



Event <sup>3</sup>	Relative Risk CEMPA vs. Placebo (95% nCI) <sup>4</sup>	CEMPA n = 8,506		Placebo n = 8,102	
		Absolute Risk per 10,000 Women-Years		Absolute Risk per 10,000 Women-Years	
CHD events <sup>5</sup>	1.23 (0.99 – 1.53)	41	34		
Non-fatal MI	1.28 (1.00 – 1.63)	31	25		
CHD death	1.10 (0.79 – 1.75)	8	6		
All strokes	1.31 (1.03 – 1.68)	33	25		
Ischemic stroke	1.44 (1.08 – 1.90)	26	18		
Deep vein thrombosis <sup>6</sup>	1.95 (1.43 – 2.67)	26	13		
Pulmonary embolism	2.13 (1.45 – 3.11)	18	8		
Invasive breast cancer <sup>7</sup>	1.24 (1.01 – 1.54)	41	33		
Colorectal cancer	0.61 (0.42 – 0.87)	10	16		
Endometrial cancer <sup>8</sup>	0.81 (0.48 – 1.36)	6	7		
Cervical cancer <sup>9</sup>	1.44 (0.47 – 4.42)	2	1		
Hip fracture	0.67 (0.47 – 0.96)	11	16		
Vertebral fractures <sup>10</sup>	0.65 (0.46 – 0.92)	11	17		
Lower arm/wrist fractures <sup>11</sup>	0.71 (0.59 – 0.85)	44	62		
Total fractures <sup>12</sup>	0.76 (0.69 – 0.83)	152	199		
Overall mortality <sup>13</sup>	1.00 (0.83 – 1.19)	52	52		
Global Index <sup>14</sup>	1.13 (1.02 – 1.25)	184	165		

<sup>1</sup> Adapted from numerous WHI publications. WHI publications can be viewed at [www.nhlbi.nih.gov/whi](http://www.nhlbi.nih.gov/whi).  
<sup>2</sup> Results are based on centrally adjudicated data.  
<sup>3</sup> Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.  
<sup>4</sup> Not included in "global index".  
<sup>5</sup> Includes metastatic and non-metastatic breast cancer, with the exception of in situ breast cancer.  
<sup>6</sup> All deaths, except from breast or colorectal cancer, defined as probable CHD, PE or cerebrovascular disease.  
<sup>7</sup> 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.

Timing of the initiation of estrogen plus progestin therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen plus progestin substudy stratified for age showed in women 50 to 59 years of age a non-significant trend toward reduced risk for overall mortality (p=0.69) (95 percent CI, 0.44–1.07).

#### 14.3 Women's Health Initiative Memory Study

The WHI estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy postmenopausal women 65 to 79 years of age (45 percent were 65 to 69 years of age, 36 percent were 70 to 74 years of age, and 19 percent were 75 years of age and older) to evaluate the effects of daily CE (0.625 mg) alone on the incidence of probable dementia (primary outcome) compared to placebo.

After an average follow-up of 5.2 years, the relative risk of probable dementia for CE-alone versus placebo was 1.49 (95 percent CI, 0.83–2.66). The absolute risk of probable dementia for CE-alone versus placebo was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included

Alzheimer disease (AD), vascular dementia (VaD) and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See Warnings and Precautions (5.3), and Use in Specific Populations (8.5)).

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

After an average follow-up of 4 years, the relative risk of probable dementia for CE plus MPA was 2.05 (95 percent CI, 1.21–3.48). The absolute risk of probable dementia for CE plus MPA versus placebo was 45 versus 22 per 10,000 women-years. Probable dementia as defined in this study included AD, VaD and mixed type (having features of both AD and VaD). The most common classification of probable dementia in the treatment group and the placebo group was AD. Since the ancillary study was conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women. (See Warnings and Precautions (5.3), and Use in Specific Populations (8.5)).

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 percent CI, 1.19–2.60). Differences between groups became apparent in the first year of treatment. It is unknown whether these findings apply to younger postmenopausal women. (See Warnings and Precautions (5.3), and Use in Specific Populations (8.5)).

