

NDA 20-908  
VAGIFEM™ 25 µg

Physician Package Insert

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**ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.**

Three independent, case controlled studies have reported an increased risk of endometrial cancer in post-menopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incident rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer-reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.

The three case-controlled studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed, on at least a semi-annual basis, to determine the need for continued therapy.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or reoccurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that “natural” estrogens are more or less hazardous than “synthetic” estrogens at equi-estrogenic doses.

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## DESCRIPTION

VAGIFEM™ (estradiol vaginal tablet) is a small, white, film-coated tablet containing 25.8 µg of estradiol hemihydrate equivalent to 25 µg of estradiol.

Each tablet contains the following inactive ingredients: hydroxypropyl methylcellulose, lactose monohydrate, maize starch and magnesium stearate. The film coating contains hydroxypropyl methylcellulose and polyethylene glycol. Each white tablet is 6 mm in diameter and is placed in a disposable applicator. Each tablet-filled applicator is packaged separately in a blister pack.

17β-estradiol hemihydrate is a white, almost white or colorless crystalline solid, chemically described as estradiol hemihydrate.

The chemical formula is  $C_{18}H_{24}O_2 \cdot \frac{1}{2} H_2O$  with a molecular weight of 281.4.

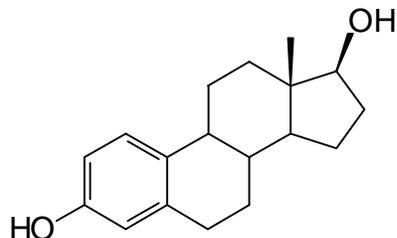
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The structural formula is:



## CLINICAL PHARMACOLOGY

*In vivo* estrogens diffuse through cell membranes, distribute throughout the cell, bind to and activate the estrogen receptors, thereby eliciting their biological effects. Estrogen receptors have been identified in tissue of the reproductive tract, breast, pituitary, hypothalamus, liver and bone of women. The estrogen contained in VAGIFEM, 17  $\beta$ -estradiol is chemically and biologically identical to the endogenous human 17  $\beta$ -estradiol and is, therefore, classified as a human estrogen. Estrogens regulate growth, differentiation and functioning of many different tissues within and outside of the reproductive system. Estrogens are intricately involved with other hormones, especially progesterone, and during the ovulatory phase of the menstrual cycle cause proliferation of the endometrium. Most of the activity of estrogens appear to be exerted via estrogen receptors in target cells of tissues of the woman's reproductive tract: breast, pituitary, hypothalamus, brain, liver, and bone. The steroid-receptor complex is bound to the cell's DNA and induces synthesis of specific proteins. Maturation of the vaginal epithelium is dependent on estrogen as it increases the number of superficial and intermediate cells as

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compared with basal cells. Estrogen keeps the pH of the vagina at approximately 4.5 which enhances normal bacterial flora, predominately, *Lactobacillus döderlein*.

### **Pharmacokinetics**

#### ***Absorption***

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

A single-center, randomized, double-blind comparison study conducted in the U.S. showed that vaginal application of VAGIFEM over a 12-week course demonstrated a mean C<sub>max</sub> of estradiol of 50 pg/mL and that there was no significant accumulation of estradiol as measured by the AUC<sub>0-24</sub> (See Table 1 below).

Table 1: MEAN (±STANDARD DEVIATION) PHARMACOKINETIC PARAMETERS FOR ESTRADIOL  
(Uncorrected for base line)

PK Parameter:	Timepoint		
	Day 1	Day 14	Day 84
AUC (pg.hr/mL)	538 (±265)	567 (±246)	563 (±341)
C <sub>max</sub> (pg/mL)	51 (±34)	47 (±21)	49 (±27)

#### ***Distribution***

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Circulating, unbound estrogens are known to modulate pharmacological response. Estrogens circulate in the blood bound to sex-hormone binding globulin (SHBG) and albumin. A dynamic equilibrium exists between the conjugated and the unconjugated forms of estradiol and estrone, which undergo rapid interconversion.

### ***Metabolism***

Exogenously-delivered or endogenously-derived estrogens are primarily metabolized in the liver to estrone and estriol, which are also found in the systemic circulation. VAGIFEM intravaginal administration avoids first-pass metabolism that occurs with oral estrogens.

The levels of E<sub>1</sub> seen during 12 weeks of VAGIFEM administration do not show any accumulation of E<sub>1</sub>, and the observed values are within the postmenopausal range. See Table 2 below.

Table 2: MEAN (±STANDARD DEVIATION) PHARMACOKINETIC PARAMETERS FOR ESTRONE  
(Uncorrected for base line)

	Timepoint		
	Day 1	Day 14	Day 84
E <sub>1</sub> :			
AUC (pg.hr/mL)	649(±230)	744 (±267)	681 (±271)
C <sub>max</sub> (pg/mL)	35 (±12)	39 (±13)	35 (±12)

### ***Excretion***

Estrogen metabolites are primarily excreted in the urine as glucuronides and sulfates.

