

VAGIFEM^{10mcg}[®]

estradiol vaginal inserts

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VAGIFEM[®] safely and effectively. See full prescribing information for VAGIFEM[®].

Vagifem[®] (estradiol vaginal inserts)

Initial U.S. Approval: 1999

WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA

See full prescribing information for complete boxed warning

Estrogen-Alone Therapy

- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens (5.3)
- Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) (5.2)
- The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

Estrogen Plus Progestin Therapy

- Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia (5.2, 5.4)
- The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) (5.2)
- The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer (5.3)
- The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older (5.4)

INDICATIONS AND USAGE

- Vagifem[®] is an estrogen (estradiol) indicated for the treatment of atrophic vaginitis due to menopause (1.1).

DOSAGE AND ADMINISTRATION

Vagifem[®] should be administered intravaginally:

- 1 insert daily for 2 weeks, followed by 1 insert twice weekly (for example, Tuesday and Friday) (2.1)

DOSAGE FORMS AND STRENGTHS

- Vagifem[®] 10 mcg insert: One vaginal insert contains 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol (3)
- Vagifem[®] 25 mcg insert: One vaginal insert contains 25.8 mcg of estradiol hemihydrate equivalent to 25 mcg of estradiol (3)

CONTRAINDICATIONS

- Undiagnosed abnormal genital bleeding (4)
- Known, suspected, or history of breast cancer (4, 5.3)
- Known or suspected estrogen-dependent neoplasia (4, 5.3)
- Active DVT, PE, or history of these conditions (4, 5.2)
- Active arterial thromboembolic disease (for example, stroke and MI), or a history of these conditions (4, 5.2)
- Known anaphylactic reaction or angioedema to Vagifem
- Known liver impairment or disease (4, 5.11)
- Known protein C, protein S, or antithrombin deficient, or other known thrombophilic disorders (4)
- Known or suspected pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

- Estrogens increase the risk of gallbladder disease (5.5)
- Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertriglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
- The Vagifem[®] applicator may cause vaginal abrasion (5.17)
- Monitor thyroid function in women on thyroid replacement therapy (5.12, 5.19)

ADVERSE REACTIONS

In prospective, randomized, placebo-controlled, double-blind studies the most common adverse reactions (incidence \geq 5 percent) were upper respiratory tract infection, headache, abdominal pain, back pain, genital pruritus, moniliasis, vulvo-vaginal mycotic infection and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk at 1-888-824-4336 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inducers and inhibitors of CYP3A4 may affect estrogen drug metabolism (7.1)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Estrogen administration to nursing women has been shown to decrease the quantity and quality of breast milk (8.3)
- Geriatric Use: An increased risk of probable dementia in women over 65 years of age was reported in the Women's Health Initiative Memory ancillary studies of the Women's Health Initiative (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2017

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FULL PRESCRIBING INFORMATION**WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA****Estrogen-Alone Therapy****Endometrial Cancer**

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [see *Warnings and Precautions* (5.3)].

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [see *Warnings and Precautions* (5.2, 5.4), and *Clinical Studies* (14.2, 14.3)].

The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [see *Warnings and Precautions* (5.2), and *Clinical Studies* (14.2)].

The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.5), and *Clinical Studies* (14.3)].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy**Cardiovascular Disorders and Probable Dementia**

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [see *Warnings and Precautions* (5.2, 5.4), and *Clinical Studies* (14.2, 14.3)].

The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [see *Warnings and Precautions* (5.2), and *Clinical Studies* (14.2)].

The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [see *Warnings and Precautions* (5.4), *Use in Specific Populations* (8.5), and *Clinical Studies* (14.3)].

Breast Cancer

The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [see *Warnings and Precautions* (5.3), and *Clinical Studies* (14.2)].

In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins.

Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

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* (5.3, 5.15)].