#### 15 REFERENCES

- Rossouw JE, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA*. 2002;287:1465–1477.
- Hsia J, et al. Conjugated Equine Estrogens and Coronary Heart Disease. *Arch Int Med*. 2006;166:357–365.
- Carb JD, et al. Venous Thrombosis and Conjugated Equine Estrogen in Women Without a Uterus. *Arch Int Med*. 2006;166:772–780.
- Cushman M, et al. Estrogen Plus Progestin and Risk of Venous Thrombosis. *JAMA*. 2004;292:1573–1580.
- Stefanick ML, et al. Effects of Conjugated Equine Estrogens on Breast Cancer and Mammography Screening in Postmenopausal Women With Hysterectomy. *JAMA*. 2006;295:1647–1657.
- Chlebowski RT, et al. Influence of Estrogen Plus Progestin on Breast Cancer and Mammography in Healthy Postmenopausal Women. *JAMA*. 2003;289:3234–3253.
- Anderson GL, et al. Effects of Estrogen Plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures. *JAMA*. 2003;290:1739–1748.
- Shumaker SA, et al. Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal Women. *JAMA*. 2004;291:2947–2958.
- Jackson RD, et al. Effects of Conjugated Equine Estrogen on Risk of Fractures and BMD in Postmenopausal Women With Hysterectomy: Results From the Women's Health Initiative Randomized Trial. *J Bone Miner Res*. 2006;21:817–828.
- Hendrix SL, et al. Effects of Conjugated Equine Estrogen on Stroke in the Women's Health Initiative. *Circulation*. 2006;113:2425–2434.

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

##### 16.1 How Supplied

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.

NDC 68025-065-30, carton of 30 packets, 0.25 mg estradiol per single-dose foil packet

NDC 68025-066-30, carton of 30 packets, 0.5 mg estradiol per single-dose foil packet

NDC 68025-067-30, carton of 30 packets, 1.0 mg estradiol per single-dose foil packet

Keep out of the reach of children.

##### 16.2 Storage and Handling

Store at 20 to 25°C (68 to 77°F). Excursions permitted to 15 to 30°C (59 to 86°F). [See USP Controlled Room Temperature.]

#### 17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling

##### 17.1 Vaginal Bleeding

Inform postmenopausal women of the importance of reporting vaginal bleeding to their healthcare provider as soon as possible. (see Warnings and Precautions (5.2))

##### 17.2 Possible Serious Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible serious adverse reactions of estrogen-alone therapy including Cardiovascular Disorders, Malignant Neoplasms, and Probable Dementia. (see Warnings and Precautions (5.1, 5.2, 5.3))

##### 17.3 Possible Less Serious but More Common Adverse Reactions with Estrogen-Alone Therapy

Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headaches, breast pain and tenderness, nausea and vomiting.

##### 17.4 Instructions for Use

• 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

#### TO APPLY:

**Step 1:** Wash and dry your hands thoroughly.

**Step 2:** Sit in a comfortable position.

**Step 3:** Cut or tear the Divigel packet as shown in Figure A.

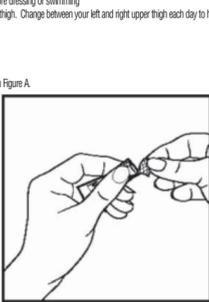


Figure A

**Step 4:** Using your thumb and index finger, squeeze the entire contents of the packet onto the skin of the upper thigh as shown in Figure B.



Figure B

**Step 5:** 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 Figure C. It is not necessary to massage or rub in Divigel.



Figure C

**Step 6:** Allow the gel to dry completely before dressing.

**Step 7:** Dispose of the empty Divigel packet in the trash.

**Step 8:** 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.

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Revised 0514

#### FDA-Approved Patient Labeling

##### Divigel®

(estradiol gel) 0.1%

Read this PATIENT INFORMATION leaflet before you start using Divigel and read what you get each time you refill your Divigel prescription. There may be new information. This information does not take the place of talking to your healthcare provider about your menopausal symptoms or your treatment.

#### WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT Divigel (AN ESTROGEN HORMONE)?

• Using estrogen-alone increases your chance of getting cancer of the uterus (womb)

Report any unusual vaginal bleeding right away while you are using Divigel. Vaginal bleeding after menopause may be a warning sign of cancer of the uterus (womb). Your healthcare provider should check any unusual vaginal bleeding to find out the cause.