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### ***Drug-Drug Interactions***

No formal *drug-drug* interaction studies have been done with VAGIFEM.

### **CLINICAL STUDIES**

A placebo-controlled comparison study was done in the U.S., in which 230 patients were randomized to receive either placebo, VAGIFEM, or 10-µg estradiol vaginal tablets. Patients inserted one tablet intravaginally each day for 14 days, then one tablet twice weekly for the remaining 10 weeks. All patients were assessed for vaginal symptoms. VAGIFEM was superior to placebo in the relief of symptoms of the dryness, soreness, and irritation associated with atrophic vaginitis. This change of symptoms was seen at Week 7 and was maintained throughout to Week 12. (See Figure 1)

An open, controlled comparison study was done in Canada in which 159 patients were randomized to receive either VAGIFEM or the conjugated estrogen vaginal cream, comparator drug. Two (2) grams (~ 1.25 mg conjugated estrogens) of the comparator drug, which is the highest approved dose, 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 was administered daily for 2 weeks, then twice weekly for the remaining 22 weeks. Of all patients entering into treatment phase of the study 10% of patients discontinued their treatment in the Vagifem group and 32% discontinued their treatment in the comparator group. In this study, patients were assessed for relief of symptoms. VAGIFEM 25 µg was not less effective than the approved comparator product at the 2.0 gm dose in the relief of symptoms.

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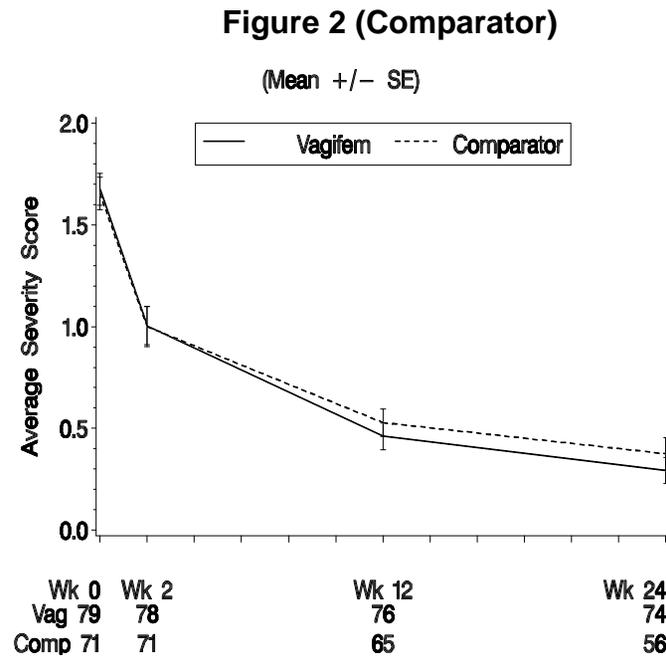
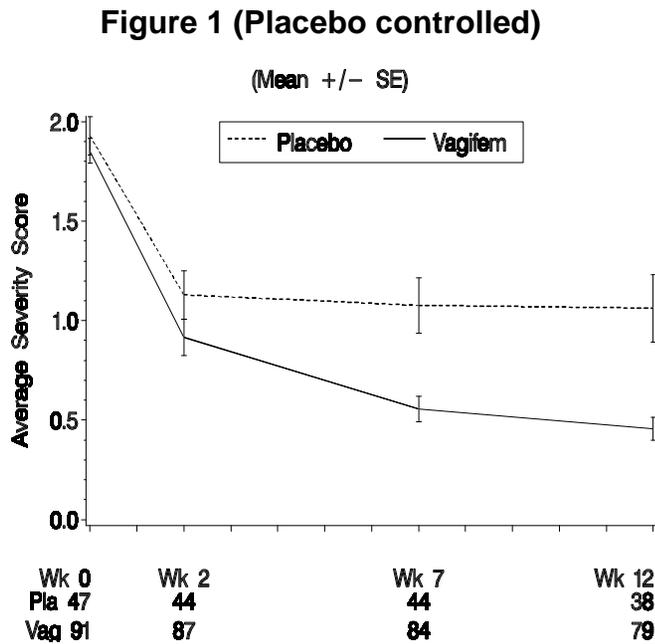
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Symptoms of dryness, soreness, and irritation were rated as 0 = none, 1 = mild, 2 = moderate and 3 = severe. The average severity score of the three symptoms over time for the placebo controlled and comparator studies are shown in the following figures:



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The endometrium was evaluated at the end of each study by endometrial biopsy. See Tables 3 & 4 below.

