Help your patients manage their moderate to severe hot flashes[1]

Think PrDivigel®

Divigel® is a transdermal gel indicated in the treatment of moderate to severe vasomotor symptoms (MSVS) associated with menopause.

PrDivigel®
Estradiol gel 0.1%

Menopause affects all women at some point in their lives[2]

Vasomotor symptoms (VS) affect 60% to 80% of women entering menopause

- Most postmenopausal women (60%) experience hot flashes for less than 7 years, but these can persist for 15 years or more.[2]
- Estrogens with or without progestins should be prescribed for the shortest period possible for the recognized indication.

Women should be offered a regimen containing both estrogen and progestogen (unless they have had a hysterectomy)[2]

- Estrogen therapy (with or without progestin therapy) remains the most effective treatment for VS associated with menopause.[2]

Help your patients manage their moderate to severe hot flashes[1]

Think Pr Divigel®

Flexible dosing and packets that are designed to be convenient and easy to use

- Divigel® comes in three dose strengths, including the lowest daily estrogen dose of transdermal estradiol gel available in Canada (0.25 mg Divigel® dose).[3]*
- Divigel® comes in small, portable packets that were designed to be easy to use at home and travel-friendly.

Divigel® packets are small enough to fit in your patients' carry-on bags!

* Comparative clinical significance has not been established.

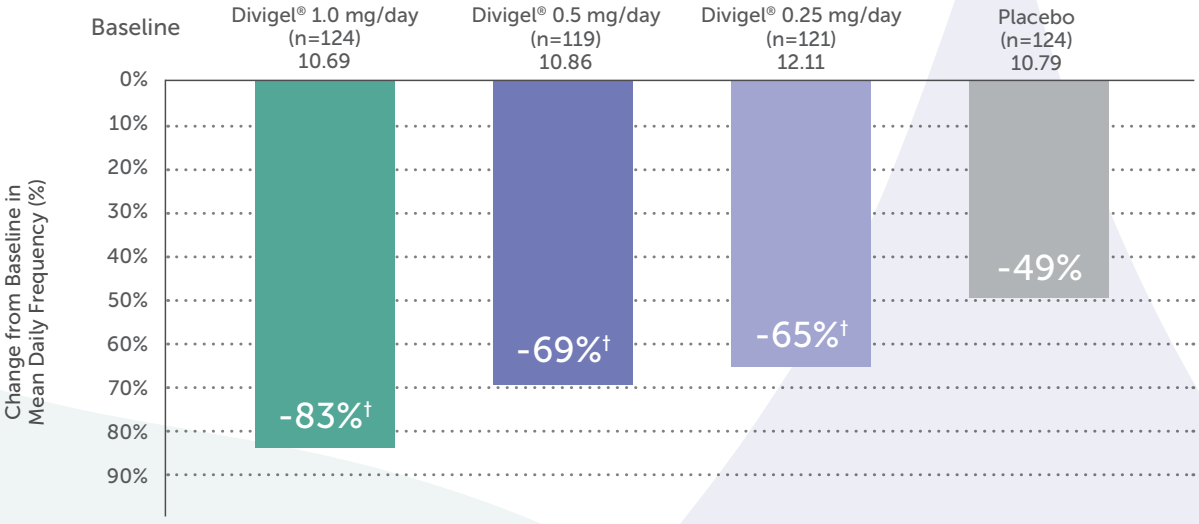
Divigel® was shown to reduce the frequency and severity of moderate to severe hot flashes[1]

Divigel® demonstrated a significant reduction in the **frequency** of daily hot flashes*

- Divigel® reduced the frequency of moderate to severe hot flashes by 65% to 83% at 12 weeks.