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. 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 (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-alone 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/or venous thromboembolism (VTE) (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 women in the same age group receiving placebo (45 versus 33 per 10,000 women-years). The increase in risk was demonstrated in year 1 and persisted [see *Clinical Studies* (14.2)]. Should a stroke occur or be suspected, estrogen-alone therapy should be discontinued immediately.

Subgroup analyses of women 50 to 59 years of age suggest no increased risk of stroke for those women receiving CE (0.625 mg)-alone versus those receiving placebo (18 versus 21 per 10,000 women-years).¹

In the WHI estrogen plus progestin substudy, a statistically significant increased risk of stroke was reported in women 50 to 79 years of age receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women in the same age group receiving placebo (33 versus 25 per 10,000 women-years) [see *Clinical Studies* (14.2)]. The increase in risk was demonstrated after the first year and persisted.¹ Should a stroke occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

Coronary Heart Disease

In the WHI estrogen-alone substudy, no overall effect on coronary heart disease (CHD) events (defined as nonfatal MI, silent MI, or

CHD death) was reported in women receiving estrogen-alone compared to placebo² [see *Clinical Studies* (14.2)].

Subgroup analysis of women 50 to 59 years of age suggests a statistically non-significant reduction in CHD events (CE [0.625 mg]-alone compared to placebo) in women with less than 10 years since menopause (8 versus 16 per 10,000 women-years).¹

In the WHI estrogen plus progestin substudy, there was a statistically non-significant increased risk of CHD events reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (41 versus 34 per 10,000 women-years).¹ An increase in relative risk was demonstrated in year 1, and a trend toward decreasing relative risk was reported in years 2 through 5 [see *Clinical Studies* (14.2)].

In postmenopausal women with documented heart disease (n=2,763), average 66.7 years of age, in a controlled clinical trial of secondary prevention of cardiovascular disease (Heart and Estrogen/Progestin Replacement Study [HERS]), treatment with daily CE (0.625 mg) plus MPA (2.5 mg) demonstrated no cardiovascular benefit. During an average follow-up of 4.1 years, treatment with CE 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 CE plus MPA-treated group than in the placebo group in year 1, but not during the subsequent years. Two thousand, three hundred and twenty-one (2,321) women from the original HERS trial agreed to participate in an open label extension of the original HERS, HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total of 6.8 years overall. Rates of CHD events were comparable among women in the CE plus MPA group and the placebo group in HERS, HERS II, and overall.

Venous Thromboembolism

In the WHI estrogen-alone substudy, the risk of VTE (DVT and PE) was increased for women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 22 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 years³ [see *Clinical Studies* (14.2)]. Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progestin substudy, a statistically significant 2-fold greater rate of VTE was reported in women receiving daily CE (0.625 mg) plus MPA (2.5 mg) compared to women receiving placebo (35 versus 17 per 10,000 women-years). Statistically significant increases in risk for both DVT (26 versus 13 per 10,000 women-years) and PE (18 versus 8 per 10,000 women-years) were also demonstrated. The increase in VTE risk was demonstrated during the first year and persisted⁴ [see *Clinical Studies* (14.2)]. Should a VTE occur or be suspected, estrogen plus progestin therapy should be discontinued immediately.

If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

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 15 years after estrogen therapy is discontinued.

Clinical surveillance of all women using estrogen-alone or estrogen plus progestin therapy is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital 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 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 important randomized clinical trial providing information about breast cancer in estrogen-alone users is the WHI 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]⁵ [see *Clinical Studies* (14.2)].

The most important randomized clinical trial providing information about breast cancer in estrogen plus progestin users is the WHI substudy of daily CE (0.625 mg) plus MPA (2.5 mg). After a mean follow-up of 5.6 years, the estrogen plus progestin 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 progestin therapy was reported by 26 percent of the women. The relative risk of invasive breast cancer was 1.24, and the absolute risk was 41 versus 33 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported prior use of hormone therapy, the relative risk of invasive breast cancer was 1.86, and the absolute risk was 46 versus 25 cases per 10,000 women-years, for CE plus MPA compared with placebo. Among women who reported no prior use of hormone therapy, the relative risk of invasive breast cancer was 1.09, and the absolute risk was 40 versus 36 cases per 10,000 women-years for CE plus MPA compared with placebo. In the same substudy, invasive breast cancers were larger, were more likely to be node positive, and were diagnosed at a more advanced stage in the CE (0.625 mg) plus MPA (2.5 mg) group compared with the placebo group. Metastatic disease was rare, with no apparent difference between the two groups. Other prognostic factors, such as histologic subtype, grade and hormone receptor status did not differ between the groups⁶ [See *Clinical Studies* (14.2)].

