1 INDICATIONS AND USAGE

1.1 Treatment of Atrophic Vaginitis due to Menopause

2 DOSAGE AND ADMINISTRATION

Generally, when estrogen is prescribed for a postmenopausal woman with a uterus, a progestin should also be considered to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin. In some cases, however, hysterectomized women with a history of endometriosis may need a progestin (see Warnings and Precautions (3.3, 5.15)). 

Use of estrogen, 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. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary. 

2.1 Treatment of Atrophic Vaginitis due to Menopause

Vagifem® should be administered intravaginally using the supplied applicator: 1 insert daily for 2 weeks, followed by 1 insert twice weekly thereafter (for example, Tuesday and Friday). Generally, women should be started at the 10 mcg dosage strength.

3 DOSAGE FORMS AND STRENGTHS

Vagifem® is a small, white, round, film-coated, bi-convex vaginal insert containing 10 mcg or 25 mcg of estradiol. Each vaginal insert is 6 mm in diameter and is administered in a disposable applicator.

4 CONTRAINDICATIONS

Vagifem® should not be used in women with any of the following conditions:
- Undiagnosed abnormal genital bleeding
- Known, suspected, or history of breast cancer
- Known or suspected estrogen-dependent neoplasia
- Active DVT, PE, or history of these conditions
- Active arterial thromboembolic disease (for example, stroke, and myocardial infarction), or a history of these conditions
- Known anaphylactic reaction or angioedema to Vagifem®
- Known liver impairment or disease
- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders
- Known or suspected pregnancy

5 WARNINGS AND PRECAUTIONS

5.1 Risks from Systemic Absorption

Vagifem® is intended only for vaginal administration. Systemic absorption occurs with the use of Vagifem®. The warnings, precautions, and adverse reactions associated with the use of systemic estrogen-alone therapy should be taken into account.

5.2 Cardiovascular Disorders

An increased risk of stroke and DVT has been reported with estrogen therapy. An increased risk of PE, DVT, stroke, and MI has been reported with estrogen plus progestin therapy. Should any of these occur or be suspected, estrogen with or without progestin therapy should be discontinued immediately.

Risk factors for arterial vascular disease (for example, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, and obesity) and for venous vascular disease (for example, personal history or family history of VTE, obesity, and systemic lupus erythematosus) should be managed appropriately.

Stroke

In the WHI estrogen-alone substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg)-alone compared to placebo (38 versus 25 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 15 per 10,000 women-years). The increase in VTE risk was demonstrated during the first 2 years.[See Clinical Studies (14.2)]. Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

5.3 Malignant Neoplasms

Endometrial Cancer

An increased risk of endometrial cancer has been reported with the use of unopposed estrogen therapy in a woman with a uterus. 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 an increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 13 years after discontinuation of therapy.[See Warnings and Precautions (5.4)].

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random random sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurrent abnormal genital bleeding.[See Warnings and Precautions (5.4, 5.15)].

There is no evidence that the use of natural estrogens results in a different endometrial cancer risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Breast Cancer

The most common randomized clinical trial providing information about breast cancer risk in estrogen-alone users in the WHI estrogen-alone substudy of daily CE (0.625 mg)-alone. In the WHI estrogen-alone substudy, after an average follow-up of 7.1 years, daily CE-alone was not associated with an increased risk of invasive breast cancer [relative risk (RR) 0.80].[See Clinical Studies (14.2)].
The most important randomized clinical trial providing information about breast cancer in estrogen plus progesterin users is the WHI substudy of daily CE (0.625 mcg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progesterin substudy reported an increased risk of invasive breast cancer in women who took daily CE plus MPA. In this substudy, prior use of estrogen-alone or estrogen plus progesterin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk in the placebo group was 1.70 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Use in Specific Populations (8.5), and Clinical Studies (14.3)].

When data from the two populations in the WHIMS estrogen-alone and estrogen plus progesterin ancillary studies were pooled as planned in the WHIMS protocol, the reported overall relative risk for probable endometrial cancer was 1.76 (95 percent CI, 1.19-2.60). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women [see Use in Specific Populations (8.5), and Clinical Studies (14.3)].