Divigel® 1.0 mg/day was shown to eliminate over 8 out of 10 hot flashes at week 12 (versus the baseline mean)

Mean change in daily **frequency** of MSVS at week 12



* A randomized, double-blind, placebo-controlled trial evaluated the efficacy of 12 weeks of treatment with three different daily doses of Divigel®: 0.25 mg, 0.5 mg, 1.0 mg for vasomotor symptoms in 495 postmenopausal women ages 34–89 years of age (mean age 54.6). Patients had at least 50 moderate to severe hot flashes per week at baseline (2-week period prior to treatment). Baseline values for frequency; Divigel® 1.0 mg: 10.69; 0.5 mg: 10.86; 0.25 mg: 12.11; Placebo: 10.79.

† Statistically significant compared to placebo at the 0.001 level.

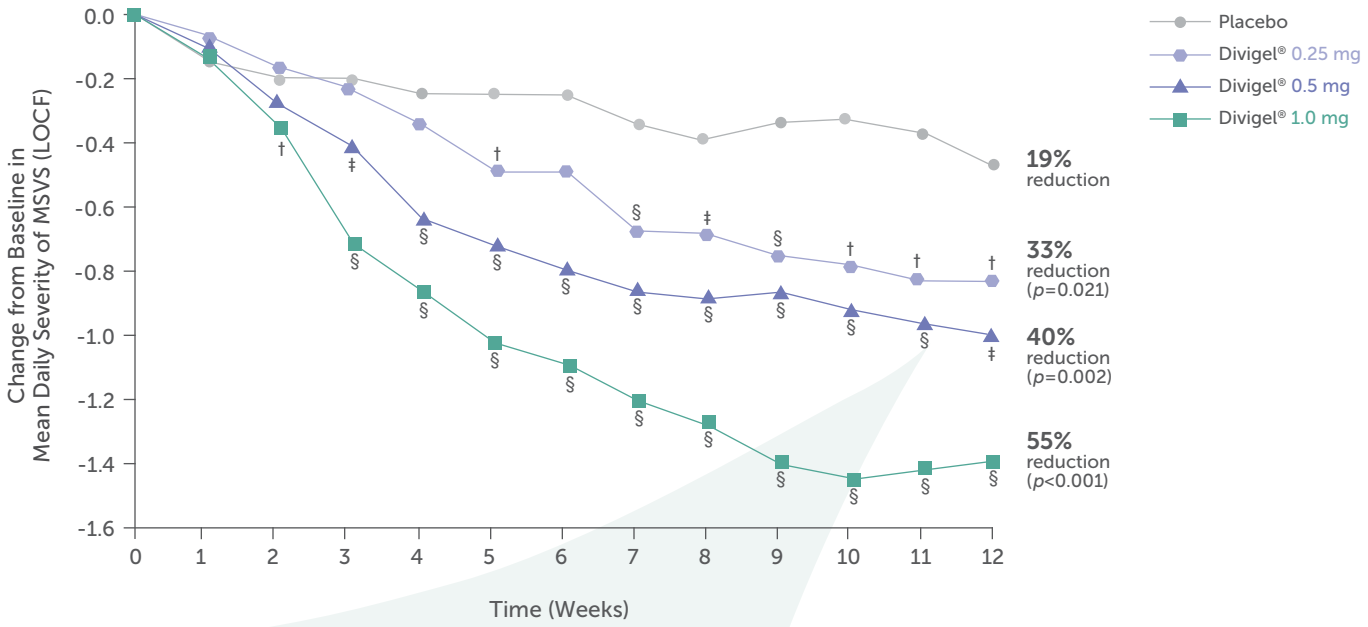
Chart adapted from Product Monograph.

Think PrDivigel®

Divigel® demonstrated a significant reduction in the **severity** of daily hot flashes*

- Severity of hot flashes was significantly reduced with Divigel® 1.0 mg compared to placebo by week 2 and with all three Divigel® doses compared to placebo by week 5.
- Divigel® was shown to reduce the severity of hot flashes by 33% to 55% (versus baseline mean) at 12 weeks.

Mean change in daily **severity** of MSVS at week 12



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†, ‡, § Statistically significant compared to placebo at the 0.001, 0.01, and 0.05 levels, respectively.

Percentages shown in the figure are % changes from baseline. *p* values are Divigel® vs. placebo.

