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)

RECENT MAJOR CHANGES
• Warnings and Precautions, Malignant Neoplasms (5.3) 11/2017

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)

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)
• Known liver impairment or disease (4, 5.11)
• 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 galbladder disease (5.5)
• Discontinue estrogen if severe hypercalcemia, loss of vision, severe hypertiglyceridemia or cholestatic jaundice occurs (5.6, 5.7, 5.10, 5.11)
• The Vagifem® applicator may cause vaginal abrasion (5.18)
• Monitor thyroid function in women on thyroid replacement therapy (5.12, 5.19)

ADVERSE REACTIONS
In a prospective, randomized, placebo-controlled, double-blind study the most common adverse reactions (incidence ≥5 percent) were back pain, vulvovaginal pruritus, vulvovaginal mycotic infection and diarrhea. (6.1)

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: ENDOMETRIAL CANCER, CARDIOVASCULAR DISORDERS, BREAST CANCER and PROBABLE DEMENTIA
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2 DOSAGE AND ADMINISTRATION
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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.

FDA-Approved Patient Labeling
Revised: 04/2019

*Sections or subsections omitted from the full prescribing information are not listed.
Vagifem® (estradiol vaginal inserts)

**1. INDICATIONS AND USAGE**

**1.1 Treatment of Atrophic Vaginitis due to Menopause**

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, thorough medical history and history of abnormal uteri should be assessed for a possible progestin need.

**1.2 DOSAGE AND ADMINISTRATION**

**2.1 Treatment of Atrophic Vaginitis due to Menopause**

Vagifem® is not intended for regular use in women with undiagnosed persistent or recurring abnormal genital bleeding (see Warnings and Precautions (5.4)).

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.

**2.2 Cardiovascular Disorders**

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.

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 (5.4)).

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 cardiovascualr benefit and an increase in coronary heart disease (CHD) death (1.7 versus 0.2 per 10,000 women-years). The absolute increased risk of CHD death reported in this study was nonstatistically significant (1.7 versus 0.2 per 10,000 women-years).

In the WHI estrogen plus progesterin substudy, a statistically significant 2-fold greater risk of VTE was reported in women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 15 per 10,000 woman-years), although only the increased risk of DVT reached statistical significance (23 versus 10 per 10,000 women-years). The difference in VTE risk was demonstrated during the first 2 years (see Clinical Studies (14.2)). Should a VTE occur or be suspected, estrogen-alone therapy should be discontinued immediately.

In the WHI estrogen plus progesterin substudy, a statistically significant 2-fold greater risk of VTE was reported in women receiving daily CE (0.625 mg)-alone compared to placebo (30 versus 15 per 10,000 women-years), although only the increased risk of DVT reached statistical significance (23 versus 10 per 10,000 women-years). The difference in VTE risk was demonstrated during the first 2 years.
follow-up of 5.6 years, the estrogen plus progesterin sub-study 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 absolute risk in women reported exposed to estrogen alone 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 and 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 tumor recurrence status did not differ between the groups [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 progesterin 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 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 progesterin compared to estrogen-alone therapy. However, these studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progesterin combinations, doses, or routes of administration.

The use of estrogen-alone and estrogen plus progesterin 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. Women who have limited or no 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 progesterin sub-study 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. A meta-analysis of 17 prospective and 35 retrospective epidemiology studies found that women who used hormonal therapy for menopausal symptoms had an increased risk for ovarian cancer. The prior estrogen use was associated with increased cancer risk. An additional ancillary studies included 12,110 cancer cases from the 17 prospective studies. The relative risks associated with current use of hormonal therapy was 1.41 (95% confidence interval [CI] 1.32 to 1.50); there was no difference in the risk estimates by duration of the exposure (less than 5 years [mean: 6.0 years] vs. greater than 5 years [median of 10 years] of use before the cancer diagnosis). The relative risk associated with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI 1.27-1.48), and the elevated risk was significant for both estrogen-alone and estrogen plus progesterin products. The duration of hormone therapy use associated with an increased risk of ovarian cancer, however, is unknown.