5.5 Gallbladder Disease

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

5.6 Hypercalcemia

Estrogen administration may lead to severe hypercalcemia in women with breast cancer and bone metastases. If hypercalcemia occurs, use of the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

5.7 Visual Abnormalities

Retinal vascular thrombosis has been reported in women receiving estrogen plus progestin therapy. Discontinue medication if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

5.8 Addition of a Progestogen When a Woman Has Not Had a Hysterectomy

Studies of the use of a progestogen for 10 or more days of a cycle of estrogen administration, or daily with estrogen in a continuous regimen, have reported a lowered incidence of endometrial hyperplasia than would be induced by estrogen treatment alone. Endometrial hyperplasia may be a precursor to endometrial cancer. There are, however, possible risks that may be associated with the use of progestins with estrogens compared with estrogen-alone regimens. These include an increased risk of breast cancer.

5.9 Elevated Blood Pressure

In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens. In a large, randomized, placebo-controlled clinical trial, a generalized effect of estrogens on blood pressure was not seen.

5.10 Hypertriglyceridemia

In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides above the normal range. These may be associated with risk of pancreatitis. Consider discontinuation of treatment if pancreatitis occurs.

5.11 Hepatic Impairment and/or Past History of Cholestatic Jaundice

Estrogens may be poorly metabolized in women with impaired liver function. For women with a history of cholestatic jaundice associated with the use of estrogens, caution should be exercised, and in the case of recurrence, medication should be discontinued.

5.12 Hypothyroidism

Estrogen administration leads to increased thyroid-binding globulin (TBG) levels. Women with normal thyroid function can compensate for the increased TBG by making more thyroid hormone, thus maintaining free T4 and T3 serum concentrations in the normal range. Women dependent on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of their thyroid replacement therapy. These women should have their thyroid hormone monitored in order to maintain their free thyroid hormone levels in an acceptable range.

5.13 Fluid Retention

Estrogens may cause some degree of fluid retention. Women with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogen-alone is prescribed.

5.14 Hypocalcemia

Estrogen therapy should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

5.15 Exacerbation of Endometriosis

A few cases of malignant transformation of residual endometriomas have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progesterin should be considered.

5.16 Hereditary Angiokaemia

Exogenous estrogens may exacerbate symptoms of angiokaemia in women with hereditary angiokaemia.

5.17 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomias and should be used with caution in women with these conditions.

5.18 Local Abrasion

A few cases of local abrasion induced by the Vagifem® applicator have been reported, especially in women with severely atrophic vaginal mucosa.

5.19 Laboratory Tests

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy.

5.20 Drug-Laboratory Test Interactions

Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII, and X; decreased factors V, VIII, and fibrinogen; increased accelerated prothrombin time in women treated post-hysterectomy with estrogen-alone therapy. Other binding proteins may be elevated in serum, for example, corticosteroid binding globulin (CBG), sex hormone-binding globulin (SHBG), leading to increased total circulating corticosteroids and sex steroids, respectively. Free hormone concentrations, such as testosterone and estradiol, may be decreased. Other plasma proteins (e.g., angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin) may be decreased.

Increased plasma high-density lipoprotein (HDL) and LDL cholesterol subfraction concentrations, reduced low-density lipoprotein (LDL) cholesterol concentrations, increased triglyceride levels. Impaired glucose tolerance.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

• Cardiovascular Disorders [see Boxed Warning, Warnings and Precautions (5.3)]

• Malignant Neoplasms [see Boxed Warning, Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience

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.

In a 12-month randomized, double-blind, parallel group, placebo-controlled study, a total of 369 postmenopausal women were randomized to receive either placebo or Vagifem® 10 mcg inserts. Adverse reactions with an incidence of ≥ 5 percent in the Vagifem® 10 mcg group and greater than those reported in the placebo group are listed in Table 1.