Table 3: Endometrial Biopsy Results comparing VAGIFEM with placebo  
Over 12 Weeks of Treatment (US Trial)

	VAGIFEM	Placebo
Total Number of Patients enrolled	91	47
Patients with uterus (non-hysterectomized)	48	24
Total Biopsies	32	21
Atrophic Endometrium	27 (84%)	18 (86%)
Weakly Proliferative	0 (0%)	0 (0%)
Proliferative	1 (3%)	0 (0%)
Simple Hyperplasia	1 (3%)	0 (0%)
Complex Hyperplasia	0 (0%)	0 (0%)
Insufficient Tissue	3 (9%)	3 (14%)

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Table 4: Endometrial Biopsy Results comparing VAGIFEM to comparator given over 24 Weeks

	VAGIFEM	COMPARATOR
Total Number of Patients enrolled	80	79
Patients with uterus (non-hysterectomized)	80	79
Total Biopsies	49	49
Atrophic Endometrium	34 (68%)	15 (30%)
Weakly Proliferative	0 (0%)	4 (8%)
Proliferative	1 (2%)	7 (14%)
Simple Hyperplasia	0 (0%)	1 (2%)
Complex Hyperplasia	0 (0%)	1 (2%)
Insufficient Tissue	14 (28%)	21 (42%)

## INDICATIONS AND USE

VAGIFEM is indicated for the treatment of atrophic vaginitis.

## CONTRAINDICATIONS

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The use of VAGIFEM is contraindicated in women who exhibit one or more of the following:

1. Known or suspected breast carcinoma.
2. Known or suspected estrogen-dependent neoplasia; e.g. endometrial carcinoma.
3. Abnormal genital bleeding of unknown etiology.
4. Known or suspected pregnancy. (See PRECAUTIONS)
5. Porphyria.
6. Hypersensitivity to any VAGIFEM constituents.
7. Active thrombophlebitis or thromboembolic disorders.
8. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast malignancy).

## **WARNINGS**

1. *Induction of malignant neoplasms.* Long-term, continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase risk of carcinoma of the endometrium in humans (See Boxed Warning).

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent long-term follow-up of a single physician's practice has raised this possibility. Because of the animal data, there is a need for caution in prescribing estrogens for

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women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms.

2. *Gallbladder disease.* A recent study has reported a 2 to 3 fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens, similar to the 2-fold increase previously noted in users of oral contraceptives.
3. *Effects similar to those caused by estrogen-progestogen oral contraceptives.* There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogens used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer.
  - a. *Thromboembolic disease.* It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic vascular diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral-contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

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While an increased rate of thromboembolism and thrombotic disease in postmenopausal users of estrogens has not been found, this does not rule out the possibility that such an increase may be present, or that subgroups of women who have underlying risk factors, or who are receiving large doses of estrogens, may have increased risk. Therefore, estrogens should not be used (except in treatment of malignancy) in a person with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease and only for those in whom estrogens are clearly needed.

Large doses of estrogens (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men, to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

- b. *Hepatic adenoma.* Benign hepatic adenomas appear to be associated with the oral contraceptives. Although benign, and rare, these may rupture and may cause death through intra-abdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestogen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives. The relationship of this malignancy to these drugs is not known at this time.
- c. *Elevated blood pressure.* Women using oral contraceptives sometimes experience increased blood pressure which, in most cases, returns to normal on discontinuing the drug. There is now a report that this

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may occur with the use of estrogens in the menopause and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. *Glucose tolerance.* A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while using estrogens.

4. *Hypercalcemia.* Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.
5. *Rare Event:* Trauma induced by the Vagifem applicator may occur, especially in patients with severely atrophic vaginal mucosa.

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## **PRECAUTIONS**

### **A. General Precautions.**

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special references to blood pressure, breast, abdomen, and pelvic organs, and should include a Papanicolaou smear. As a general rule, estrogens should not be prescribed for longer than one year without another physical exam being performed.
2. Fluid retention - Because estrogens may cause some degree of fluid retention, conditions which might be influenced by this factor, such as asthma, epilepsy, migraine, and cardiac and renal dysfunction, require careful observation.
3. Familial Hyperlipoproteinemia - Estrogen therapy may be associated with massive elevations of plasma triglycerides leading to pancreatitis and other complications in patients with familial defects of lipoprotein metabolism.
4. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.
5. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients.
6. Preexisting uterine leiomyomata may increase in size during estrogen use.
7. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

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8. Patients with a history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral-contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.
9. Estrogens may be poorly metabolized in patients with impaired liver function and should be administered with caution in such patients.
10. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.
11. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not yet complete.
12. Insertion of the VAGIFEM applicator - Patients with severely atrophic vaginal mucosa should be instructed to exercise care during insertion of the applicator. After gynecological surgery, any vaginal applicator should be used with caution and only if clearly indicated.
13. Vaginal infection - Vaginal infection is generally more common in postmenopausal women due to the lack of normal flora seen in fertile women, especially lactobacilla; hence the subsequent higher pH. Vaginal infections should be treated with appropriate antimicrobial therapy before initiation of VAGIFEM therapy.