Consistent with the WHI clinical trial, observational studies have also reported an increased risk of breast cancer for estrogen plus progestin therapy, and a smaller increased risk for estrogen-alone therapy, after several years of use. The risk increased with duration of use, and appeared to return to baseline over about 5 years after stopping treatment (only the observational studies have substantial data on risk after stopping). Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progestin therapy has been reported to result in an increase in abnormal mammograms requiring further evaluation.

All women should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. In addition, mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results.

Ovarian Cancer

The WHI estrogen plus progestin substudy reported a statistically non-significant increased risk of ovarian cancer. After an average follow-up of 5.6 years, the relative risk for ovarian cancer for CE plus MPA versus placebo was 1.58 (95 percent CI, 0.77-3.24). The absolute risk for CE plus MPA versus placebo was 4 versus 3 cases per 10,000 women-years.⁷ In some epidemiologic studies, the use of estrogen plus progestin and estrogen-only products, in particular for 5 or more years, has been associated with an increased risk of ovarian cancer. However, the duration of exposure associated with increased risk is not consistent across all epidemiologic studies, and some report no association.

5.4 Probable Dementia

In the WHIMS estrogen-alone ancillary study of WHI, a population of 2,947 hysterectomized women 65 to 79 years of age was randomized to daily CE (0.625 mg)-alone or placebo.

After an average follow-up of 5.2 years, 28 women in the estrogen-alone group and 19 women in the placebo group were diagnosed with probable dementia. 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-years⁸ [See *Use in Specific Populations* (8.5), and *Clinical Studies* (14.3)].

In the WHIMS estrogen plus progestin ancillary study of WHI, a population of 4,532 postmenopausal women 65 to 79 years of age was randomized to daily CE (0.625 mg) plus MPA (2.5 mg) or placebo. After an average follow-up of 4 years, 40 women in the CE plus MPA group and 21 women in the placebo group were diagnosed with probable dementia. 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 cases per 10,000 women-years⁸ [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 progestin ancillary studies 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). Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger post-

menopausal women⁸ [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 estrogens. Discontinue medication pending examination 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 Progestin When a Woman Has Not Had a Hysterectomy

Studies of the addition of a progestin 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 to 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 leading to 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 past estrogen use or with pregnancy, 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 function 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 endometrial implants have been reported in women treated post-hysterectomy with estrogen-alone therapy. For women known to have residual endometriosis post-hysterectomy, the addition of progestin should be considered.

5.16 Hereditary Angioedema

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

5.17 Exacerbation of Other Conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas 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 antigen, VIII antigen, VIII coagulant activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of anti-factor Xa and antithrombin III, decreased antithrombin III activity; increased levels of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Increased thyroid-binding globulin (TBG) levels leading to increased circulating total thyroid hormone as measured by protein-bound iodine (PBI), T₄ levels (by column or by radioimmunoassay) or T₃ levels by radioimmunoassay. T₃ resin uptake is decreased, reflecting the elevated TBG. Free T₄ and free T₃ concentrations are unaltered. Women on thyroid replacement therapy may require higher doses of thyroid hormone.