Table 1: Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥ 5 Percent in Women Receiving Vagifem® 10 mcg

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Treatment Number (%) of Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body As A Whole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back Pain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Digestive System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulvagin vaginal Myotic Infection</td>
</tr>
<tr>
<td>Nulvagin Pruritus</td>
</tr>
</tbody>
</table>

N = Total number of women in study.

n = Number of women who experienced adverse reactions.

In a 12-week, randomized, double-blind, placebo-controlled study, 138 postmenopausal women were randomized to receive either...
placebo or Vagifem® 25 mcg inserts. Adverse reactions with an incidence of ≥ 5 percent in the Vagifem® 25 mcg group and greater than those reported in the placebo group are listed in Table 2.

Table 2: Treatment-Emergent Adverse Reactions Reported at a Frequency of ≥ 5 Percent in Women Receiving Vagifem® 25 mcg

<table>
<thead>
<tr>
<th>Body System</th>
<th>Adverse Reaction</th>
<th>Treatment</th>
<th>Placebo</th>
<th>N (%)</th>
<th>Vagifem®</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body As A Whole</td>
<td>Headache</td>
<td>3 (6)</td>
<td>4</td>
<td>2 (4)</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain</td>
<td>4 (8)</td>
<td>5</td>
<td>4 (6)</td>
<td>5 (7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Back Pain</td>
<td>3 (6)</td>
<td>4</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>Respiratory System</td>
<td>Upper Respiratory Tract Infection</td>
<td>2 (4)</td>
<td>1</td>
<td>2 (4)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Urogenital System</td>
<td>Urolithiasis Genital</td>
<td>1 (2)</td>
<td>1</td>
<td>1 (2)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

N = Total number of women in study, n = Number of women who experienced adverse reactions.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Vagifem® 25 mcg. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

6.3 Endocrine System

Cachexia, hypercholesterolemia, anemia, proteinuria, hyperuricemia, and gout have been reported.

6.4 Metabolic and Nutritional Disorders

See Section 2.1.1.1.

6.5 Gastrointestinal System

See Section 2.1.1.1.

6.6 Respiratory System

See Section 2.1.1.1.

6.7 Cardiovascular System

See Section 2.1.1.1.

6.8 Skin and Appendages

Urticaria, erythematous or pruritic rash, genital pruritus, and atopic dermatitis have been reported.

6.9 Central Nervous System

Dizziness, headache, loss of consciousness, confusion, and depression have been reported.

6.10 Ocular System

See Section 2.1.1.1.

6.11 Genitourinary System

Painful urination, dysuria, postvoid dribbling, and vaginitis have been reported.

6.12 Reproductive System

Menorrhagia, metrorrhagia, and dysmenorrhea have been reported.

6.13 Body As A Whole

See Section 2.1.1.1.

7. DRUG INTERACTIONS

No drug-drug interaction studies have been conducted for Vagifem®.

7.1 Metabolic 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 (Hypericum perforatum) preparations, photobiliaribital, 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, rifampin, and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Vagifem® should not be used during pregnancy [see Contraindications (4)]. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins as an oral contraceptive inadvertently during early pregnancy.

8.3 Nursing Mothers

Vagifem® should not be used during lactation. Estrogen administration to nursing women has been shown to decrease the quantity and quality of the breast milk. Detectable amounts of estrogens have been identified in the breast milk of women receiving estrogen therapy. Caution should be exercised when Vagifem® is administered to a nursing woman.

8.4 Pediatric Use

Vagifem® is not indicated in children. Clinical studies have not been conducted in the pediatric population.

8.5 Geriatric Use

There have been sufficient numbers of geriatric women involved in clinical studies utilizing Vagifem® to determine whether those over 65 years of age differ from younger subjects in their response to Vagifem®.

8.6 Renal Impairment

The effect of renal impairment on the pharmacokinetics of Vagifem® has not been studied.

8.7 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of Vagifem® has not been studied.

10. OVERDOSAGE

Overdosage of estrogen may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness and fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Vagifem® therapy with institution of appropriate symptomatic care.

11. DESCRIPTION

Vagifem® 10 mcg (estradiol vaginal inserts) are small, white, film-coated inserts containing 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol. Vagifem® 25 mcg (estradiol vaginal inserts) are small, white, film-coated inserts containing 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of estradiol.