**B. Information for the Patient**

See Text of patient Package Insert which appears below.

**C. Drug/Laboratory Test Interactions**

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Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogens:

- a. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin III; increased norepinephrine induced platelet aggregability.
- b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T<sub>4</sub> by column, or T<sub>4</sub> by radioimmunoassay. Free T<sub>4</sub> resin uptake is decreased, reflecting the elevated TBG, free T<sub>4</sub> concentration is unaltered.
- c. Impaired glucose tolerance.
- d. Reduced response to metyrapone test.
- e. Reduced serum folate concentration.
- f. Increased serum triglyceride and phospholipid concentration.

**D. Carcinogenesis, Mutagenesis and 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, vagina and liver. (See CONTRAINDICATIONS AND WARNINGS)

**E. Pregnancy Category X**

Estrogens are not indicated for use during pregnancy or the immediate postpartum period. Estrogens are ineffective for the prevention or treatment of threatened or habitual abortion. Treatment with diethylstilbesterol (DES) during pregnancy has been associated with an increased risk of congenital defects and cancer in the reproductive organs of the fetus, and possibly other birth defects. The use of

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DES during pregnancy has also been associated with a subsequent increased risk of breast cancer in the mothers.

**F. Nursing Mothers**

As a general principle, administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk. In addition, estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Estrogens are not indicated for the prevention of postpartum breast engorgement.

**G. Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**H. Geriatric Use**

Clinical studies of Vagifem did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic renal, or cardiac function, and of concomitant disease or other drug therapy.

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## ADVERSE EVENTS

Adverse events generally have been mild: vaginal spotting, vaginal discharge, allergic reaction and skin rash. Adverse events with an incidence of 5% or greater are reported for two comparative trials. Data for patients receiving either VAGIFEM or placebo in the double blind study are listed in Table 5, and data for patients receiving VAGIFEM in the open label comparator study are listed in Table 6.

Table 5: Adverse Events reported in 5% or greater number of patients receiving VAGIFEM in the placebo controlled trial.

	VAGIFEM (n=91)	Placebo (n=47)
ADVERSE EVENT	%	%
HEADACHE	9	6
ABDOMINAL PAIN	7	4
UPPER RESPIRATORY TRACT INFECTION	5	4
MONILIASIS GENITAL	5	2
BACK PAIN	7	6

Table 6: Adverse Events reported in 5% or greater number of patients receiving VAGIFEM in the open label study.

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VAGIFEM

(n=80)

ADVERSE EVENT	%
PRURITUS GENITAL	6
HEADACHE	10
UPPER RESPIRATORY TRACT INFECTION	11

Other adverse events that occurred in 3-5% of Vagifem subjects included: allergy, bronchitis, dyspepsia, haematuria, hot flashes, insomnia, pain, sinusitis, vaginal discomfort, vaginitis. A causal relationship to VAGIFEM has not been established.

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## **OVERDOSAGE**

Numerous reports of ingestion of large doses of estrogen containing oral contraceptives by young children indicate that acute serious ill effects do not occur. Overdosage with estrogens may cause nausea, and withdrawal bleeding may occur in females.

## **DOSAGE AND ADMINISTRATION**

VAGIFEM is gently inserted into the vagina as far as it can comfortably go without force, using the supplied applicator.

- Initial dose: One (1) VAGIFEM tablet, inserted vaginally, once daily for two (2) weeks. It is advisable to have the patient administer treatment at the same time each day.
- Maintenance dose: One (1) VAGIFEM tablet, inserted vaginally, twice weekly.

The need to continue therapy should be assessed by the physician with the patient. Attempts to discontinue or taper medication should be made at three to six month intervals.

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## **HOW SUPPLIED**

Each VAGIFEM (estradiol vaginal tablet), 25µg is contained in a disposable, single-use applicator, packaged in a blister pack. Cartons contain 15 applicators with inset tablets.

**NDC xxxx-xxxx-xx**

**STORAGE:** Store at 25°C (77°F); excursions permitted to 15°C - 30°C (59°F - 86°F).

[See USP Controlled Room Temperature.]

**CAUTION:** Rx only

Manufactured for

Novo Nordisk Pharmaceuticals Inc.

Princeton, NJ 08540

by Novo Nordisk A/S

Bagsvaerd, DK

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