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 may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

Increased plasma high-density lipoprotein (HDL) and HDL₂ 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* (5.2)]
- 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 309 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

Body System Adverse Reaction	Treatment Number (%) of Women	
	Placebo N = 103 n (%)	Vagifem® N = 205 n (%)
Body As A Whole		
Back Pain	2 (2)	14 (7)
Digestive System		
Diarrhea	0	11 (5)
Urogenital System		
Vulvovaginal Mycotic Infection	3 (3)	17 (8)
Vulvovaginal Pruritus	2 (2)	16 (8)

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

Body System Adverse Reaction	Treatment Number (%) of Women	
	Placebo N = 47 n (%)	Vagifem® N = 91 n (%)
Body As A Whole		
Headache	3 (6)	8 (9)
Abdominal Pain	2 (4)	6 (7)
Back Pain	3 (6)	6 (7)
Respiratory System		
Upper Respiratory Tract Infection	2 (4)	5 (5)
Urogenital System		
Moniliasis Genital	1 (2)	5 (5)

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 post-approval 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.

Genitourinary System

Endometrial cancer, endometrial hyperplasia, vaginal irritation, vaginal pain, vaginismus, vaginal ulceration

Breast

Breast cancer

Cardiovascular

Deep vein thrombosis

Gastrointestinal

Diarrhea

Skin

Urticaria, erythematous or pruritic rash, genital pruritus

Central Nervous System

Aggravated migraine, depression, insomnia

Miscellaneous

Fluid retention, weight increase, drug ineffectiveness, hypersensitivity, blood estrogen increase

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

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, 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 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 not 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®.

The Women's Health Initiative Studies

In the WHI estrogen-alone substudy (daily CE [0.625 mg]-alone versus placebo), there was a higher relative risk of stroke in women greater than 65 years of age [see *Clinical Studies* (14.2)].

In the WHI estrogen plus progestin substudy (daily CE [0.625 mg] plus MPA [2.5 mg] versus placebo), there was a higher relative risk of nonfatal stroke and invasive breast cancer in women greater than 65 years of age [see *Clinical Studies* (14.2)].

The Women's Health Initiative Memory Study

In the WHIMS ancillary studies of postmenopausal women 65 to 79 years of age, there was an increased risk of developing probable dementia in women receiving estrogen-alone or estrogen plus progestin when compared to placebo [see *Warnings and Precautions* (5.4), and *Clinical Studies* (14.3)].

Since both ancillary studies were conducted in women 65 to 79 years of age, it is unknown whether these findings apply to younger postmenopausal women⁸ [see *Warnings and Precautions* (5.4), and *Clinical Studies* (14.3)].

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. Each insert of Vagifem® 10 mcg and 25 mcg contains the following excipients: hypromellose, lactose monohydrate, maize starch and magnesium stearate. The film coating contains hypromellose and polyethylene glycol. Each Vagifem® insert is 6 mm in diameter and is placed in a disposable applicator. Each insert-filled applicator is packaged separately in a blister pack. Vagifem® inserts are used intravaginally. When the insert comes in contact with the vaginal mucosa, estradiol is released into the vagina.

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

Uncorrected for baseline, N=29

	E2			E1			E1S		
	AUC ₀₋₂₄ (h.pg/mL)	C _{ave} (0-24) (pg/mL)	%CV ^b	AUC ₀₋₂₄ (h.pg/mL)	C _{ave} (0-24) (pg/mL)	%CV ^b	AUC ₀₋₂₄ (h.pg/mL)	C _{ave} (0-24) (pg/mL)	%CV ^b
Day 1	242.08	10.09	33.02	485.21	20.22	44.86	5158.32	214.93	53.57
Day 14	176.49	7.35	43.69	496.14	20.67	30.88	6323.41	263.48	50.07
Day 83	132.04	5.50	59.69	411.08	17.13	39.58	3804.65	158.53	49.76

^aPatients 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.