Additional postmarketing adverse reactions have been reported in patients receiving other forms of hormone therapy.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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 estrogen in the 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 FSH, through a negative feedback mechanism. Estrogens act to reduce the elevated levels of these hormones seen in postmenopausal women.

12.2 Pharmacodynamics

Currently, there are no pharmacodynamic data known for Vagifem®.

12.3 Pharmacokinetics

Absorption

Estrogen drug products are well absorbed through the skin, mucous membranes, and the gastrointestinal tract. The vaginal delivery of estrogens circumvents first-pass metabolism.

In a single-center, randomized, open-label, multiple-dose, parallel group study conducted in 58 patients, Vagifem® 10 mcg and 25 mcg demonstrated a mean estradiol (E2) Cmax at Day 83 of 5.5 pg/mL and 11.59 pg/mL, respectively after 12 weeks of treatment (see Tables 3 and 4).

Table 3: Arithmetic Means of Estradiol (E2), Estrone (E1), and Estrone Sulfate (E1S) PK Parameters Following Multiple Doses of Vagifem® 10 mcg

<table>
<thead>
<tr>
<th>E2</th>
<th>E1</th>
<th>E1S</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-24) (h.pg/mL)</td>
<td>Cmax (0-24) (h.pg/mL)</td>
<td>%CV</td>
</tr>
<tr>
<td>Day 1</td>
<td>242.08</td>
<td>10.09</td>
</tr>
<tr>
<td>Day 14</td>
<td>176.49</td>
<td>7.35</td>
</tr>
<tr>
<td>Day 83</td>
<td>132.94</td>
<td>5.50</td>
</tr>
</tbody>
</table>

Patients received vaginal inserts as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks.

%CV: Coefficient of Variance for both AUC(0-24) and Cmax(0-24)

Table 4: Arithmetic Means of Estradiol (E2), Estrone (E1), and Estrone Sulfate (E1S) PK Parameters Following Multiple Doses of Vagifem® 25 mcg

<table>
<thead>
<tr>
<th>E2</th>
<th>E1</th>
<th>E1S</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-24) (h.pg/mL)</td>
<td>Cmax (0-24) (h.pg/mL)</td>
<td>%CV</td>
</tr>
<tr>
<td>Day 1</td>
<td>495.27</td>
<td>20.64</td>
</tr>
<tr>
<td>Day 14</td>
<td>466.63</td>
<td>19.44</td>
</tr>
<tr>
<td>Day 83</td>
<td>278.27</td>
<td>11.59</td>
</tr>
</tbody>
</table>

Patients received vaginal inserts as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks.

%CV: Coefficient of Variance for both AUC(0-24) and Cmax(0-24)

N=28 for treatment before Day 14 and N=27 for treatments from Day 14.
Vagifem® (estradiol vaginal inserts)

10 mcg group who had a biopsy performed at end of study, 92 subjects had endometrial tissue that was atrophic or inactive and 73 subjects had no tissue or tissue insufficient for diagnosis. There was one case of adenocarcinoma grade 2 and one case of complex hyperplasia without atypia. Three subjects exhibited polyps (two atrophic polyps and one adenomyomatous type polyp) and two others had adenomyosis and an atypical epithelial proliferation.

Endometrial safety of Vagifem® 10 mcg was additionally evaluated in a second, 12 month, open-label, multicenter safety study. Of the 297 subjects who had a biopsy performed at end of study, 183 subjects had endometrial tissue that was atrophic or inactive and 111 subjects had no tissue or tissue insufficient for diagnosis. There was one case of complex hyperplasia without atypia. Two subjects exhibited polyps.

Vagifem® 25 mcg

A placebo-controlled comparison study was done in the U.S., in which 230 women were randomized to receive either placebo, Vagifem® 25 mcg or 10 mcg estradiol vaginal inserts. Women included the earliest occurrence of CHD, invasive breast cancer, colorectal 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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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.

Results are based on an average follow-up of 7.1 years.

All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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 7 fewer hip fractures.6 The absolute risk event of all deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.