• Do not use estrogen-alone to prevent heart disease, heart attacks, strokes or dementia (decline of brain function)

• Using estrogen-alone may increase your chances of getting strokes or blood clots

• Using estrogen-alone may increase your chance of getting dementia, based on a study of women 65 years of age or older

• Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia

• Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots

• Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older

• You and your healthcare provider should talk regularly about whether you still need treatment with Divigel

• Do not use estrogens with progestins to prevent heart disease, heart attacks, strokes or dementia

• Using estrogens with progestins may increase your chances of getting heart attacks, strokes, breast cancer, or blood clots

• Using estrogens with progestins may increase your chance of getting dementia, based on a study of women 65 years of age or older

• You and your healthcare provider should talk regularly about whether you still need treatment with Divigel

#### What is Divigel?

Divigel is a medicine that contains the estrogen hormone estradiol, which is the same hormone made by a woman's ovaries. Divigel is a clear, colorless, smooth gel that is odorless when dry. When applied to the skin, estradiol is absorbed through the skin into the bloodstream.

#### What is Divigel used for?

Divigel is used after menopause to:

- Reduce moderate to severe hot flashes

Estrogens are hormones made by a woman's ovaries. The ovaries normally stop making estrogens when a woman is between 45 to 55 years old. This drop in body estrogen levels causes the "change of life" or menopause (the end of monthly menstrual periods). Sometimes, both ovaries are removed during an operation before natural menopause takes place. The sudden drop in estrogen levels causes "surgical menopause."

When the estrogen levels begin dropping, some women develop very uncomfortable symptoms, such as feelings of warmth in the face, neck, and chest, or sudden strong feelings of heat and sweating ("hot flashes" or "hot flushes"). In some women, the symptoms are mild, and they will not need estrogens. In other women, symptoms can be more severe. You and your healthcare provider should talk regularly about whether you still need treatment with Divigel.

#### Who should not use Divigel?

Do not start using Divigel if you:

- Have unusual vaginal bleeding
- Currently have or have had certain cancers
- Had a stroke or heart attack
- Currently have or have had blood clots
- Currently have or have had liver problems
- Have been diagnosed with a bleeding disorder
- Are allergic to Divigel or any of its ingredients
- Think you may be pregnant

See the list of ingredients in Divigel at the end of this leaflet.

#### TELL YOUR HEALTHCARE PROVIDER:

- If you have any unusual vaginal bleeding
- About all of your medical problems
- Your healthcare provider may need to check you more carefully if you have certain conditions, such as asthma (wheezing), epilepsy (seizures), diabetes, migraine, endometriosis, lupus, problems with your heart, liver, thyroid, kidneys, or have high calcium levels in your blood.

#### • About all the medicines you take

This includes prescription and nonprescription medicines, vitamins, and herbal supplements. Some medicines may affect how Divigel works. Divigel may also affect how your other medicines work.

• If you are going to have surgery or will be on bedrest

You may need to stop using Divigel.

• If you are breastfeeding

The hormone in Divigel can pass into your breast milk.

#### How should I use Divigel?

• Divigel should be used once daily.

• Take the dose recommended by your healthcare provider and talk to him or her about how well that dose is working for you.

• Estrogens should be used at the lowest dose possible for your treatment and only as long as needed.

You and your healthcare provider should talk regularly (for example, every 3 to 6 months) about the dose you are taking and whether you still need treatment with Divigel.

#### 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

• You and your healthcare provider should talk regularly about whether you still need treatment with Divigel

#### TO APPLY:

**Step 1:** Wash and dry your hands thoroughly.

**Step 2:** Sit in a comfortable position.

**Step 3:** Cut or tear the Divigel packet as shown in Figure A.

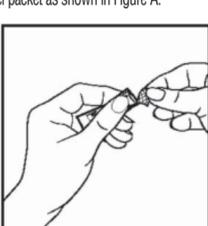


Figure A

**Step 4:** Using your thumb and index finger, squeeze the entire contents of the packet onto the skin of the upper thigh as shown in Figure B.



Figure B

**Step 5:** 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 Figure C. It is not necessary to massage or rub in Divigel.



Figure C

**Step 6:** Allow the gel to dry completely before dressing.

**Step 7:** Dispose of the empty Divigel packet in the trash.

**Step 8:** 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

• 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

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