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-years [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 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. 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. 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 dependant on thyroid hormone replacement therapy who are also receiving estrogens may require increased doses of thyroid hormone 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 hyperparathyroidism. Severe hypocalcemia and the onset of hypocalcemic symptoms after 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 erythema- tosus, and hepatic hemangiomata 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 follicular 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

Activated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII, antigen, VIII, antithrombin activity, IX, X, XII, VII-X complex, II-VII-X complex, and beta-thromboglobulin; decreased levels of factor Xa and antithrombin III, decreased antithrombin III activity, increased levels of fibrinogen and fibrin activitiy; increased plasmaglobulin 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. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, antithrombin III).

Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subtraction 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 ≥ 2 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>Treatment Number (%) of Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placenta</td>
<td>Vagifem®</td>
</tr>
<tr>
<td>Body As A Whole</td>
<td>N = 103</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Digestive System</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Urogenital System</td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal Mycotic Infection</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Vulvovaginal Pruritus</td>
<td>2 (2)</td>
</tr>
<tr>
<td>N = Total number of women in study. n = Number of women who experienced adverse reactions.</td>
<td></td>
</tr>
</tbody>
</table>
6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Vagifem® 10 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.

Gastrointestinal disorders
Diarhoea
General disorders and administration site conditions
Drug ineffective
Immune system disorders
Hypersensitivity
Investigations
Blood estrogen increased
Weight increased
Metabolism and nutrition disorders
Fluid retention
Neoplasms benign and malignant
Breast cancer
Endometrial cancer
Psychiatric disorders
Depression
Insomnia
Central Nervous System
Agitated migraine
Reproductive system and breast disorders
Endometrial hyperplasia
Vulval/vaginal burning sensation
Vulval/vaginal pain
Genital pruritus
Vulval/vaginal rash
Vulval/vaginal swelling
Vaginismus
Vaginal ulceration
Skin and subcutaneous tissue disorders
Rash
Rash erthyematous
Rash pruritic
Urticaria
Vascular disorders
Deep vein thrombosis
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, rifonavir 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®.

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) is small, white, film-coated inserts containing 10.3 mcg of estradiol hemihydrate equivalent to 10 mcg of estradiol. Each insert of Vagifem® 10 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.

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 predominant intracellular human estrogen and is substantially more potent than its metabolites, estrone and estradiol, 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.

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 study conducted in 29 patients, Vagifem® 10 mcg demonstrated a mean estradiol (E2) Cmax at Day 83 of 5.5 pg/mL after 12 weeks of treatment (see Table 2).

Table 2: Arithmetic Means of Estradiol (E2), Estrone (E1), and Estrone Sulfate (E1S) PK Parameters Following Multiple Doses of Vagifem® 10 mcg

<table>
<thead>
<tr>
<th></th>
<th>E2</th>
<th></th>
<th></th>
<th>E1</th>
<th></th>
<th></th>
<th>E1S</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC0-24</td>
<td>(h.pg/mL)</td>
<td>Cmax</td>
<td>(0-24)</td>
<td>(pg/mL)</td>
<td>%CV</td>
<td>AUC0-24</td>
<td>(h.pg/mL)</td>
<td>Cmax</td>
</tr>
<tr>
<td>Day 1</td>
<td>242.08</td>
<td>10.09</td>
<td>32.02</td>
<td>485.21</td>
<td>22.22</td>
<td>44.86</td>
<td>5158.32</td>
<td>214.93</td>
<td>53.57</td>
</tr>
<tr>
<td>Day 14</td>
<td>176.49</td>
<td>7.35</td>
<td>43.69</td>
<td>496.14</td>
<td>20.67</td>
<td>30.88</td>
<td>6323.41</td>
<td>263.48</td>
<td>50.07</td>
</tr>
<tr>
<td>Day 83</td>
<td>132.04</td>
<td>5.50</td>
<td>59.69</td>
<td>411.08</td>
<td>17.13</td>
<td>39.58</td>
<td>3804.65</td>
<td>158.53</td>
<td>49.76</td>
</tr>
</tbody>
</table>

Note: 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.