©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.
WHI Estrogen Plus Progestin Substudy

The WHI estrogen plus progestin substudy was stopped early. According to the predefined stopping rule, after an average follow-up of 5.6 years of treatment, the increased risk of invasive 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.

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 plus MPA were 7 more CHD events, 8 more strokes, 10 more PEs, and 8 more invasive breast cancers, while the absolute risk reductions per 10,000 women-years were 6 fewer colorectal cancers and 5 fewer hip fractures.

Results of the CE plus MPA substudy, which included 16,608 women (average 63 years of age, range 50 to 79; 83.9 percent White, 5.4 percent Hispanic, 3.9 percent Other) are presented in Table 8. These results reflect centrally adjudicated data after an average follow-up of 5.6 years.

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

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE+MPA vs Placebo (95% nCI)</th>
<th>Absolute Risk per 10,000 Women-Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>1.23 (0.99-1.53)</td>
<td>41</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1.28 (1.00-1.63)</td>
<td>31</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.70 (0.70-4.3)</td>
<td>8</td>
</tr>
<tr>
<td>All Strokes</td>
<td>1.31 (1.03-1.68)</td>
<td>33</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.44 (1.09-1.90)</td>
<td>26</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.95 (1.43-2.67)</td>
<td>26</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.13 (1.45-3.31)</td>
<td>18</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>1.24 (1.01-1.54)</td>
<td>11</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>0.61 (0.42-0.87)</td>
<td>7</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>0.81 (0.48-1.36)</td>
<td>6</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1.44 (0.47-4.42)</td>
<td>2</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.67 (0.47-0.96)</td>
<td>11</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>0.65 (0.46-0.92)</td>
<td>11</td>
</tr>
<tr>
<td>Lower arm/wrist fractures</td>
<td>0.71 (0.59-0.85)</td>
<td>44</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.76 (0.59-0.93)</td>
<td>152</td>
</tr>
<tr>
<td>Overall Mortality</td>
<td>1.00 (0.83-1.19)</td>
<td>52</td>
</tr>
<tr>
<td>Global Index</td>
<td>1.13 (1.02-1.25)</td>
<td>184</td>
</tr>
</tbody>
</table>

- Adapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.
- Results are based on centrally adjudicated data.
- Nominal confidence intervals unadjusted for multiple looks and multiple comparisons.
- Not included in "global index".
- Includes metastatic and non-metastatic breast cancer, with the exception of in situ cancer.
- All deaths, except from breast or colorectal cancer, definite or probable CHD, PE or cerebrovascular disease.
- 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 by age showed in women 50-59 years of age, a non-significant trend toward reduced risk for overall mortality [HR 0.69 (95 percent CI, 0.44-1.07)].

14.3 Women's Health Initiative Memory Study

The WHIMS estrogen-alone ancillary study of WHI enrolled 2,947 predominantly healthy hysterectomized postmenopausal women 65 to 79 years of age and older (45 percent were 65 to 69 years of age; 36 percent were 70 to 74 years of age; 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, 1.19-1.86). The absolute risk of probable dementia for CE-alone was 37 versus 25 cases per 10,000 women-years. Probable dementia as defined in this study included Alzheimer's disease (AD), vascular dementia (VaD) and mixed types (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 (5.4), and Use in Specific Populations (8.5)).

The WHIMS estrogen plus progestin ancillary study of WHI enrolled predominantly healthy postmenopausal women 65 years of age and older (45 percent were 65 to 69 years of age; 35 percent were 70 to 74 years; 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 versus placebo 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 types (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 (5.4), 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 (5.4), and Use in Specific Populations (8.5)).

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
Each Vagifem® (estradiol vaginal inserts), 10 mcg and 25 mcg, is contained in a disposable, single-use applicator, packaged in a blister pack. Cartons contain 8 or 18 applicators with inset inserts.

16.2 Storage and Handling
Store at 25°C (77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Do not refrigerate. [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 (5.3)].

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 (5.2, 5.3, 5.4)].