Baseline values for severity: Divigel® 1.0 mg: 2.52; 0.5 mg: 2.52; 0.25 mg: 2.53; Placebo: 2.53.

Chart adapted from Product Monograph

PrDivigel® Estradiol gel 0.1%

Safety and tolerability profile[1]

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

System Organ Class Preferred term	Divigel®			Placebo
	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 hemorrhage	4 (3.3)	3 (2.4)	10 (8.0)	0

Divigel® was studied at doses of 0.25, 0.5 and 1.0 g/day in a 12-week, double-blind, placebo-controlled study.

The first follow-up examination should be done within 3–6 months after initiation of treatment to assess response to treatment.

Application site reactions were demonstrated in <1% of patients using Divigel®

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

Divigel®
safety information[1]

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.

Contraindications:

- Hypersensitivity to this drug or to any ingredient in the formulation or component of the container
- Liver dysfunction or ongoing disease
- Known or suspected estrogen-dependent malignant neoplasia
- Endometrial hyperplasia
- Known, suspected, or history of breast cancer
- Undiagnosed abnormal genital bleeding
- Known or suspected pregnancy
- Active or history of arterial thromboembolic disease
- Active or history of confirmed venous thromboembolism or active thrombophlebitis
- Ophthalmic vascular disease resulting in vision loss
- Breast feeding
- Classic migraine
- Use in children
- Geriatric use ≥65

Most serious warnings and precautions:

The Women's Health Initiative (WHI) trial (estrogen plus progestin arm) indicated increased risk of:

Myocardial infarction (MI), stroke, invasive breast cancer, pulmonary emboli and deep vein thrombosis: Based on the Women's Health Initiative (WHI) trial (estrogen plus progestin arm).

Stroke and deep vein thrombosis: Based on the estrogen-alone arm of the WHI.

Therefore when prescribing estrogens with or without progestins, the following should be given serious consideration:

- **Should not** be prescribed for primary or secondary prevention of cardiovascular diseases
- Should be prescribed at the **lowest effective dose**
- Should be prescribed for the **shortest period** possible

Ovarian Cancer: Some recent studies have found that HRT (estrogen-alone and estrogen plus progestin) therapies have been associated with an increased risk of ovarian cancer.

Other relevant warnings and precautions:

- Increased blood pressure
- Monitor for diabetic patients or patients predisposed to diabetes
- Monitor for patients with familial hyperlipidemias or porphyria – lipid-lowering measures are recommended prior to treatment
- Use with caution in metabolic and malignant bone diseases associated with hypercalcemia and in renal insufficiency
- Hypothyroidism - monitor thyroid function regularly
- Abnormal vaginal bleeding should prompt appropriate diagnostic measures
- Pre-existing uterine leiomyomata may increase in size
- Previous diagnosis of endometriosis may reappear or become aggravated
- Increased risk of developing venous thromboembolism
- Increase in the risk of gallbladder disease
- Use with caution in patients with a history of liver and/or biliary disorders
- Conduct liver function tests periodically in patients with suspected hepatic disease
- Discontinue in patients with visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness
- Increased risk of developing probable dementia in women over 65
- Fluid retention – caution in patients with cardiac or renal dysfunction, epilepsy or asthma

For more information:

Please consult the Product Monograph at https://pdf.hres.ca/dpd_pm/00050175.PDF for important information relating to adverse reactions, drug interactions, and dosing information. The Product Monograph is also available by calling 1-855-519-8382.

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Applying Divigel® to the body[1]

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When

Divigel® should be applied once daily, at the same time each day. The patient's hands should be washed and dried thoroughly before selecting a single foil packet (one daily dose).