The structural formula is:

\[
\text{estradiol} (\text{E}_2) = \text{C}_12\text{H}_20\text{O}_2 \cdot \frac{1}{2} \text{H}_2\text{O}
\]

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.
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
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 mg 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 the 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 mg 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 3).

Table 3: Mean Change from Baseline to Week 12 in a Composite Score of Most Bothersome Symptoms Compared to Placebo – ITT Population

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE vs. Placebo (95% CI)*</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>0.95 (0.78-1.16)</td>
<td>54</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.91 (0.73-1.14)</td>
<td>40</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.01 (0.71-1.43)</td>
<td>16</td>
</tr>
<tr>
<td>All Strokes</td>
<td>1.33 (1.05-1.68)</td>
<td>45</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.55 (1.19-2.01)</td>
<td>38</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.47 (1.06-2.03)</td>
<td>23</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.37 (0.90-2.07)</td>
<td>14</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>0.80 (0.62-1.04)</td>
<td>28</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.08 (0.75-1.55)</td>
<td>17</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.65 (0.45-0.94)</td>
<td>12</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>0.64 (0.44-0.93)</td>
<td>11</td>
</tr>
<tr>
<td>Lower arm/wrist fractures</td>
<td>0.58 (0.47-0.72)</td>
<td>35</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.71 (0.64-0.80)</td>
<td>144</td>
</tr>
<tr>
<td>Death due to other causes</td>
<td>1.08 (0.88-1.32)</td>
<td>53</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>1.04 (0.88-1.22)</td>
<td>79</td>
</tr>
<tr>
<td>Global index</td>
<td>1.02 (0.92-1.13)</td>
<td>206</td>
</tr>
</tbody>
</table>

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 and deaths 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 therapy.

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 4.

Table 4: Relative and Absolute Risk Seen in the Estrogen-Alone Substudy of WHI

<table>
<thead>
<tr>
<th>Event</th>
<th>Relative Risk CE vs. Placebo (95% CI)*</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD events</td>
<td>0.95 (0.78-1.16)</td>
<td>54</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.91 (0.73-1.14)</td>
<td>40</td>
</tr>
<tr>
<td>CHD death</td>
<td>1.01 (0.71-1.43)</td>
<td>16</td>
</tr>
<tr>
<td>All Strokes</td>
<td>1.33 (1.05-1.68)</td>
<td>45</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.55 (1.19-2.01)</td>
<td>38</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>1.47 (1.06-2.03)</td>
<td>23</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1.37 (0.90-2.07)</td>
<td>14</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>0.80 (0.62-1.04)</td>
<td>28</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.08 (0.75-1.55)</td>
<td>17</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0.65 (0.45-0.94)</td>
<td>12</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>0.64 (0.44-0.93)</td>
<td>11</td>
</tr>
<tr>
<td>Lower arm/wrist fractures</td>
<td>0.58 (0.47-0.72)</td>
<td>35</td>
</tr>
<tr>
<td>Total fractures</td>
<td>0.71 (0.64-0.80)</td>
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</tr>
</tbody>
</table>

14.3 Women’s Health Initiative Memory Study
The WHIMS estrogen-progestin 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, 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)].

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 How Supplied
Each Vagifem® (estradiol vaginal inserts), 10 mcg, is contained in a disposable, single-use applicator, packaged in a blister pack. Cartons contain 6 or 18 applicators with inset inserts.

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.

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.

Figure A
Figure B
Figure C
Figure D

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Date of Issue: 04/2019

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1-888-824-4336

Manufactured by:
Novo Nordisk A/S
2860 Bagsvaerd, Denmark

© 2003-2019 Novo Nordisk
Vagifem® (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 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®

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.
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 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].

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

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