17.3 Possible Less Serious but Common Adverse Reactions with Estrogen-Alone Therapy
Inform postmenopausal women of possible less serious but common adverse reactions of estrogen-alone therapy such as headache, breast pain and tenderness, nausea and vomiting.

17.4 Instructions for Use of Applicator
Step 1: Tear off a single applicator.
Step 2: Separate the plastic wrap and remove the applicator from the plastic wrap as shown in Figure A. If after opening the package you see that the insert has come out of the applicator but has not fallen out of the package, carefully put it back into the applicator for insertion. Please keep your hands clean and dry while handling the insert.

Figure A
Step 3: Hold the applicator so that the finger of one hand can press the applicator plunger as shown in Figure B.

Figure B
Step 4: Next select the best position for vaginal insertion of Vagifem® (estradiol vaginal inserts) that is most comfortable for you. See suggested reclining Figure C or standing Figure D position illustrated below.
Step 5: Using the other hand, guide the applicator gently and comfortably through the vaginal opening (see Figures C and D above). If prior to insertion the insert falls out of the applicator, throw the insert and applicator away and use a new insert-filled applicator.

Step 6: The applicator should be inserted (without forcing) as far as comfortably possible, or until half of the applicator is inside your vagina, whichever is less.

Step 7: Once the insert-filled applicator has been inserted, gently press the plunger until the plunger is fully depressed. This will eject the insert inside your vagina where it will dissolve slowly over several hours.

Step 8: After depressing the plunger, gently remove the applicator and dispose of it the same way you would a plastic tampon applicator. The applicator is of no further use and should be discarded properly. Insertion may be done at any time of the day. It is advisable to use the same time daily for all applications of Vagifem® (estradiol vaginal inserts). If you have any questions, please consult your healthcare provider or pharmacist.
What is Vagifem®?
Vagifem® is a medicine that contains estradiol (an estrogen hormone) in a vaginal insert.

What is Vagifem® used for?
Vagifem® is used after menopause to:

- Treat menopausal changes in and around the vagina

You and your healthcare provider should talk regularly about whether you still need treatment with Vagifem® to control these problems.

Who should not use Vagifem®?
Do not start using Vagifem® if you:

- Have unusual vaginal bleeding
- Currently have or have had certain cancers

Estrogens may increase the chances of getting certain types of cancers, including cancer of the breast or uterus. If you have or have had cancer, talk with your healthcare provider about whether you should use Vagifem®.

- 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

Tell your healthcare provider:

- If you have any unusual vaginal bleeding
- Think you may be pregnant

Tell your healthcare provider:

- If you have any unusual vaginal bleeding
- Think you may be pregnant

Report any unusual vaginal bleeding right away while you are using Vagifem®. 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
- Use 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 attack, 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 Vagifem®

How should I use Vagifem®?
Vagifem® is an insert that you place in your vagina with an applicator.

- 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 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 using and whether you still need treatment with Vagifem®.

Step 1: Tear off a single applicator.

Step 2: Separate the plastic wrap and remove the applicator from the plastic wrap as shown in Figure A. If after opening the package you see that the insert has come out of the applicator but has not fallen out of the package, carefully put it back into the applicator for insertion. Please keep your hands clean and dry while handling the insert.

Step 3: Hold the applicator so that the finger of one hand can press the applicator plunger as shown in Figure B.

Step 4: Next select the best position for vaginal insertion of Vagifem® (estradiol vaginal inserts) that is most comfortable for you. See suggested reclining Figure C or standing Figure D position illustrated below:

Step 5: Using the other hand, guide the applicator gently and comfortably through the vaginal opening (see Figures C and D above). If prior to insertion the insert falls out of the
applicator, throw the insert and applicator away and use a new insert-filled applicator.

**Step 6:** The applicator should be inserted (without forcing) as far as comfortably possible, or until half of the applicator is inside your vagina, whichever is less.

**Step 7:** Once the insert-filled applicator has been inserted, gently press the plunger until the plunger is fully depressed. This will eject the insert inside your vagina where it will dissolve slowly over several hours.

