and large veins with the use of estrogen plus progestin therapy.
- There is an increased risk of stroke and blood clots in the large veins with the use of estrogen-alone therapy.
- Estrogens with or without progestins should not be used to prevent heart disease or stroke.
- Estrogens with or without progestins should be used at **the lowest effective dose** and for **the shortest period of time** possible. Regular medical follow-up is advised.

Breast Cancer
The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

The results of the WHI trial indicated no difference in the risk of breast cancer in post-menopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

Estrogens with or without progestins should not be taken by women who have a personal history of breast cancer. In addition, women with a family history of breast cancer or women with a history of breast lumps, breast biopsies or abnormal mammograms (breast x-rays) should consult with their doctor before starting HRT.

Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their doctor.

Regular breast examinations by a doctor and regular breast self-examinations are recommended for all women. You should review the technique for breast self-examination with your doctor.

Overgrowth of the lining of the uterus and cancer of the uterus

Ovarian Cancer:

In some studies the use of estrogen-alone therapy and estrogen plus progestin therapies for 5 or more years has been associated with an increased risk of ovarian cancer.

The use of *estrogen-alone* therapy by post menopausal women who still have a uterus increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus), which increases the risk of endometrial cancer (cancer of the lining of the uterus).

If you plan to take estrogen therapy and you still have your uterus, you should take a progestin medication (another hormone drug) regularly for a certain number of days of each month to reduce the risk of endometrial hyperplasia.

You should discuss progestin therapy and risk factors for endometrial hyperplasia and endometrial carcinoma with your doctor. You should also report any unexpected or unusual vaginal bleeding to your doctor.

If you have had your uterus removed, you are not at risk of developing endometrial hyperplasia or endometrial carcinoma. Progestin therapy is therefore not generally required in women who have had a hysterectomy.

Heart Disease and Stroke
The results of the WHI trial indicated an increased risk of stroke and coronary heart disease in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of stroke, but no difference in the risk of coronary heart disease in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

Abnormal Blood Clotting
The results of the WHI trial indicated an increased risk of blood clots in the lungs and large veins in post-menopausal women taking combined *estrogen plus progestin* compared to women taking placebo.

The results of the WHI trial indicated an increased risk of blood clots in the large veins, but no difference in the risk of blood clots in the lungs in post-menopausal women with prior hysterectomy taking *estrogen-alone* compared to women taking placebo.

The risk of blood clots also increases with age, if you or a family member has had blood clots, if you smoke or if you are severely overweight. The risk of blood clots is also temporarily increased

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

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

Dementia
The Women's Health Initiative Memory Study (WHIMS) was a substudy of the WHI trial and indicated an increased risk of dementia (loss of memory and intellectual function) in post-menopausal women age 65 and over taking oral combined *estrogen plus progestin* compared to women taking placebo.

The WHIMS indicated no difference in the risk of dementia in post-menopausal women age 65 and over with prior hysterectomy taking oral *estrogen-alone* compared to women taking placebo.

BEFORE you use 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 lumps) and/or breast biopsies, or a family history of breast cancer
- have experienced any unusual or undiagnosed vaginal bleeding
- have a history of uterine fibroids or endometriosis
- have a history of liver disease, jaundice (yellowing of the eyes and/or skin) or itching related to estrogen use or during pregnancy
- have a history of migraine headache
- have a history of high blood pressure
- have a personal or family history of blood clots, or a personal history of heart disease or stroke
- have a history of kidney disease, asthma or epilepsy (seizures)
- have a history of bone disease (this includes certain metabolic conditions or cancers that can affect blood levels of calcium and phosphorus)
- have been diagnosed with diabetes
- have been diagnosed with porphyria (a disease of blood pigment)
- have a history of high cholesterol or high triglycerides
- are pregnant or may be pregnant
- have had a hysterectomy (surgical removal of the uterus);
- smoke
- have a thyroid problem (hypothyroidism)

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with DIVIGEL include:
Barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone or rifampin, atorvastin, antibiotics, aminoglutethimide, some herbal products (e.g., St. John's Wort), phenobarbital, phenytoin, troglitazone, ascorbic acid, acetaminophen, oral contraceptives containing ethinyl estradiol, progestin.