^bCV: Coefficient of Variance for both AUC₀₋₂₄ and C_{ave(0-24)}

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

Uncorrected for baseline, N=28 or 27

	E2			E1			E1S		
	AUC ₀₋₂₄ (h.pg/mL)	C _{ave} (0-24) (pg/mL)	%CV ^b	AUC ₀₋₂₄ (h.pg/mL)	C _{ave} (0-24) (pg/mL)	%CV ^b	AUC ₀₋₂₄ (h.pg/mL)	C _{ave} (0-24) (pg/mL)	%CV ^b
Day 1	495.27	20.64	25.70	567.07	23.63	28.96	5738.32	239.10	47.72
Day 14	466.63	19.44	33.53	662.94	27.62	24.36	7725.90	321.91	43.67
Day 83	278.27	11.59	61.83	500.06	20.84	34.99	4110.84	171.29	51.38

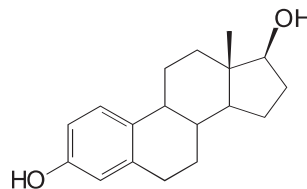
^aPatients received vaginal inserts as a once daily intravaginal treatment for the first 2 weeks and a twice weekly intravaginal maintenance for the following 10 weeks.

^bCV: Coefficient of Variance for both AUC₀₋₂₄ and C_{ave(0-24)}

^cN=28 for treatment before Day 14 and N=27 for treatments from Day 14.

Estradiol hemihydrate is a white, almost white or colorless crystalline solid, chemically described as *estra-1,3,5* (10 β)-triene-3,17 β -diol. The chemical formula is C₁₈H₂₄O₂ • ½ H₂O with a molecular weight of 281.4.

The structural formula is:



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 estrone 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) C_{ave} at Day 83 of 5.5 pg/mL and 11.59 pg/mL, respectively after 12 weeks of treatment (see Tables 3 and 4).

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 SHBG and albumin.

Metabolism

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. 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 gut followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Excretion

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Use in Specific Populations

No pharmacokinetic studies were conducted in specific populations, including patients with renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

14 CLINICAL STUDIES

14.1 Effects on Atrophic Vaginitis

Vagifem® 10 mcg

A 12-month double-blind, randomized, parallel group, placebo-controlled multicenter study was conducted in the U.S. and Canada to evaluate the efficacy and safety of Vagifem® 10 mcg in the treatment of atrophic vaginitis in 309 postmenopausal women between 46 and 81 years of age (mean 57.6 years of age) who at baseline identified their most bothersome symptom of atrophic vaginitis from among six symptoms (vaginal dryness, vaginal and/or vulvar irritation/itching, vaginal soreness, dysuria, dyspareunia and vaginal bleeding associated with intercourse). Women inserted one insert intravaginally each day for 14 days, then one insert twice weekly for the remaining 50 weeks. The majority (92.9 percent) of the women were Caucasian (n=287), 3.2 percent were Black (n=10), 1.6 percent were Asian (n=5) and 2.2 percent were Other (n=7). All subjects were assessed for improvement in the mean change from baseline to Week 12 for co-primary efficacy variables of: a composite of most bothersome symptoms of atrophic vaginitis; percentage of vaginal superficial cells and percentage of vaginal parabasal cells on a vaginal smear; and vaginal pH.

Relief of Vaginal Symptoms

Vagifem® 10 mcg was statistically superior to placebo in reducing the severity of a composite score of most bothersome symptoms associated with atrophic vaginitis at Week 12 (see Table 5).

Table 5: Mean Change from Baseline to Week 12 in a Composite Score of Most Bothersome Symptoms Compared to Placebo – ITT Population^a

	Placebo	Vagifem® 10 mcg
ITT Population^a		
N	93	190
Baseline mean composite score	2.29	2.35
Change from baseline at Week 12 (LOCF)	-0.84	-1.20
p-value versus Placebo	—	0.002

^aAll randomized subjects who received at least one dose of study drug and had at least one post-baseline evaluation.

Also demonstrated for Vagifem® 10 mcg compared to placebo was a statistically significant increase in the percentage of superficial cells at Week 12 (13.2 percent compared to 3.8 percent for matching placebo, p<0.001), a statistically significant decrease in parabasal cells at Week 12 (-37.0 percent compared to -9.3 percent for matching placebo, p<0.001), and a statistically significant mean reduction between baseline and Week 12 in vaginal pH score (-1.3 compared to -0.4 for matching placebo, p<0.001).