**Step 8:** After depressing the plunger, gently remove the applicator and dispose of it the same way you would a plastic tampon applicator. The applicator is of no further use and should be discarded properly. Insertion may be done at any time of the day. It is advisable to use the same time daily for all applications of Vagifem® (estradiol vaginal inserts). If you have any questions, please consult your healthcare provider or pharmacist.

**Dosage**

Vagifem® therapy consists of the following dosing regimen:

One (1) Vagifem® insert intravaginally once daily for the first two (2) weeks, then one (1) insert twice weekly (for example Tuesday and Friday) for as long as you use Vagifem®.

**What are the possible side effects of Vagifem®?**

Vagifem® is only used in the vagina; however, the risks associated with oral estrogens should be taken into account.

**Side effects are grouped by how serious they are and how often they happen when you are treated.**

**Serious but less common side effects include:**
- Heart attack
- Stroke
- Blood clots
- Dementia
- Breast cancer
- Cancer of the lining of the uterus (womb)
- Cancer of the ovary
- High blood pressure
- High blood sugar
- Gallbladder disease
- Liver problems
- Enlargement of benign tumors of the uterus (“fibroids”)

**Call your healthcare provider right away if you get any of the following warning signs or any other unusual symptoms that concern you:**
- New breast lumps
- Unusual vaginal bleeding
- Changes in vision or speech
- Sudden new severe headaches
- Severe pains in your chest or legs with or without shortness of breath, weakness and fatigue

**Less serious, but common, side effects include:**
- Headache
- Breast pain
- Irregular vaginal bleeding or spotting
- Stomach or abdominal cramps, bloating
- Nausea and vomiting
- Hair loss
- Fluid retention
- Vaginal yeast infection

These are not all the possible side effects of Vagifem®. For more information, ask your healthcare provider or pharmacist for advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**What can I do to lower my chances of a serious side effect with Vagifem®?**

- Talk with your healthcare provider regularly about whether you should continue using Vagifem®
- If you have a uterus, talk with your healthcare provider about whether the addition of a progestin is right for you
  
  The addition of a progestin is generally recommended for a woman with a uterus to reduce the chance of getting cancer of the uterus. See your healthcare provider right away if you get vaginal bleeding while using Vagifem®.

- Have a pelvic exam, breast exam and mammogram (breast X-ray) every year unless your healthcare provider tells you something else
  
  If members of your family have had breast cancer or if you have ever had breast lumps or an abnormal mammogram, you may need to have breast exams more often.

- If you have high blood pressure, high cholesterol (fat in the blood), diabetes, are overweight, or if you use tobacco, you may have higher chances for getting heart disease
  
  Ask your healthcare provider for ways to lower your chances for getting heart disease.

**General information about the safe and effective use of Vagifem®.**

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Vagifem® for conditions for which it was not prescribed. Do not give Vagifem® to other people, even if they have the same symptoms you have. It may harm them.

**Keep Vagifem® out of the reach of children.**

This leaflet provides a summary of the most important information about Vagifem®. If you would like more information, talk with your healthcare provider or pharmacist. You can ask for information about Vagifem® that is written for health professionals. You can get more information by calling the toll free number 1-888-824-4336.

**What are the ingredients in Vagifem®?**

Vagifem® (estradiol vaginal inserts) are small, white, film-coated inserts containing estradiol. Each insert also contains hypromellose, lactose monohydrate, maize starch and magnesium stearate. The film coating contains hypromellose and polyethylene glycol.

Each Vagifem® insert is contained in a disposable applicator, packaged in a blister pack. Cartons contain 8 or 18 applicators with insert inserts.

**Store at 25ºC (77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF). Do not refrigerate.**  
[see USP Controlled Room Temperature].

---

**Novo Nordisk is a registered trademark owned by** Novo Nordisk Health Care AG.

**Date of Issue: 11/2017**

**For Information contact:** Novo Nordisk Inc. 800 Scudders Mill Road Plainsboro, NJ 08536, USA 1-888-824-4336

**Manufactured by:** Novo Nordisk A/S 2880 Bagsvaerd, Denmark 

© 2003-2017 Novo Nordisk USA17BIO03834 November 2017