Estrogens may diminish the effectiveness of anticoagulant (substances that prevent coagulation), antidiabetic (drugs treating diabetes mellitus) and antihypertensive agents (drugs treating high blood pressure).

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

PROPER USE OF THIS MEDICATION

How should DIVIGEL be applied?
DIVIGEL should be applied once a day, around the same time each day.

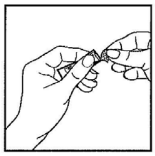
Apply DIVIGEL to clean, dry, and unbroken (without cuts or scrapes) skin. If you take a bath or shower, be sure to apply your DIVIGEL after your skin is dry. The application site should be completely dry before dressing or swimming.

Apply DIVIGEL to either your left or right upper thigh. Change between your left and right upper thigh each day to help prevent skin irritation.

How and when to apply DIVIGEL:

1. Wash and dry your hands thoroughly.
2. Sit in a comfortable position.
3. Cut or tear the DIVIGEL packet as shown in Diagram 1.

Diagram 1

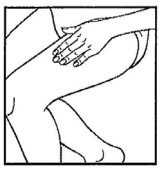


4. Using your thumb and index finger, squeeze the entire contents of the packet onto the skin of the upper thigh as shown in Diagram 2.

Diagram 2

Gently spread the gel in a thin layer on your upper thigh over an area of about 5 by 7 inches, or two palm prints as shown in Diagram 3. It is not necessary to massage or rub in DIVIGEL.

Diagram 3



5. Allow the gel to dry completely before dressing.
6. Dispose of the empty DIVIGEL packet in the trash.
7. Wash your hands with soap and water immediately after applying DIVIGEL to remove any remaining gel and reduce the chance of transferring DIVIGEL to other people.

Important things to remember when using DIVIGEL®

- **Wash your hands with soap and water after applying the gel to reduce the chance that the medicine will be spread from your hands to other people**
- Allow the gel to dry before dressing. Try to keep the area dry for as long as possible
- Do not allow others to come in contact with the area of skin where you applied the gel for at least one hour after you apply Divigel
- You should not allow others to apply the gel for you. However, if this is necessary, the individual should wear a disposable plastic glove to avoid direct contact with Divigel
- Do not apply Divigel to your face, breast, or irritated skin. If you get Divigel in your eyes, flush your eyes right away with lukewarm tap water.
- Never apply Divigel in or around the vagina
- **Divigel contains alcohol. Alcohol based gels are flammable. Avoid fire, flame or smoking until the gel has dried**

Overdose:

In the case of accidental overdosage or ingestion (swallowing) of Divigel, contact your doctor and/or your local Poison Control Cenre.

Missed Dose:

If you miss a dose, do not double the dose on the next day to catch up. If your next dose is less than 12 hours away, it is best just to wait and apply your normal dose the next day. If it is more than 12 hours until the next dose, apply the dose you missed and resume your normal dosing the next day. Do not apply Divigel more than once each day. If you accidentally spill some of the contents of a Divigel packet, do not open a new packet. Wait and apply your normal dose the next day.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Adverse drug reactions occur most commonly during the first months of treatment. They are usually mild and subside with continued treatment. Very rarely skin irritation can occur with DIVIGEL. Using alternate thighs for each dosing is recommended.

The following side effects generally do not require medical attention, and will go away as your body adjusts to DIVIGEL:

Common: headache, breast pain, breast tenderness, bloating, weight increase, nausea/vomiting, abdominal pain (cramping), skin irritation.

Uncommon: Migraine, changes in mood.

If you think you are reacting poorly to Divigel or are having other problems, please tell your doctor.

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

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

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

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

To monitor drug safety, Health Canada through the Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

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

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

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

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found by contacting the sponsor, http://www.tevacanadainnovation.ca
or by contacting the sponsor, Teva Canada Innovation, at:
1-855-519-8382

This leaflet was prepared by Teva Canada Innovation

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