Endometrial safety was assessed by endometrial biopsy at the screening and final study visit. Of the 172 subjects in the Vagifem® 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 inserted one insert intravaginally each day for 14 days, then one insert twice weekly for the remaining 10 weeks. All subjects were assessed for vaginal symptoms. Vagifem® 25 mcg was superior to placebo in reducing the severity of a composite score of symptoms associated with atrophic vaginitis (see Table 6).

An open-label, controlled comparison study was done in Canada in which 159 women were randomized to receive either Vagifem® 25 mcg or a comparator drug. Two (2) grams of the comparator drug was given daily for 3 weeks, withheld for 1 week, then repeated cyclically (3 weeks on, 1 week off) for up to 24 weeks; Vagifem® 25 mcg was administered daily for 2 weeks, then twice weekly for the remaining 22 weeks. In this study, subjects were assessed for relief of symptoms. Vagifem® 25 mcg was equally effective as the approved comparator product at the 2.0 gm dose in the relief of symptoms.

Table 6: Mean Change from Baseline to Week 7 and Week 12 in a Composite Score of Symptoms Compared to Placebo – ITT Population^a

	Placebo	Vagifem® 25 mcg
ITT Population^a		
N	47	91
Baseline mean	1.93	1.85
Change from baseline at Week 7 (LOCF)	-0.85	-1.22
Change from baseline at Week 12 (LOCF)	-0.83	-1.33
p-value versus Placebo – Week 7 (LOCF)	—	0.016
p-value versus Placebo – Week 12 (LOCF)	—	0.005

^aAll randomized subjects who received at least one dose of study drug and had at least one post-baseline evaluation.

In the placebo-controlled study endometrial biopsies in non-hysterectomized women at week 12 were performed on 86 subjects (Vagifem® 25 mcg: 32 subjects, estradiol 10 mcg: 33 subjects, Placebo: 21 subjects). Of these, 3 subjects each from the Vagifem® 25 mcg and placebo groups and 8 from the 10 mcg estradiol group had insufficient tissue samples. Among those with biopsies that yielded sufficient tissue, results were normal with the exception of one subject in the Vagifem® 25 mcg group, who had a simple hyperplasia without atypia.

In the open-label study comparing Vagifem® 25 mcg with a comparator vaginal cream on 49 women in each treatment group, endometrial biopsies were obtained at the screening visit and at the end of treatment. At the end of the study (Week 24), all subjects in the Vagifem® treatment group whose biopsies yielded sufficient tissue showed an atrophic endometrium with the exception of one subject who had a proliferative endometrium.

14.2 Women's Health Initiative Studies

The WHI enrolled approximately 27,000 predominantly healthy postmenopausal women in two substudies to assess the risks and benefits of daily oral CE (0.625 mg)-alone or in combination with MPA (2.5 mg) compared to placebo in the prevention of certain chronic diseases. The primary endpoint was the incidence of CHD (defined as nonfatal MI, silent MI and CHD death), with invasive breast cancer as the primary adverse outcome. A "global index" included the earliest occurrence of CHD, invasive breast cancer, stroke, PE, endometrial cancer (only in the CE plus MPA substudy), colorectal cancer, hip fracture, or death due to other causes. These

substudies did not evaluate the effects of CE-alone or CE plus MPA on menopausal symptoms.