Where

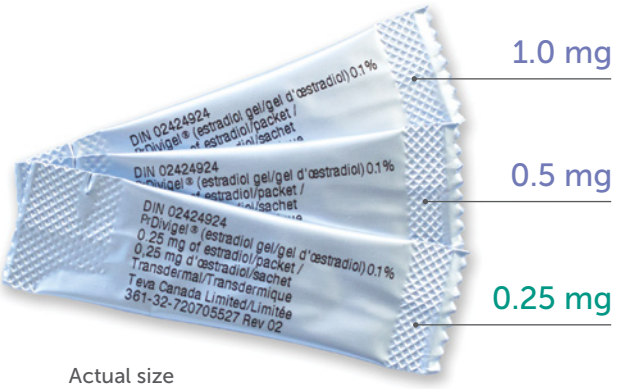
Divigel® should be applied to clean, dry, intact skin (without cuts or scrapes) on the upper right or left thigh. Patients should alternate between the right and left thigh each day to help prevent skin irritation.

Divigel® is applied to a small portion of the upper thigh – an area of about 5 by 7 inches (approximately the size of one hand).

Three different Divigel® doses

Divigel® comes in three dose strengths, including the lowest daily estrogen dose of transdermal estradiol gel available (0.25 mg Divigel® dose).[3]*

Flexible dosing may facilitate upward or downward titration.



Actual size

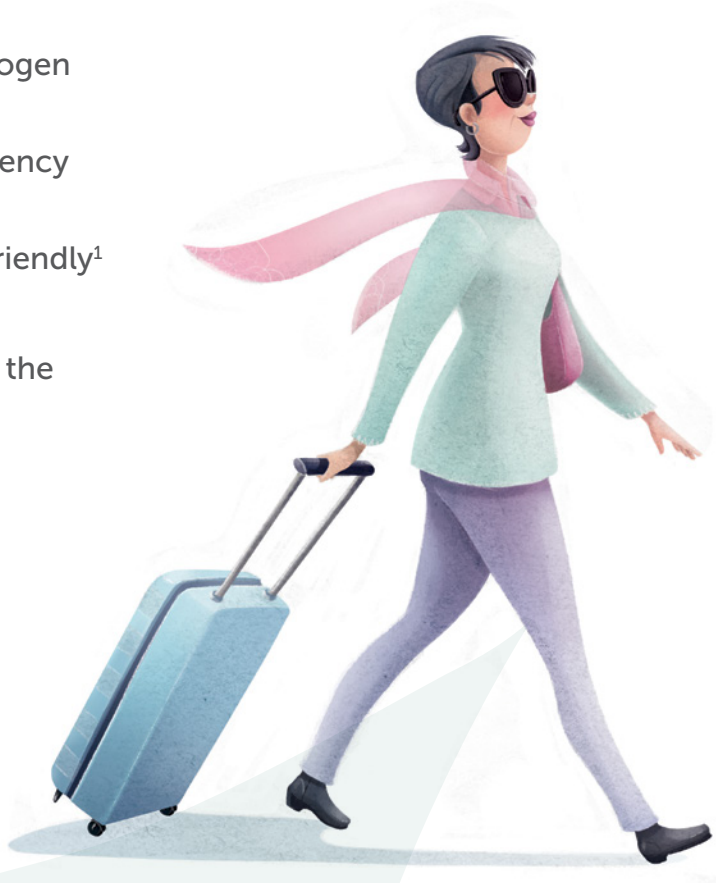
The 0.25 mg Divigel® dose is the lowest daily estrogen dose available in Canada![5]*

* Comparative clinical significance has not been established.

Think PrDivigel®

Key points about Divigel®

- Divigel® 0.25 mg is the lowest daily estrogen dose available in Canada[3]*
- Shown to reduce the severity and frequency of daily hot flashes[1]
- Designed to be easy to use and travel-friendly[1]
- Clear, colourless, smooth gel[1]
- Applied to a small (5- by 7-inch) area of the upper thigh[1]
- Flexible dosing[1]



References: 1. Divigel® Product Monograph. Searchlight Pharma Inc. March 14, 2019.
2. Reid R, *et al.* JOGC 2014; 311:S1-S80. **3.** Data on file. Searchlight Pharma Inc. Letter dated January 7, 2021.

* Comparative clinical significance has not been established.

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REVIEWED BY PAAB

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