WHI Estrogen-Alone Substudy

The WHI 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 63 years of age, range 50 to 79; 75.3 percent White, 15.1 percent Black, 6.1 percent Hispanic, 3.6 percent Other) after an average follow-up of 7.1 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 ^b)	CE n = 5,310	Placebo n = 5,429
		Absolute Risk per 10,000 Women-Years	
CHD events ^c	0.95 (0.78-1.16)	54	57
Non-fatal MI ^c	0.91 (0.73-1.14)	40	43
CHD death ^c	1.01 (0.71-1.43)	16	16
All Strokes ^c	1.33 (1.05-1.68)	45	33
Ischemic stroke ^c	1.55 (1.19-2.01)	38	25
Deep vein thrombosis ^{c,d}	1.47 (1.06-2.06)	23	15
Pulmonary embolism ^c	1.37 (0.90-2.07)	14	10
Invasive breast cancer ^c	0.80 (0.62-1.04)	28	34
Colorectal cancer ^e	1.08 (0.75-1.55)	17	16
Hip fracture ^e	0.65 (0.45-0.94)	12	19
Vertebral fractures ^{c,d}	0.64 (0.44-0.93)	11	18
Lower arm/wrist fractures ^{c,d}	0.58 (0.47-0.72)	35	59
Total fractures ^{c,d}	0.71 (0.64-0.80)	144	197
Death due to other causes ^{e,f}	1.08 (0.88-1.32)	53	50
Overall mortality ^{c,d}	1.04 (0.88-1.22)	79	75
Global Index ^g	1.02 (0.92-1.13)	206	201

^aAdapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

^bNominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^cResults are based on centrally adjudicated data for an average follow-up of 7.1 years.

^dNot included in "global index".

^eResults are based on an average follow-up of 6.8 years.

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

^gA 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.⁹ The absolute excess risk of events included in the "global index" was a non-significant 5 events per 10,000 women-years. There was no difference between the groups in terms of all-cause mortality.

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 was reported in final centrally adjudicated results from the estrogen-alone substudy, after an average follow up of 7.1 years.

Centrally adjudicated results for stroke events from the estrogen-alone substudy, after an average follow-up of 7.1 years, reported no significant difference in distribution of stroke subtype or severity, including fatal strokes, in women receiving CE-alone compared to placebo. Estrogen-alone increased the risk for ischemic stroke, and this excess risk was present in all subgroups of women examined.¹⁰

Timing of the initiation of estrogen-alone therapy relative to the start of menopause may affect the overall risk benefit profile. The WHI estrogen-alone substudy, stratified by age, showed in women 50-59 years of age a non-significant trend toward reduced risk for CHD [hazard ratio (HR) 0.63 (95 percent CI, 0.36-1.09)] and overall mortality [HR 0.71 (95 percent CI, 0.46-1.11)].

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, 6.8 percent Black, 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^{a,b}

Event	Relative Risk CE/MPA vs Placebo (95% nCI ^c)	CE/MPA n = 8,506	Placebo n = 8,102
		Absolute Risk per 10,000 Women-Years	
CHD events	1.23 (0.99-1.53)	41	34
<i>Non-fatal MI</i>	1.28 (1.00-1.63)	31	25
<i>CHD death</i>	1.10 (0.70-1.75)	8	8
All Strokes	1.31 (1.03-1.68)	33	25
<i>Ischemic stroke</i>	1.44 (1.09-1.90)	26	18
Deep vein thrombosis ^d	1.95 (1.43-2.67)	26	13
Pulmonary embolism	2.13 (1.45-3.11)	18	8
Invasive breast cancer ^e	1.24 (1.01-1.54)	41	33
Colorectal cancer	0.61 (0.42-0.87)	10	16
Endometrial cancer ^d	0.81 (0.48-1.36)	6	7
Cervical cancer ^d	1.44 (0.47-4.42)	2	1
Hip fracture	0.67 (0.47-0.96)	11	16
Vertebral fractures ^d	0.65 (0.46-0.92)	11	17
Lower arm/wrist fractures ^d	0.71 (0.59-0.85)	44	62
Total fractures ^d	0.76 (0.69-0.83)	152	199
Overall Mortality ^f	1.00 (0.83-1.19)	52	52
Global Index ^g	1.13 (1.02-1.25)	184	165

^aAdapted from numerous WHI publications. WHI publications can be viewed at www.nhlbi.nih.gov/whi.

^bResults are based on centrally adjudicated data.

^cNominal confidence intervals unadjusted for multiple looks and multiple comparisons.

^dNot included in "global index".

^eIncludes metastatic and non-metastatic breast cancer, with the exception of *in situ* cancer.

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

^gA 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 predominately 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,

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'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 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; 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)].

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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.

Vagifem® 25 mcg	
8 applicators:	NDC 0169-5173-03
18 applicators:	NDC 0169-5173-04
Vagifem® 10 mcg	
8 applicators:	NDC 0169-5176-03
18 applicators:	NDC 0169-5176-04

Keep out of reach of children

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.

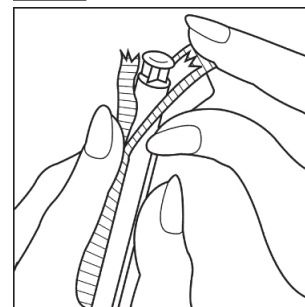


Figure A

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

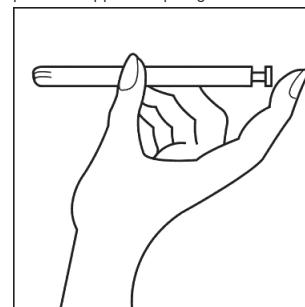


Figure B

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:

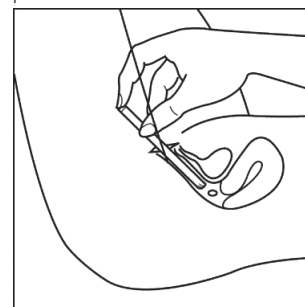


Figure C

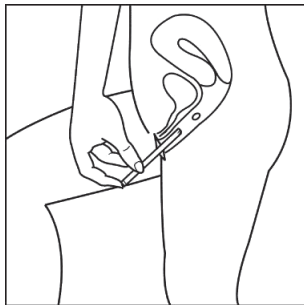


Figure D

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.

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

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VAGIFEM[®]

10mcg
estradiol vaginal inserts

FDA-Approved Patient Labeling

Read this PATIENT INFORMATION before you start using Vagifem® and read what you get each time you refill your Vagifem® 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 VAGIFEM® (an estrogen hormone)

- Using estrogen-alone may increase your chance of getting cancer of the uterus (womb)

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
- 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 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 progestin 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®

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**
- **Are allergic to Vagifem® or any of its ingredients**
See the list of ingredients in Vagifem® at the end of this leaflet.
- **Think you may be pregnant**

Tell your healthcare provider:

- **If you have any unusual vaginal bleeding**
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.
- **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 Vagifem® works. Vagifem® may also affect how your other medicines work.
- **If you are going to have surgery or will be on bed rest**
You may need to stop using Vagifem®.
- **If you are breast feeding**
The hormone in Vagifem® can pass into your breast milk.

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.

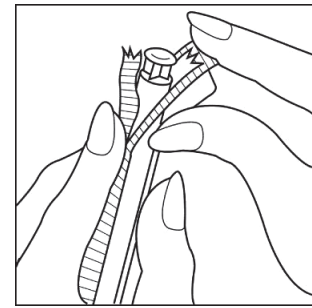


Figure A

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

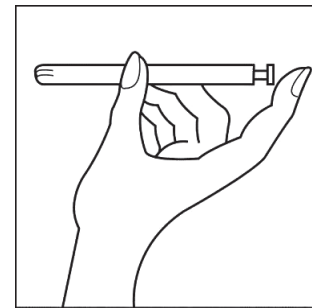


Figure B

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:

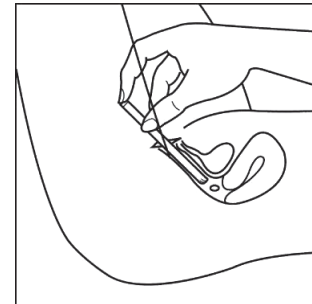


Figure C



Figure D

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 inset inserts.

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].

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